Enantiospecific Synthesis of (+)-Alstonisine via a Stereospecific Osmylation Process[1]

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The first enantiospecific total synthesis of (+)-alstonisine has been accomplished from D-tryptophan methyl ester **13** in 12% overall yield (in 17 reaction vessels). A diastereospecific osmylation process has been employed as a key step to convert indole **18** into spirocyclic oxindole **19**. Mechanistic studies of the stereoselective osmylation of the 2,3-indole double bond of indole alkaloids has been carried out. Compelling evidence for the intramolecular delivery of OsO_4 via N_b-complexation was obtained for the osmylation process. The correct structure of (+)-alstonisine (**1**) was determined by NOE spectroscopic experiments and further confirmed by single-crystal X-ray analysis.

Oxindole alkaloids are an important group of monoterpene alkaloids that contain the spirocyclic oxindole nucleus.[2] It is still unclear whether oxindole alkaloids serve a specific function in plant species or are simply present as indole alkaloid catabolites, but biogenetic considerations suggest that the indole alkaloid alstonerine (**5**) may serve as a precursor to alstonisine (**1**).[3] Oxindole alkaloids are often associated with significant pharmacological activity.[4] The *Gardneria* oxindole alkaloids such as chitosenine (**7**) and alkaloid I (**9**) exhibit short-lived inhibitory activity *in vivo* of ganglionic transmission in both rats and rabbits.[4g] The spirocyclic oxindole **10**, prepared by Sakai and co-workers as an analogue of **9**, has been employed in a formulation known to inhibit ulcers.[6–9] The bisindole gardmultine (**11**), isolated from *Gardneria multifora*, has been shown to display antitumor activity.[5,6] The alkaloids **7** and **9** are the two monomeric bases of bisindole **11**.[5] A number of alkaloids from *Alstonia angustifolia* have been reported to possess potent antimalarial activity;[4b–f] however, none of the *Alstonia* oxindoles **1**−**4** have been evaluated biologically in detail because of the paucity of isolated material.

Alstonisine (**1**), the first macroline-related oxindole alkaloid, was isolated by Elderfield and Gilman from *Alstonia muelleriama* Domin in 1972.[10] The original structure and relative configuration of this alkaloid were established through single-crystal X-ray analysis by Nordman et al.[11] However, the absolute configuration reported for this molecule was chosen to agree with that deduced for ajmalicine and resulted in an incorrect representation of the structure of alstonisine (**1**).[11] The structures of alstonisine (**1**) and N_b-demethylalstophylline oxindole (**3**) illustrated by Wong et al. would on this basis, presumably, also be incorrect.[4f] The absolute configuration of alstonisine (**1**) was later determined by a biomimetic transformation of alstonisine (**1**) into talpinine;[3] however, direct confirmation of the configuration at the spirocenter had not been reported. This constituted the principal interest in the enantiospecific total synthesis of this alkaloid. After this initial report, alstonisine (**1**) was also found in *Alstonia angustifolia* and *A. macrophylla*.[12,4f] Other macroline-related oxindole alkaloids have been isolated from *A. macrophylla* Wall, including alstonal (**2**),[4f] N_b-demethylalstophylline oxindole (**3**),[13] and 16-hydroxy-N_b-demethylalstophylline oxindole (**4**).[14] All of these macroline-related oxindole alkaloids **1**−**4** contain the 8-azabicyclo[3.2.1]nonane substructure represented in oxindole **6**. The structures of oxindole alkaloids **2** and **3** have been determined by NOE spectroscopic experiments and are believed to be correct, as they correlate well with previously reported biogenetic proposals.[3,13,14] The *Gardneria* alkaloids **7**−**12** also contain the spirocyclic oxindole system present in **6**, but the configuration at the spirocyclic C(7) atom is opposite the proposed structure of alstonisine (**1**). The structure of gardmultine (**11**) was deduced by chemical and spectroscopic evidence[6,8] and concurrently established by single-crystal X-ray analysis.[7] The structure of alstonisine (**1**) [especially the configuration at the spirocenter C(7)], however, has not been unambiguously established to date.[11,15–17] Therefore, development of an efficient approach to that of the synthesis of both series of oxindole alkaloids would not only provide sufficient quantities of synthetic material for structure determination [i.e., for alstonisine (**1**)] and for biological screening but also provide a general route for the synthesis of other related oxindole alkaloids or their antipodes.

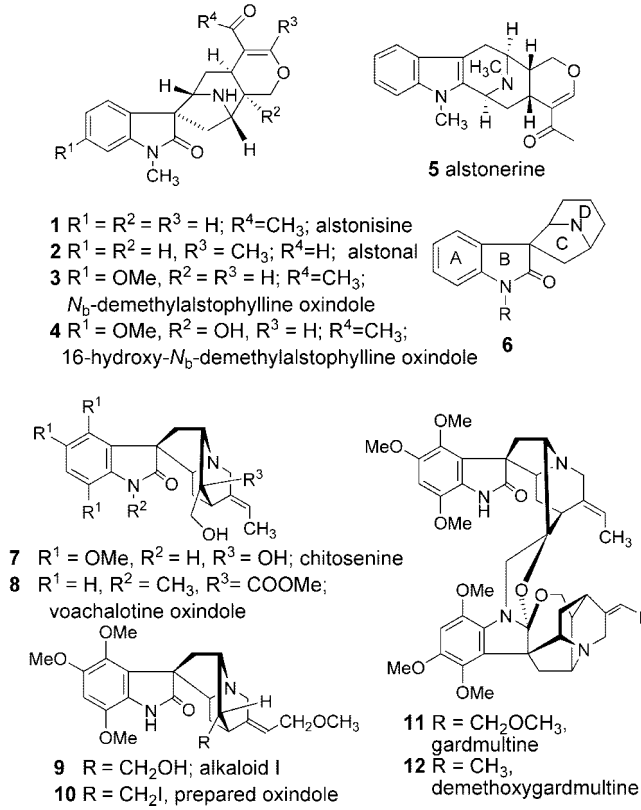

Figure 1. Examples of oxindole alkaloids.

Herein we report the enantiospecific total synthesis of alstonisine (**1**). This work has culminated in the establishment of the correct absolute configuration of alstonisine (**1**). It also confirmed the

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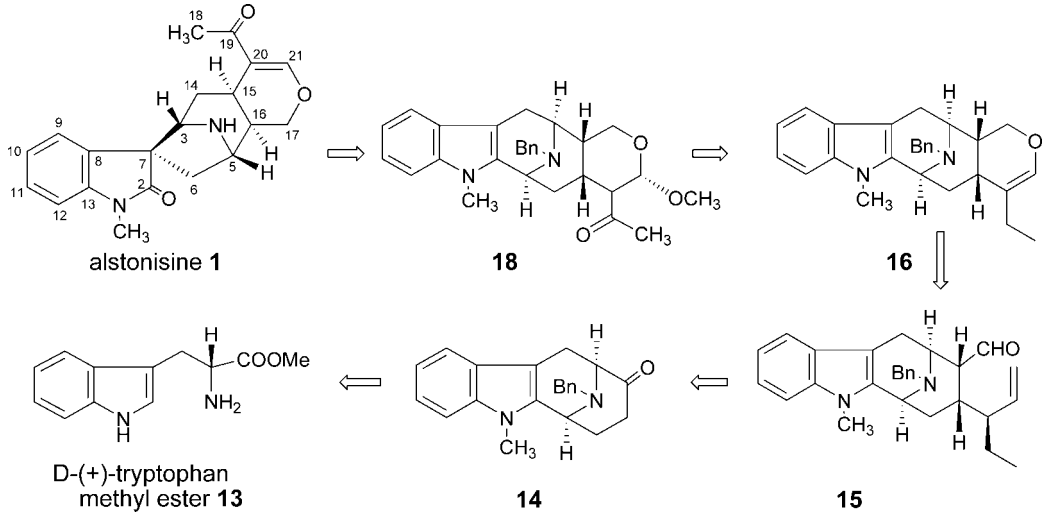
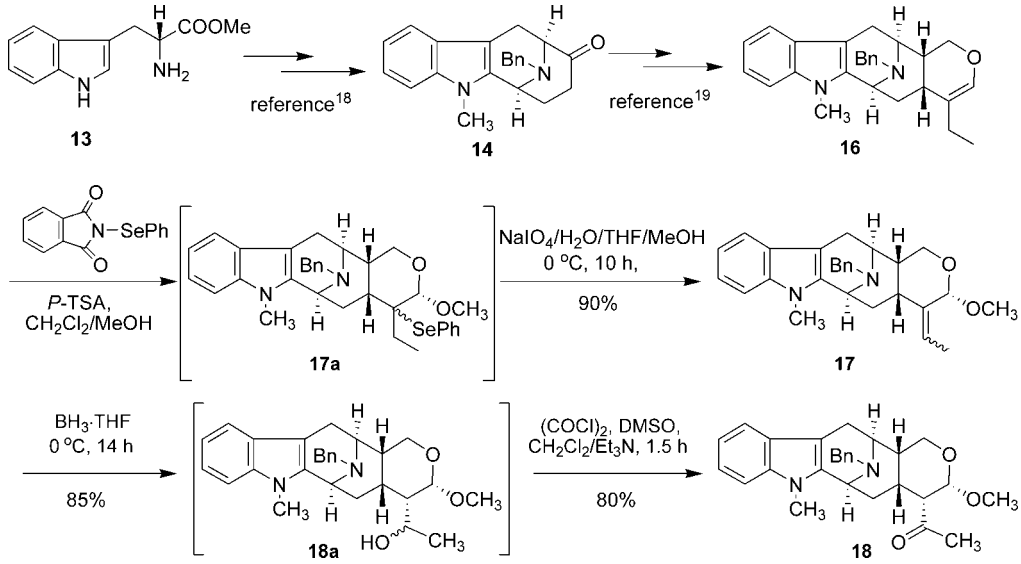
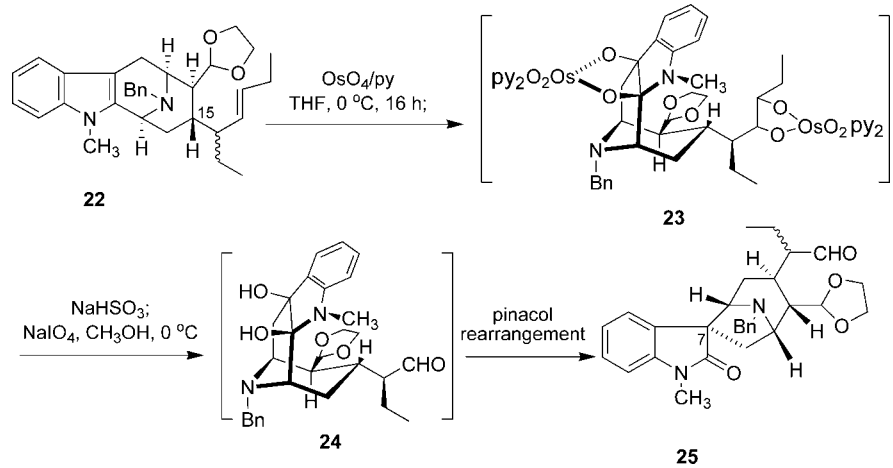
Scheme 1



Scheme 2. [19]



Scheme 3. [29a,d]

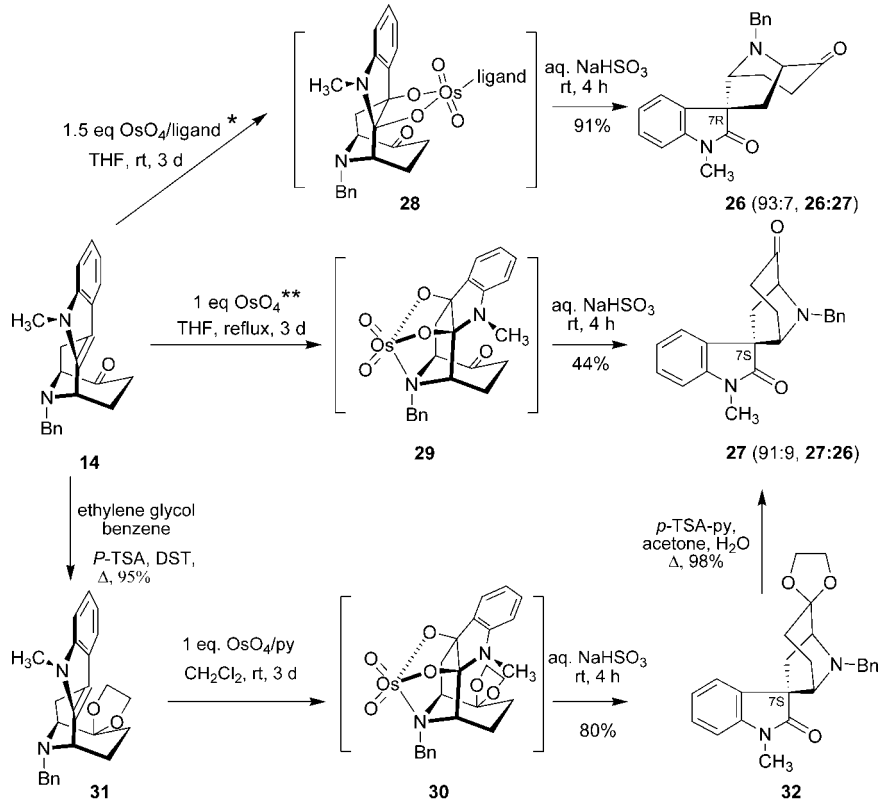


correct structure of alstonisine (**1**) in agreement with that proposed earlier based on biogenetic grounds.[3] In addition, an osmylation process that provides entry into either spirocyclic oxindole, diastereomeric at C-7, has been developed in the course of this work. As shown in the retrosynthetic analysis in Scheme 1, the synthetic protocol rested on the readily available (−)-N_b-benzyl tetracyclic ketone **14**, prepared from ester **13** in greater than 98% ee.[18]

Results and Discussion

The synthesis began with the readily available (−)-N_a-methyl tetracyclic ketone **14** prepared on 300 g scale from ester **13** (>98% ee).[18] Ester **13** had been converted into **16** via an enantiospecific, stereospecific sequence (Scheme 2). This synthesis (Scheme 2) provided the first stereocontrolled entry into the correct chirality of

Scheme 4



*ligand = quinuclidine, DHQ-CLB, DHQD-CLB, $(DHQ)_2PHAL$, $(DHQD)_2PHAL$
**When this reagent was OsO_4/py, the yield was 66%.

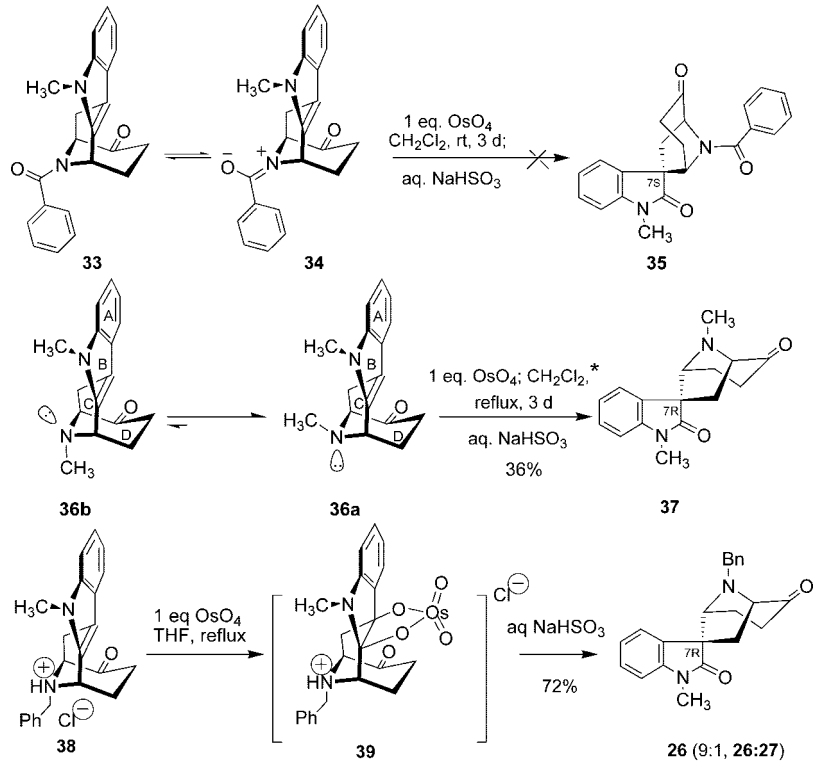
alstonisine at C-3, C-5, C-15, and C-16.[18,19] The regiospecific oxyselenation of olefin **16** using *N*-phenylselenophthalimide[20,21] in CH_2Cl_2/MeOH in the presence of *p*-TSA at 0 °C for 20 h provided the isomeric mixture of selenoacetals **17a** in high yield. This mixture of selenoacetals was directly treated with $NaIO_4$ in THF/MeOH/H_2O solution at 0 °C for 10 h without separation to afford **17** in 90% yield as a 4:1 mixture of *Z*/*E* isomers (Scheme 2).[19] Hydroboration of the mixture of olefins represented by **17** with BH_3·THF complex in THF at 0 °C for 14 h, followed by H_2O_2-mediated oxidation, provided the corresponding isomeric alcohols **18a**, which were directly converted into the intermediate ketoacetal **18** under the modified Swern oxidation conditions of Zhang[22] (−78 to −10 °C, 1.5 h). With the ketoacetal **18** in hand, it was decided to approach the synthesis of alstonisine (**1**) in a stereocontrolled manner to establish the correct chirality at C-7.

Recently, a number of successful approaches have emerged for the construction of spirocyclic oxindoles,[23] such as Mannich reactions,[24] anionic routes,[25] aryl radical cyclizations,[26] intramolecular Heck reactions,[27] oxidations of indole double bonds,[28] osmylations,[17,22,29] and the use of NBS or *t*-BuOCl.[15,16] Earlier, Fu et al.[29a,d] had reported that treatment of N_b-benzyl tetracyclic monoketal **22** with OsO_4/py, followed by periodate oxidation, provided oxindole **25** (Scheme 3). This conversion occurred with complete diastereoselectivity with the correct configuration relative to alstonisine (**1**). Esmond et al.[29e] had also observed a similar formation of an oxindole during dihydroxylation of a key intermediate with OsO_4/pyridine in the biomimetic synthesis of macroline.

A proposed pathway for this transformation is depicted in Scheme 3.[17] The attack of the osmium reagent on the indole 2,3-double bond has occurred from the less hindered convex face to afford the intermediate bisosmate ester **23**, which reacted with $NaIO_4$ to furnish the diol-aldehyde **24**. The ensuing pinacol rearrangement of diol **24** that followed afforded the oxindole **25**.[29a,d]

Since the intermediate ketone **14** was available on large scale, it was employed to investigate the conversion of **14** into either oxindole **26** (required for *Gardneria* oxindoles **7**−**12**) or oxindole **27** (needed for *Alstonia* oxindoles **1**−**4**). Earlier work in our group had initiated investigation of the indole−oxindole conversion using Sharpless ligated osmylation reagents and demonstrated excellent diastereoselectivity.[17] In the absence of the Sharpless ligands, oxindole **27** was the major diastereomer (91:9 **27**:**26**) in this process; in a similar case with OsO_4/py, the OsO_4 was believed to form a reversible complex with pyridine in the reaction mixture. When this osmium reagent coordinated with the N_b-piperidine nitrogen atom of **14** and formed the OsO_4 complex in the equatorial configuration, attack on the indole 2,3-double bond readily occurred from the convex face to afford the intermediate osmate ester **29** (see Scheme 4). The complexation of the OsO_4 with the N_b-nitrogen atom to increase the reaction rate and provide enhanced diastereoselectivity postulated by Peterson[17] was in complete agreement with the work of Donohoe et al.[30a–c] in TMEDA/OsO_4-directed dihydroxylations. Surprisingly, in the presence of the Sharpless ligand, the opposite diastereomer **26** was formed in overwhelming preponderance (93:7 **26**:**27**). It is difficult to rationalize this result on the basis of simple collision interactions, and in this context it is also remarkable that reaction of (±)-**14** with the Sharpless reagents led to no differences between the enantiomers of **14** in the ratios of products.[17] However, it was felt that the osmium complexed with the Sharpless ligand and could not coordinate with the N_b-piperidine nitrogen atom of **14**; the attack on the indole 2,3-double bond occurred from the concave face and formed the intermediate osmate ester **28**. It is believed the OsO_4/Sharpless ligand complex was too strong to be replaced with an N_b-nitrogen/osmium complex. In addition, because of nitrogen inversion at the N_b-benzyl position, presumably, the benzyl group occupied the equatorial position a portion of the time, inhibiting approach of the OsO_4/Sharpless ligand complex from the convex face.[31] It appears that the diastereoselectivity in the case of **26** rested on the size of the ligands. When 1.5 equiv of OsO_4 was employed at room temperature for 3 days with pyridine, quinuclidine,[30a–d] or the Sharpless ligands, the ratio of **26**:**27** went from 1:1, to 3:1, to 9:1.[17] Obviously, the small

Scheme 5



* The reaction was also carried out with 1.5 equiv of OsO_4/py, rt, 3 d; then aq. $NaHSO_3$, 40% or 1.5 equiv of OsO_4/DHQ-CLB, rt, 3 d: then aq $NaHSO_3$, 66%

size of the pyridine ligand did not promote discrimination between the diastereomeric faces of the 2,3-double bond of substrate **14** by the attacking osmium reagent. Moreover, when the bulky Sharpless ligands were employed, the attack of the osmium complex occurred preferentially from the concave face without regard to asymmetry in the pendent ligand.[17]

In order to increase the yield of the oxindole and further improve the diastereoselectivity of osmylation for the generation of **27**, ketone **14** was converted into ketal **31** to block the concave face of the 2,3-indole double bond. In this fashion, it was felt that the OsO_4 could approach the indole moiety of **31** only from the convex face (**30**, Scheme 4). In this manner, ketal oxindole **32** was obtained as a single isomer in 80% yield. Removal of the ketal function in **32** under mild acidic conditions provided the desired diastereomer at C(7) in oxindole **27** as a single diastereomer in almost quantitative yield. This ketooxindole was identical to **27** obtained from ketone **14** with OsO_4/py.

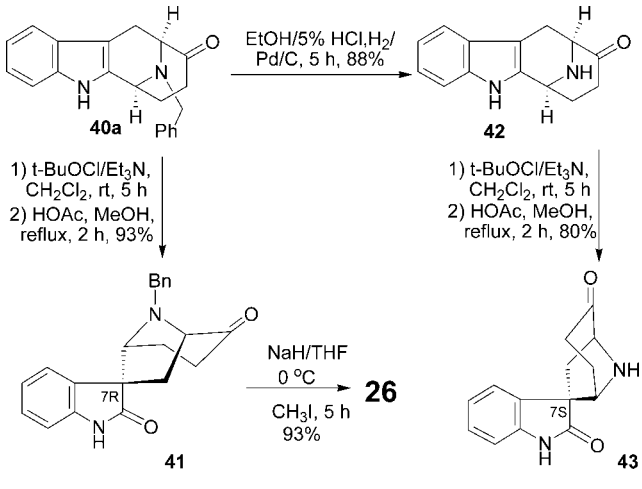
The importance of the N_b-piperidine nitrogen atom for the complexation/intramolecular delivery of OsO_4 in this process was further investigated. Hence the N_b-benzoyl ketone **33** was chosen as a substrate for this process. The N_b-benzoyl group of substrate **33** was approximately the same size as the benzyl group in ketone **14**, but the lone pair of electrons of the piperidine nitrogen atom were delocalized into the carbonyl group of the amide function to form **34** and not readily available to coordinate with OsO_4 (Scheme 5). Execution of this process failed to convert the N_b-benzoyl ketone **33** into N_b-benzoyloxindole **35** or its diastereomer. Only the starting ketone **33** was recovered from this sequence. This example demonstrated that the nitrogen atom of amides could not coordinate with osmium and the attack of the indole 2,3-double bond would not occur from the convex face; moreover, the OsO_4 was not reactive enough in this system at room temperature to react with the substrate **33** even from the concave face of the indole 2,3-double bond without previous ligation to a nitrogen function.[17]

In addition, when the N_a-methyl, N_b-methyl tetracyclic ketone was subjected to oxidation with osmium tetraoxide, osmium tetraoxide/pyridine, or osmium tetraoxide/DHQ-CLB, only one diastereomeric N_b-methyl oxindole (chitosenine stereochemistry) was formed in 36%, 40%, or 66% yield, respectively. In contrast to the N_b-benzyl group of **14**, which occupies the axial position,[31] the smaller N_b-methyl substituent in ketone **36a** and in the other macroline-related indoles is believed to preferentially occupy the equatorial position of the D ring (see **36a**, Scheme 5).[32] As a result, the attack of the osmium reagent would be hindered by the N_b-methyl group of the piperidine nitrogen. Furthermore, the lone pair of electrons of the piperidine nitrogen atom would not be available at the equatorial position for the formation of the equatorial OsO_4 complex. Hence the ligation and subsequent attack of the osmium reagent could only approach the indole moiety of **36a** from the concave face (Scheme 5) in the absence or presence of the pyridine or other ligands.[17] The pinacol rearrangement that followed afforded the spirocyclic oxindole **37** with complete diastereoselectivity. The chirality at C(7) of N_b-methyloxindole **37** is identical to that of **26**.

Finally, compelling evidence for the N_b-complexation/intramolecular delivery of OsO_4 to provide **27** was obtained when the hydrochloride salt of ketone **14** was employed as the substrate in the osmylation process (Scheme 5). The lone pair of electrons of the N_b-piperidine nitrogen atom were not available for coordination with OsO_4 in this hydrochloride salt **38**. Consequently, OsO_4 preferentially attacked the indole 2,3-double bond from the concave face in refluxing THF (**39**, Scheme 5). Oxindole **26**, with the chitosenine stereochemistry, was obtained in 72% yield (**26**:**27**, 9:1). It was now clear that when the lone pair of electrons of the N_b-nitrogen atom are not available to form the N_b-nitrogen/OsO_4 complex, attack of OsO_4 occurred from the concave face to provide the chitosenine stereochemistry (Scheme 5).

It also should be noted that when an electron-rich ligand (DMAP) was used to replace pyridine in the previous example in the OsO_4/pyridine process (Scheme 4), the yield of the oxindole decreased from 66% to only 15%, although the alstonisine stereochemistry in oxindole **27** was produced as the major isomer in 86% de. Presumably, the OsO_4 formed a strong complex with DMAP (due to its electron-rich character) and reactivity with the nucleophilic indole double bond via

Scheme 6



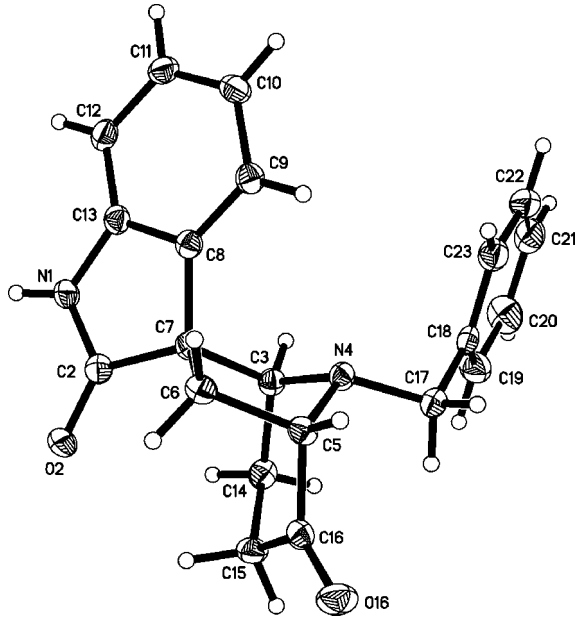


Figure 2. Crystal structure of oxindole **41**. Displacement ellipsoids are at the 50% level.

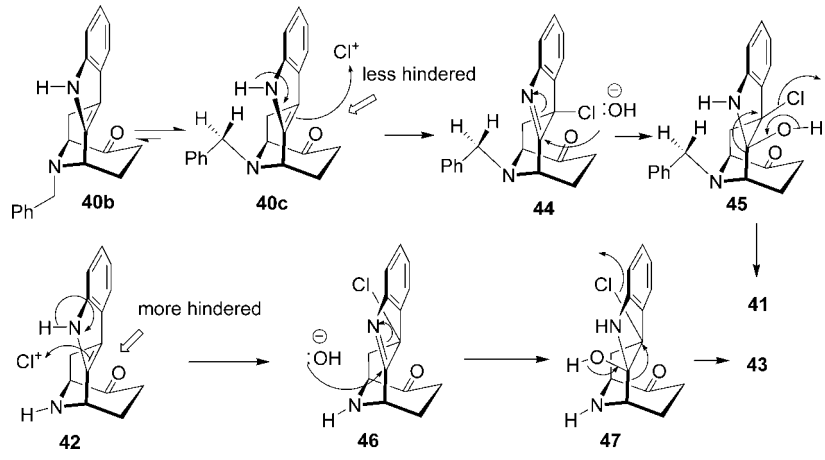
the N_b-piperidine nitrogen atom was reduced. Any remaining (dissociated) OsO_4 attacked **14** from the convex face of the indole 2,3-double bond following the usual coordination with the N_b-piperidine nitrogen atom and furnished **27** (15% yield).

As illustrated in Schemes 4 and 5, ketooxindole **26** could be obtained via the Sharpless osmylation process from ketone **14** with very good diastereoselectivity in excellent yield. In view of the cost and toxicity of osmium tetraoxide, various Sharpless AD ligands were employed with a catalytic amount of OsO_4 via the Sharpless osmylation process.[33] However, these attempts failed and only starting material was recovered. The failure of the catalytic dihydroxylation process, presumably, was derived from the slow hydrolysis of the osmate ester intermediate, in agreement with similar findings reported by Donohoe et al.,[30a–c] which disrupted the metal-mediated catalytic cycle.

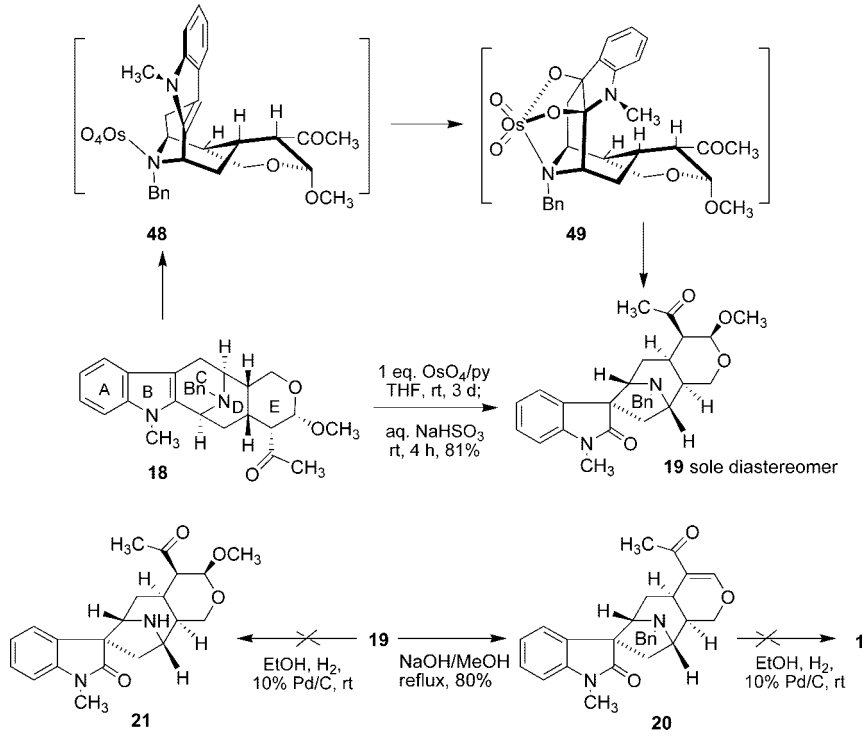
Alternative routes to generate the configuration at the spirocenter required for the *Gardneria* or *Alstonia* alkaloids have been explored with *tert*-butylhypochlorite (*t*-BuOCl). Earlier,[16] it had been demonstrated that the isomeric spiro[pyrrolidine-3,3′-oxindole] system with the alstonisine stereochemistry could be obtained stereospecifically upon reaction of the N_a-H, N_b-benzoyl tetracyclic ketone with *t*-BuOCl/Et_3N, followed by treatment with acetic acid. In this same approach, when N_a-H, N_b-benzyl tetracyclic ketone **40a** was reacted directly with *t*-BuOCl, the oxindole **41**, which was structurally related to chitosenine, was obtained in 93% yield in diastereospecific fashion. In contrast, when the N_a-H, N_b-H tetracyclic ketone **42** was employed, oxindole **43**, which was structurally related to alstonisine, was diastereospecifically formed (Scheme 6). The structure of oxindole **41** was confirmed by single-crystal X-ray analysis,[15,31a] and the NMR spectroscopic data of the oxindole **43** were in agreement with the reported values for racemic **43**.[16] Oxindole **41** was also converted into **26** by N_a-methylation in 93% yield (Scheme 6).

As illustrated in Scheme 7, the 100% diastereoselectivity obtained here was a result of the difference in reactivity of *tert*-butylhypochlorite with the N_b-benzyl vs N_b-H tetracyclic ketone. In contrast to the N_a-methyl, N_b-benzyl tetracyclic ketone **14**, whose N_b-benzyl group preferably occupied the axial position of the N_b-piperidine nitrogen atom,[31] the N_b-benzyl group in the N_a-H, N_b-benzyl tetracyclic ketone **40a** series, presumably, occupied the equatorial position (see **40c**, Scheme 7) and, therefore, blocked one face of the 2,3-indole double bond. This promoted attack by Cl^+ from the concave face. In the subsequent pinacol-type rearrangement the migrating group must attack from the face opposite the C−Cl bond to provide oxindole **41**. Meanwhile, in the case of the N_a-H, N_b-H ketone **42**, the concave face was more hindered when compared to N_b-benzyl **40a** (Scheme 7). In indole **42**, the 2,3-indole double bond was presumably attacked from the convex face to form oxindole **43**, with the alstonisine stereochemistry.[3] It was of interest to attempt the *t*-BuOCl oxidation with the corresponding N_a-methyl tetracyclic ketones **14** and **33**. However, this method failed for conversion of N_a-methyl derivatives **14** and **33** into the corresponding oxindoles, as these N_a-methyl analogues will not readily undergo oxidation of the indole 2,3-double bond with *t*-BuOCl. Presumably, formation of the indolenine intermediate iminium ion similar to **44** in Scheme 7 was too high in energy in the N_a-methyl series.

Scheme 7



Scheme 8



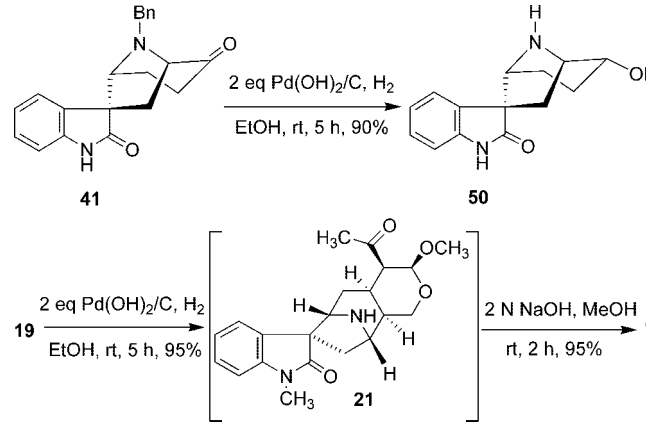
With this information in hand, the ketoacetal **18** was treated with a premixed OsO_4 solution (THF/py, 5:1) at room temperature for 3 days, followed by reductive workup with aqueous $NaHSO_3$, the diol of which underwent pinacol rearrangement to provide the spirocyclic oxindole **19** as the sole diastereomer in 81% yield (Scheme 8). As described above, it was felt that the 100% diastereoselectivity of this conversion was a result of coordination between OsO_4 and the N_b-nitrogen atom of the piperidine ring **48** (Scheme 8), which delivered the intramolecular attack of the osmium reagent from the convex face of ketoacetal **18** and furnished the osmate ester **49**. The osmate ester **49** that resulted was converted into a cis-diol intermediate, which underwent pinacol rearrangement to offer oxindole **19**.

After the diastereomer **19** was obtained, attention turned to the process for N_b-debenzylation and elimination of CH_3OH to complete the enantiospecific synthesis of alstonisine (**1**). As illustrated in Scheme 8, oxindole **19** was first treated with NaOH to eliminate the elements of methanol and provided the N_b-benzylalstonisine **20**. Various attempts were made to execute the catalytic N_b-debenzylation process; however, they failed to generate the compound alstonisine (**1**) from **20**. The failure of these attempts prompted the search for alternative routes for the synthesis of alstonisine (**1**) from **19**. A catalytic amount of 10% Pd/C in ethanol in the presence of hydrogen was employed to convert **19** into **21**; however, this conversion failed probably due to steric hindrance in the 8-azabicyclo[3.2.1]nonane system (**6**, Figure 1).[31a]

Since oxindole **41** was readily available on a large scale, it was decided to take advantage of model reactions. As shown in Scheme 9, the benzyl group of **41** was successfully removed by hydrogenolysis when 2 equiv of Pearlman's catalyst ($Pd(OH)_2/C$)[34] was employed with hydrogen. Consequently, the treatment of N_b-benzyl derivative **19** with 2 equiv of Pearlman's catalyst in the presence of H_2 permitted successful removal of the benzyl function to provide N_b-H analogue **21**. Base-mediated elimination of the elements of methanol was then carried out to furnish alstonisine (**1**) in 86% (two steps) yield. It should be feasible to execute the reduction and then add NaOH to the crude mixture to reduce this to a one-pot process.

The NMR (^1H NMR in Table 1 and ^{13}C NMR in Table 2) data and physical properties including the specific rotation $[\alpha]^{25}_D = +197$ (*c* 1.0 in EtOH) [lit.[4] $[\alpha]^{25}_D = +200$ (*c* 1.0 in EtOH)] and IR spectrum [(Nujol mulls) 1691, 1646, doublets at 1619 and 1610 cm^{-1}) [lit.[10]

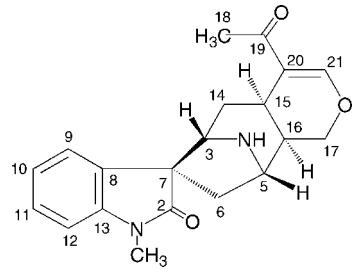
Scheme 9



(Nujol mulls) 1690, 1645, doublets at 1615 and 1605 cm^{-1}] of **1** were in excellent agreement with the published values for the natural product alstonisine.[4f,10,11,36] However, since the possibility existed that the sample from *A. macrophylla*[4f] required for literature ^{13}C NMR comparisons may not be identical to that from *A. muelleriana* obtained much earlier by Elderfield et al.,[10] a mixed sample was employed for ^{13}C NMR data comparison. A ^{13}C NMR spectrum of a mixed sample [1.5 mg of synthetic **1** and 1.5 mg of authentic alstonisine isolated from *A. muelleriana*] contained only 20 signals, which indicated that the synthetic compound was unambiguously identical to the natural product and (*vida infra*) to that isolated from *A. macrophylla*.[4f]

Selected NOE experiments were then carried out on synthetic alstonisine (**1**) (Figure 3). Irradiation of H-9 effected enhancement of H-15 by 20% and vice versa, which would not have been observed in the other diastereomer at C-7, thus confirming the configuration of the spirocenter in alstonisine as the same in the structure proposed earlier based on biomimetic grounds[3] and also found in N_b-demethylalstophylline oxindole by Atta-ur-Rahman.[13,14] The other NOEs, shown in Figure 3, permitted the complete assignment of the stereochemistry of alstonisine (**1**). The structure of alstonisine (**1**) was further confirmed by single-crystal X-ray analysis. Therefore, the original structure of alstonisine reported by Nordman (X-ray crystal-

Table 1. Comparison of the ^{1}H NMR Data for Synthetic Alstonisine (**1**) to that Obtained from *A. macrophylla*[4f]



position	natural **1**[4f]	synthetic **1**
3	3.15−3.20(1 H, m)	3.20 (1 H, m)
5	3.68 (1 H, d, J = 7 Hz)	3.70 (1 H, d, J = 6.9 Hz)
6	2.19 (1 H, d, J = 14 Hz)	2.20 (1 H, d, J = 13.4 Hz)
6	2.52 (1 H, dd, J = 14, 7 Hz)	2.53 (1 H, dd, J = 13.5, 7.5 Hz)
9	6.86 (1 H, dd, J = 7, 1.5 Hz)	6.86 (1 H, d, J = 7.8 Hz)
10	7.30 (1 H, dd, J = 7, 1.5 Hz)	7.30 (1 H, td, J = 7.6, 1.2 Hz)
11	7.32 (1 H, dd, J = 7, 1.5 Hz)	7.34 (1 H, td, J = 7.6, 1.2 Hz)
12	8.25 (1 H, dd, J = 7, 1.5 Hz)	8.26 (1 H, d, J = 7.7 Hz)
14	1.47−1.58 (1 H, m)	1.53−1.58(1 H, m)
14	2.20−2.33(1 H, m)	2.24−2.26 (1 H, m)
15	3.35−3.41 (1 H, m)	3.39 (1 H, dt, J = 11.8, 6.0 Hz)
16	1.90−2.00 (1 H, m)	1.96 (1 H, m)
17	4.26 (1 H, ddd, J = 11, 4, 1.5 Hz)	4.25 (1 H, ddd, J = 11.0, 4.0, 1.5 Hz)
17	4.45 (1 H, t, J = 11 Hz)	4.45 (1 H, t, J = 11.0 Hz)
18	2.24 (3 H, s)	2.25 (3 H, s)
21	7.62 (1 H, s)	7.63 (1 H, s)
N_a-methyl	3.19 (3 H, s)	3.21 (3 H, s)

Table 2. Comparison of the ^{13}C NMR Data for Synthetic Alstonisine (**1**) to that Obtained from *A. macrophylla*[35]

carbon atom	natural **1**[35] (δ ppm)	synthetic **1** (δ ppm)	carbon atom	natural **1**[35] (δ ppm)	synthetic **1** (δ ppm)
2	181.9	182.6	13	143.6	144.2
3	63.4	64.0	14	30.6	31.2
5	55.9	56.5	15	23.8	24.4
6	41.5	42.1	16	36.5	37.2
7	56.5	57.1	17	68.2	68.5
8	128.7	129.2	18	24.5	25.2
9	125.1	125.8	19	196.0	196.8
10	122.8	123.6	20	121.3	121.9
11	127.5	128.2	21	157.2	157.8
12	107.5	108.2	N_a-methyl	25.8	26.4

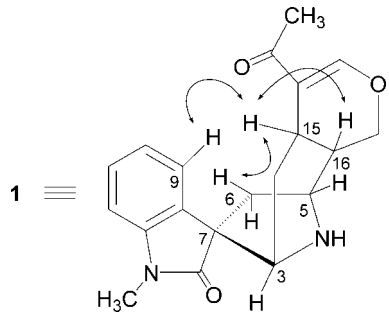


Figure 3. Selected NOE interactions of alstonisine, **1**.

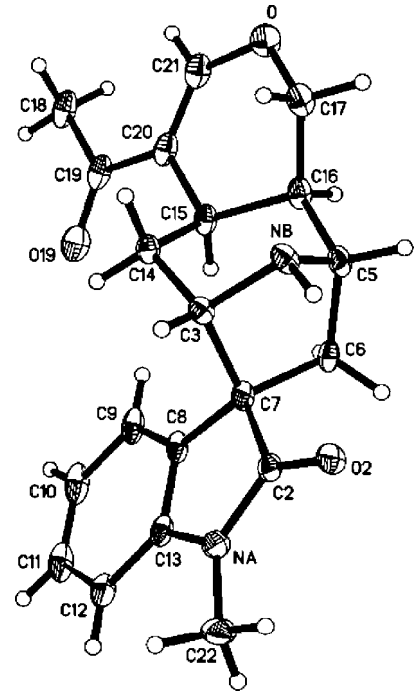


Figure 4. Crystal structure of alstonisine, **1**. Displacement ellipsoids are at the 30% level. See the Cambridge Structural Database entry ALKCAM01 for complete details.

lography) in 1963 was the enantiomer of natural alstonisine (**1**). The ORTEP (Figure 4) of synthetic alstonisine (**1**) was in agreement with the structure of alstonisine proposed on biogenetic grounds.[3]

In summary, mechanistic studies of the stereoselective osmylation of the 2,3-indole double bond of indole alkaloids has been carried out. Compelling evidence for the intramolecular delivery of OsO_4 via N_b-complexation was obtained in the osmylation process. While it is easy to understand the preferred attack of indole **14** (convex face) with either OsO_4/THF or OsO_4/py/THF to provide the alstonisine (**1**) stereochemistry (**27**, Scheme 4),[17,30a–d] the situation is much more complicated in the presence of the Sharpless ligands, on the basis of the results of the achiral DMAP experiment (15% yield, **27**:**26**, 86% de). It is clear that the asymmetry in the OsO_4/Sharpless ligand complex has provided entry into the chitosenine (**7**) stereochemistry (**26**, Scheme 4) in high de. This, presumably, is because the OsO_4/Sharpless ligand complex is irreversible under the conditions employed here, and the fit with indole **14** is better from the concave face. Although it is tempting to speculate that this preferred asymmetric fit is observed from the concave face in the OsO_4/Sharpless ligand process, it must be remembered that identical results were obtained with both types of Sharpless ligands (DHQ-CLB vs DHQD-CLB and $(DHQ)_2PHAL$ vs $(DHQD)_2PHAL$). Additional work in this area is required to fully understand these phenomena. The first enantiospecific total synthesis

of (+)-alstonisine (**1**) has been accomplished from D-tryptophan methyl ester **13** in 12% overall yield (in 17 reaction vessels). The stereospecific conversion of D-(+)-tryptophan methyl ester **13** into tetracyclic ketone **14** was carried out in two reaction vessels on 300 g scale. The ketoacetal **18** was prepared from **14** by following the steps employed in the improved synthesis of alstonerine.[19] A diastereospecific osmylation process has been investigated and employed as a key step to convert ketoacetal **18** into spirocyclic oxindole **19**. This could serve as a general approach for synthesis of other macroline-related oxindoles. The N_b-benzyl group of **19** was successfully removed by treating it with 2 equiv of Pearlman's catalyst in the presence of H_2, followed by base-mediated elimination to provide **1**. The absolute structure of (+)-alstonisine was determined by NOE spectroscopic experiments and further confirmed by single-crystal X-ray analysis. The original structure of alstonisine reported by Nordman (X-ray crystallography) in 1963 therefore was the enantiomer of natural alstonisine (**1**). In addition, the structures of the two oxindoles in the report of Wong et al.[4f] were illustrated incorrectly. It is important to note that experiments with *t*-BuOCl also provide stereospecific entry into the chtosenine stereochemistry or the alstonisine stereochemistry depending on the presence or absence of the N_b-benzyl group. Future work now rests on the synthesis of *Gardneria* alkaloids [diastereomic at C-7 with respect to **1**], since a route to the chitosenine stereochemistry **26** has also been developed in high de.

Experimental Section

General Experimental Procedures. Reagent and solvent purification, workup procedures, and analyses were in general performed as described previously.[19] The ketoacetal intermediate **18** was prepared according to the published procedure.[19]

Protection of N_a-Methyl, N_b-Benzyl, Tetracyclic Ketone 14 with Ethylene Glycol to Provide Ketal 31. To a round-bottom flask (50 mL) that contained a solution of N_a-methyl, N_b-benzyl, tetracyclic ketone **14** (2.0 g, 0.6 mmol) in benzene (20 mL) were added ethylene glycol (5 mL) and *p*-TSA (0.2 g, 7 mmol). The resulting solution was heated to reflux for 24 h in the presence of a DST. After examination by TLC (Si gel, EtOAc/hexanes, 3:1) indicated the disappearance of ketone **14**, the reaction mixture was allowed to cool to rt and then poured into a cold aqueous solution of cold NH_4OH (10%, 20 mL). The aqueous layer was separated and extracted with benzene (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue that resulted was purified by crystallization (MeOH/CH_2Cl_2, 10:1) to provide the ketal **31** (1.8 g, 95%).

31: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67−1.76 (m, 3H), 2.14−2.20 (m, 1H), 2.22−2.29 (m, 1H), 2.43 (d, J = 13.5 Hz, 1H), 2.97 (s, 1H), 3.04−3.16 (m, 1H), 3.21 (s, 3H), 3.27 (d, J = 7.39 Hz, 1H), 3.75−3.81 (m, 1H), 3.81−3.92 (m, 2H), 4.01−4.03 (m, 1H), 4.04 (d, J = 12.5 Hz, 1H), 4.36 (d, J = 12.9 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.23−7.27 (m, 2H), 7.32 (t, J = 7.2 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.7, 26.2, 28.5, 39.0, 51.9, 54.8, 60.01, 63.3, 64.9, 65.4, 106.9, 108.1, 122.3, 123.6, 126.6, 127.3, 127.9, 129.2, 138.1, 139.8, 141.9, 177.7; EIMS (*m*/*z*, relative intensity) 374 (M^+, 56), 273 (100); HREIMS, *m*/*z* 375.2070 (M + H) (calcd for $C_{24}H_{26}N_2O_2$, 375.2073 (M + H)); *anal*. C, 76.74; H, 7.15; N, 7.48, calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48.

Reaction of Ketal 31 with Osmium Tetraoxide to Provide Ketal Oxindole 32. To a round-bottom flask (100 mL) was charged a lightly yellow-colored solution of OsO_4 (266 mg, 1.0 mmol) in dry THF (5 mL) and pyridine (2 mL, freshly distilled), and this was stirred at rt for 2 h. To this solution was added the solution of ketal **31** (350 mg, 1.0 mmol) in dry THF (20 mL) and pyridine (freshly distilled, 1.5 mL) at 0 °C. The resulting black-colored mixture was stirred at rt for 72 h under an atmosphere of Ar. An aqueous solution of $NaHSO_3$ (0.6 g in 3 mL of H_2O) was then added, and the slurry that resulted was stirred at rt for 5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), and the aqueous layer was separated and then extracted with CH_2Cl_2/MeOH (4:1, 5 × 50 mL). The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The residue that resulted was purified by flash chromatography (Si gel, EtOAc/hexanes, 1:4) to provide the ketal oxindole **32** (292 mg, 80%).

32: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.57 (m, 2H), 1.57−1.68 (m, 3H), 2.07−2.31 (m, 1H), 2.87−3.14 (m, 3H), 3.57 (s, 3H), 3.70 (s, 3H), 3.90−4.06 (m, 5H), 6.86 (t, J = 7.0 Hz, 1H), 7.03−7.41 (m, 7H), 7.53 (d, J = 7.71 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.5, 27.0, 28.9, 49.9, 57.3, 58.0, 64.3, 64.4, 106.5, 108.7, 108.8, 118.1, 118.7, 120.7, 126.6, 126.8, 128.1, 128.7, 133.4, 137.0, 139.0; EIMS (*m*/*e*, relative intensity) 390 (M^+, 100); HREIMS *m*/*z* 391.2017 (M + H) (calcd for $C_{24}H_{26}N_2O_3$, 391.2022 (M + H)); *anal*. C, 72.55; H, 6.74; N, 6.97, calcd for $C_{24}H_{26}N_2O_3 \cdot 1/2H_2O$: C, 72.16; H, 6.81; N, 7.01.

***p*-TSA/py-Mediated Transfer of the Ketal Group from the Ketal Oxindole 32 to Provide Ketooxindole 27.** To a round-bottom flask (50 mL) that contained a solution of ketal oxindole **32** (110 mg, 0.3 mmol) in aqueous acetone (20 mL, 50%) was added freshly prepared *p*-TSA/py complex (50 mg). The resulting solution was heated to reflux for 24 h. Analysis by TLC (Si gel, EtOAc/hexanes, 3:7) indicated the disappearance of the ketal oxindole **32**. The above reaction mixture was cooled to rt and then neutralized with an aqueous solution of $NaHCO_3$. The aqueous layer was separated and then extracted with CH_2Cl_2/MeOH (9:1, 3 × 20 mL). The combined organic layers were washed with brine (3 × 20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the resulting residue was purified by flash chromatography (Si gel, EtOAc/hexanes, 1:4) to provide the ketooxindole **27** (292 mg, 80%), the spectroscopic data of which were identical to the published values.[17]

27: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (m, 1H), 2.09 (d, J = 13.9 Hz, 1H), 2.19 (m, 1H), 2.60 (m, 1H), 2.69 (m, 1H), 2.91 (dd, J = 13.9, 7.7 Hz, 1H), 3.19 (s, 3H), 3.45 (d, J = 6.1 Hz, 1H), 3.72 (d, J = 7.6 Hz, 1H), 4.01 (d, J = 12.8 Hz, 1H), 4.24 (d, J = 12.8 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.4 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.48 (m, 2H); CIMS (*m*/*z*, relative intensity) 347 (M^+ + 1, 100).

Reaction of N_a-Methyl, N_b-Benzyl Tetracyclic Ketone Hydrochloride Salt 38 with Osmium Tetraoxide to Provide Ketooxindole 26 as the Major Diastereomer. The N_a-methyl, N_b-benzyl, tetracyclic ketone **14** (512 mg, 1.55 mmol) was dissolved in anhydrous ethanolic HCl (5%, 20 mL), after which the solvent was removed under reduced pressure. The solid was washed with cold dry ether a few times and then dissolved in THF (25 mL). To this solution was added a solution of osmium tetraoxide (394 mg, 1.55 mmol) in THF (15 mL) at 0 °C. The resulting black-colored mixture was allowed to stir at rt for 2 h and then at reflux for 3 days. The reaction mixture was cooled to 0 °C before it was neutralized with an aqueous solution of NH_4OH (10%), and then a solution of $NaHSO_3$ (800 mg) in H_2O (10 mL) was added. The resulting mixture was stirred at rt for 4 h. Water (50 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 400 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (Si gel, EtOAc/hexanes, 1:4) furnished 386 mg (72% of a 9:1 mixture of diastereomeric oxindoles **26**:**27**).

Major diastereomer 26: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (dd, J = 14.5, 9.7 Hz, 1H), 2.29 (m, 1H), 2.42 (dd, J = 13.7, 0.7 Hz, 1H), 2.44 (dd, J = 17.5, 8.6 Hz, 1H), 2.54 (dd, J = 13.7, 7.3 Hz, 1H), 3.16 (br d, J = 4.0 Hz, 1H), 3.23 (s, 3H), 3.55 (dt, J = 17.5, 9.8 Hz, 1H), 3.70 (br d, J = 7.3 Hz, 1H), 3.87 (d, J = 13.0 Hz, 1H), 4.05 (d, J = 13.0 Hz, 1H), 6.81 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.27 (t, J = 7.4 Hz, 1H), 7.28 (t, J = 7.4 Hz, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H), 7.85 (d, J = 7.4 Hz, 1H); CIMS (*m*/*z*, relative intensity) 347 (M^+ + 1, 100). The spectral data for the major isomer **26** were identical to that of an authentic sample.[17]

Diastereospecific Conversion of the N_a-H, N_b-Benzylketone 40 into the N_a-H, N_b-Benzylketooxindole 41 via *tert*-Butyl Hypochlorite. To a round-bottom flask (100 mL) that contained a stirred solution of N_a-H, N_b-benzylketone **40** (816 mg, 2.5 mmol) and Et_3N (0.28 g, 1.1 equiv) in CH_2Cl_2 (30 mL) was added the freshly prepared *tert*-butyl hypochlorite[16] (0.36 g, 0.4 mL, 3 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure, and the resulting solid was dissolved in a solution of MeOH/10% AcOH (1:1, 20 mL). The resulting reaction mixture was heated to reflux for 2 h, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), and the organic layer was washed with an aqueous solution of $NaHCO_3$ (20 mL), brine (2 × 20 mL), and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (Si gel, EtOAc/hexanes, 3:7) to provide the N_a-H, N_b-benzylketooxindole **41** (770 mg, 93%).

41: mp 203−204 °C; $[\alpha]^{25}_D$ +182.3 (*c* 0.95, $CHCl_3$); IR (KBr) 3236, 1707, 1676, 1466 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14−2.28 (m, 2H), 2.31−2.48 (m, 3H), 3.11 (d, J = 3.0 Hz, 1H), 3.41(dt, J = 7.7, 8.5

Hz, lH), 3.50 (d, $J = 7.3$ Hz, lH), 3.80 (dd, $J = 4.7$, 14.5 Hz, 2H), 6.72 (d, $J = 6.1$ Hz, lH), 7.03 (t, $J = 6.1$ Hz, lH), 7.15−7.33 (m, 6H), 7.67 (d, $J = 6.0$ Hz, lH), 8.05 (s, lH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.7, 34.3, 39.6, 51.7, 55.7, 65.3, 67.5, 109.0, 122.9, 124.0, 127.3, 127.9, 128.4, 128.8, 137.5, 137.6, 139.0, 179.4, 212.5; EIMS (*m/z*, relative intensity) 332 (M^+, 26), 304 (80), 173 (100); HREIMS *m/z* 333.1609 (M + H) (calcd for $C_{21}H_{20}N_2O_2$, 333.1603 (M + H)); *anal.* C, 74.80; H, 5.89; N, 8.18, calcd for $C_{21}H_{20}N_2O_2 \cdot 1/4H_2O$: C, 74.87; H, 6.13; N, 8.32.

Diastereospecific Conversion of the N_a-H, N_b-H Ketone 42 into the N_a-H, N_b-H Ketooxindole 43 via *tert*-Butyl Hypochlorite. To a round-bottom flask (50 mL) that contained a stirred solution of N_a-H, N_b-H ketone **42** (113 mg, 0.5 mmol) and Et_3N (0.1 g, 1.2 equiv) in CH_2Cl_2 (20 mL) was added the freshly prepared *tert*-butyl hypochlorite[16] (72 mg, 80 μL, 0.6 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure, and the resulting solid was dissolved in a solution of MeOH/10% AcOH (1:1, 15 mL). The resulting solution was heated to reflux for 2 h, and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (20 mL), and the organic layer was washed with an aqueous solution of $NaHCO_3$ (10 mL), brine (2 × 10 mL), and dried Na_2SO_4. After removal of the solvent under reduced pressure, the crude oxindole was purified by flash chromatography (Si gel, EtOAc/hexanes, 3:5) to provide the N_a-H, N_b-H ketooxindole **43** (97 mg, 80%), the spectroscopic data of which were identical to the published values.[15,16]

N_a-Methylation of N_a-H, N_b-Benzylketooxindole 41 to Provide N_a-Methyl, N_b-Benzylketooxindole 26. To a round-bottom flask (50 mL) that contained a suspension of NaH (70 mg, 2.5 mmol) in THF (5 mL) was added the solution of N_a-H, N_b-benzylketooxindole **41** (160 mg, 0.5 mmol) in THF (20 mL) at 0 °C. The resulting reaction mixture was allowed to stir at rt for 2 h and cooled to 0 °C. Methyl iodide (180 mg, 1.8 mmol) was added, and the resulting solution was allowed to stir at 0 °C for 6 h. Analysis by TLC indicated the disappearence of **41**. The reaction was quenched by addition of CH_3OH (0.5 mL) and was then neutralized with an aqueous solution of NH_4Cl. The aqueous layer was separated and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure, and the resulting residue was subjected to a wash column (Si gel, EtOAc/hexanes, 2:8) to provide the N_a-methyl, N_b-benzylketooxindole **26** (159 mg, 93%), which was identical to **26** from the osmylation of ketone **14**.

Reaction of Ketoacetal 18 with Osmium Tetraoxide to Provide (3*S*,3′*S*,4a*R*,6*S*,9*S*,9a*R*)-4-Acetyl 3,4,4a,5,6,8,9,9a-octahydro-3-methoxy-1′-methyl-10-(phenylmethyl)spiro[cyclohepta[*c*]pyran]-6,9-imino-7(1*H*),3′-[3*H*]indol-2′(1′*H*)-one (19). The ketoacetal **18** was prepared according to the published procedure, the spectroscopic data of which were identical to the published values.[19]**18**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77−1.84 (m, 2H), 1.93 (s, 3H), 2.28 (m, 1H), 2.35−2.44 (m, 2H), 2.55 (dt, $J = 12.9$, 4.0 Hz, 1H), 2.98 (d, $J = 7.0$ Hz, 1H), 3.20 (dd, $J = 9.5$, 7.0 Hz, 1H), 3.35−3.40 (m, 1H), 3.41 (s, 3H), 3.49 (s, 3H), 3.53 (s, 2H), 3.90 (t, $J = 3.2$ Hz, 1H), 4.38 (t, $J = 11.6$ Hz, 1H), 5.02 (q, $J = 3.4$ Hz, 1H), 7.07 (t, $J = 7.8$ Hz, 1H), 7.14 (t, $J = 6.8$ Hz, 1H), 7.20−7.27 (m, 6H), 7.46 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.7, 26.2, 27.4, 28.2, 28.9, 42.9, 51.7, 52.8, 54.7, 55.4, 57.4, 59.8, 98.3, 106.7, 108.9, 117.7, 118.6, 120.6, 126.4, 126.8, 128.1, 128.5, 133.8, 137.0, 139.5, 205.1; CIMS (*m/z*, relative intensity) 445 ($M^+ + 1$, 100). This material was used directly in the next step.

To a round-bottom flask (100 mL) was charged a light yellow-colored solution of OsO_4 (114.4 mg, 0.45 mmol) in dry THF (15 mL) and pyridine (3 mL, freshly distilled), which had been prestirred at rt for 2 h. To this solution was added at 0 °C the solution of ketoacetal **18** (200 mg, 0.45 mmol) in dry THF (15 mL) and pyridine (3 mL, freshly distilled). The resulting black-colored mixture was stirred at rt for 72 h under an atmosphere of Ar. An aqueous solution of $NaHSO_3$ (1.6 g in 8 mL of H_2O) was then added at 0 °C, and the resulting slurry was allowed to stir at rt for 5 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), and the aqueous layer was separated and then extracted with CH_2Cl_2/MeOH (4:1, 5 × 15 mL). The combined organic layers were dried (K_2CO_3), and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (Si gel, EtOAc/hexanes, 1:4) to provide the ketoacetal oxindole **19** as a white solid (167.5 mg, 81%).

19: IR (KBr) 1702, 1610 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35−1.38 (ddd, $J = 13.9$, 5.7, 2.0 Hz, 1H), 2.10 (m, 1H), 2.24−2.30 (m, 1H), 2.29 (s, 3H), 2.39 (m, 2H), 2.69 (m, 1H), 2.98 (m, 1H), 3.11 (s, 3H), 3.30−3.40 (m, 3H), 3.45 (s, 3H), 3.59 (m,1H), 4.05 (m, 1H), 4.20 (m, 1H), 4.85 (d, $J = 2.6$ Hz, 1H), 6.65 (d, $J = 7.3$ Hz, 1H), 6.80 (t, $J = 10.8$ Hz, 1H), 7.16−7.34 (m, 6H), 7.46 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.3, 26.4, 26.8, 29.0, 40.4, 42.8, 54.9, 55.6, 55.8, 55.9, 58.7, 59.5, 67.3, 98.2, 107.5, 122.7, 124.0, 127.5, 127.8, 128.3, 128.7, 129.3, 129.4, 138.5, 139.5, 142.2, 178.55, 208.6; EIMS (*m/z,* relative intensity) 460 (M^+, 10.0), 301 (38.0), 228 (42.0), 258 (30.0), 196 (30.0), 170 (100.0), 146 (100.0), 130 (40.0), 106 (41.4). This material was used directly in the next step.

Base-Mediated Elimination of the Elements of Methanol from Ketoacetal 19 to Provide N_b-Benzylastonisine 20. To a round-bottom flask (10 mL) that contained a stirred solution of the ketoacetal oxindole **19** (6 mg, 0.013 mmol) in CH_3OH (2 mL) was added an aqueous solution of NaOH (2 N, 1 mL) at 0 °C. The resulting reaction mixture was allowed to stir at rt for 12 h and then was cooled to 0 °C. The above solution was neutralized with an aqueous solution of saturated NH_4Cl (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were washed with brine (2 × 2 mL) and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified by flash chromatography (Si gel, EtOAc/hexanes, 3:7) to provide N_b-benzylalstonisine **20** (5.2 mg, 90%).

20: IR (KBr) 1650, 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, $J = 5.0$ Hz, 1H), 1.46−1.73 (m, 1H), 1.91 (m, 1H), 2.12 (m, 1H), 2.17 (dd, $J = 6.2$, 3.8 Hz, 1H), 2.21 (s, 3H), 2.36 (d, $J = 12.6$ Hz, 1H), 2.46 (dd, $J = 16.5$, 7.2 Hz, 1H), 3.05 (m, 1H), 3.15 (s, 3H), 3.64 (d, $J = 6.9$ Hz, 1H), 3.89−3.94 (m, 1H), 3.99 (d, $J = 3.9$ Hz, 1H), 4.15 (d, $J = 12.6$ Hz, 1H), 4.29−4.36 (m, 1H), 6.63 (d, $J = 8.1$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 7.10 (t, $J = 7.8$ Hz, 1H), 7.20−7.33 (m, 5H), 7.44 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 22.6, 24.5, 26.0, 26.4, 31.5, 39.3, 42.2, 54.9, 55.7, 58.5, 67.5, 67.7, 107.0, 121.87, 121.9, 123.4, 127.1, 127.3, 128.3, 128.9, 137.7, 138.8, 142.3, 155.9, 177.6, 197.5; HRMS *m/z* 428.2125 (calcd for $C_{27}H_{28}N_2O_3$, 428.2110).

Debenzylation of N_a-H, N_b-Benzyl Ketooxindole 41 to Provide N_a-H, N_b-H Spirooxindole 50. To a round-bottom flask (25 mL) that contained a solution of N_a-H, N_b-benzyl ketooxindole **41** (100 mg, 0.31 mmol) in absolute EtOH (10 mL) was added 2 equiv (20 wt %) of $Pd(OH)_2$/C. The resulting slurry was allowed to stir at rt under 1 atm of H_2 for 6 h. Examination of the mixture by TLC (EtOAc/hexanes, 1:1) indicated the disappearance of starting material **41** and the appearance of a new component, **50**. The catalyst was filtered from the medium and washed with EtOH (5 × 10 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash chromatography (Si gel, $CHCl_3$/MeOH, 1:19) to provide the N_a-H, N_b-H spirooxindole **50** (69 mg, 90%).

50: FTIR 3419, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (m, 2H), 2.10 (m, 2H), 2.28 (dd, $J = 14.1$, 7.2 Hz, 1H), 2.39 (dd, $J = 14.0$, 1.4 Hz, 1H), 3.40 (s, 1H), 3.75 (m, 1H), 4.13 (m, 1H), 6.98 (d, $J = 7.7$ Hz, 1H), 7.10 (td, $J = 7.6$, 0.9 Hz, 1H), 7.29 (td, $J = 7.7$, 0.9 Hz, 1H), 7.55 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.7, 25.8, 33.1, 56.2, 59.3, 61.6, 67.5, 109.9, 122.3, 124.3, 128.07, 128.4, 142.3, 184.1; CIMS (*m/z,* relative intensity) 244 ($M^+ + 1$, 100).

Debenzylation of (3*S*,3′*S*,4a*R*,6*S*,9*S*,9a*R*)-4-Acetyl-3,4,4a,5,6,8,9,9a-octahydro-3-methoxy-1′-methyl-10-(phenylmethyl)spiro[cyclohepta[*c*]pyran]-6,9-imino-7(1*H*),3′-[3*H*]indol-2′(1′*H*)-one (19) Followed by Base-Mediated Elimination of the Elements of Methanol to Provide Alstonisine (1). To a round-bottom flask (10 mL) that contained a solution of N_a-methyl, N_b-benzyl ketoacetal oxindole **19** (40 mg, 0.087 mmol) in absolute EtOH (5 mL) was added 2 equiv of 20 wt % $Pd(OH)_2$/C (Pearlman's catalyst; 122.1 mg). The resulting slurry was allowed to stir at rt under 1 atm of H_2 for 5 h. Examination of the mixture by TLC (EtOAc/hexanes, 1:1) indicated the disappearance of starting material and the appearance of a new component. The solvent was removed after the catalyst was filtered and washed with EtOH (5 × 10 mL). This N_b-H ketoacetal oxindole intermediate **21** was directly employed for the next step without further purification. To a round-bottom flask (10 mL) that contained a stirred solution of the above intermediate in CH_3OH (5 mL) was added an aqueous solution of NaOH (2 N, 4 mL) at 0 °C. The resulting reaction mixture was allowed to stir at rt for 2 h. The above solution was neutralized with an aqueous solution of saturated NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried (Na_2SO_4). After the solvent was removed under reduced pressure, the residue was purified by flash chromatography (Si gel, EtOAc/hexanes, 2:3) to provide (+)-alstonisine (**1**) (25.2 mg, 86%).

1: mp 169−170 °C (lit.[10] mp 168−169 °C); $[\alpha]^{25}_{D}$ +197 (*c* 1.0 in EtOH), [lit.[10] $[\alpha]^{25}_{D}$ +200 (*c* 1.0 in EtOH)]; IR (Nujol mulls) 1691, 1646, doublets at 1619, 1610 cm^{-1}, [lit.[10] Nujol mulls, 1690, 1645, doublets at 1615 and 1605 cm^{-1}]; ^{1}H NMR (500 MHZ, $CDCl_3$) δ 1.53−1.58 (m, 1H), 1.96 (m, 1H), 2.20 (d, J = 13.4 Hz, 1H) 2.25 (s, 3H), 2.24−2.26 (m, 1H), 2.53 (dd, J = 13.5, 7.5 Hz, 1H), 3.20 (s, 1H), 3.21 (s, 3H), 3.39 (dt, J = 11.8, 6 Hz, 1H), 3.70 (s, 1H), 4.25 (ddd, J = 11.0, 4.0, 1.5 Hz, 1H), 4.45 (t, J = 11.0 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 7.30 (td, J = 7.6, 1.2 Hz, 1H), 7.34 (td, J = 7.6, 1.1 Hz, 1H), 7.63 (s, 1H), 8.26 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.4, 25.2, 26.4, 31.2, 37.3, 42.1, 56.5, 57.1, 64.0, 68.5, 108.2, 121.9, 123.6, 125.8, 128.2, 129.3, 144.2, 157.8, 182.6, 196.8; EIMS (*m/z,* relative intensity) 338 (M^+, 38), 192 (9), 179 (55), 160 (100), 136 (57), 118 (18). The spectral data for this material were identical to that reported for natural alstonisine.[3]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **1**, **18**, **19**, **31**, **32**, **41**, and **50**; HSQC for **50**; NOE and NOESY spectra of **1**; and the X-ray crystal parameters for alstonisine (**1**) and compound **41**. These materials are available free of charge via the Internet at http://pubs.acs.org.

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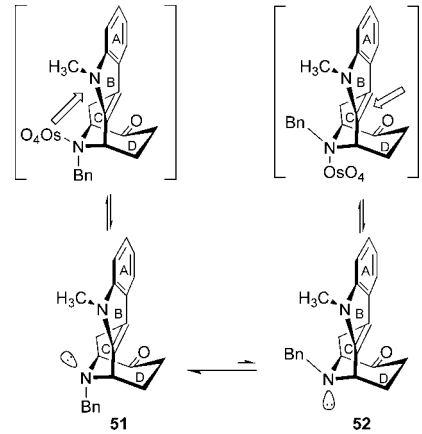
(31) (a) Wearing, X. Z. Ph.D. Thesis, University of Wisconsin−Milwaukee, 2004. The N_b-benzyl group of **14** was believed to be favored in the axial position (with respect to ring D) according to the previous results from a study (NMR) in the N_a-Me, N_b-Bn tetracyclic series **14**. (b) In earlier work, a single-crystal X-ray analysis of an N_b-benzyltetracyclic derivative also indicated that the benzyl group rested in the axial position of the D ring in the crystal: Zhang, L. H.; Trudell, M. L.; Hollinshead, S. P.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8263. In solution this has been supported by analysis of NOE studies. The concomitant complexation of osmium at the equatorial position (with respect to ring D) of indole **51** facilitated intramolecular attack of the osmium reagent to furnish osmate ester **29** (Scheme 4) upon heating at reflux. If complexation occurred at the axial position (with respect to the D ring) of indole **52** to give a complex, the intramolecular delivery of the osmium reagent to the 2,3-indole double bond would be unlikely; see ref 17.



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