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Enantiospecific, Stereospecific Total Synthesis of the Oxindole Alkaloid Alstonisine

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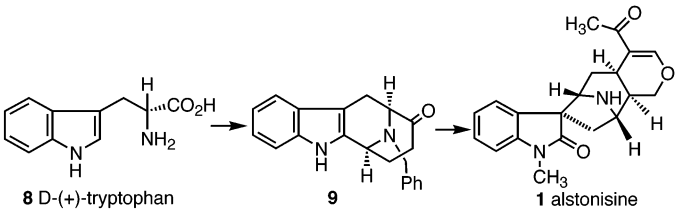
ABSTRACT



The total synthesis of alstonisine was accomplished in enantiospecific fashion in an overall yield of 12% (from tryptophan methyl ester) in 17 reaction vessels. The structure of alstonisine (1) has been determined by NOE spectroscopic experiments and was confirmed by single-crystal X-ray analysis.

In 1972 Elderfield and Gilman reported the isolation of the first macroline-related oxindole alkaloid from *Alstonia muelleriana* Domin and termed it alstonisine (**1**).[1] Since this initial report, alstonisine (**1**) has also been isolated from *Alstonia angustifolia* Wall[2] and *Alstonia macrophylla*.[3] The original structure and relative configuration of this alkaloid were established through single-crystal X-ray analysis by Nordman.[4] The absolute configuration he reported for the molecule was chosen to agree with that deduced for ajmalicine. On the basis of biogenetic grounds,[5] this structure appeared to be the enantiomer of alstonisine. Le Quesne reported a series of biomimetic transformations of alstonisine in 1978.[5] He demonstrated that reduction of alstonisine with lithium aluminum hydride (2 equiv), followed by workup with 0.2 N HCl to initiate a spiroindolenine rearrangement, provided talpinine. The structures of alstonisine and N_b-demethylalstophylline oxindole illustrated by W-H. Wong et al.[3] would presumably also be incorrect. Several other macroline-related oxindole alkaloids have been isolated from *Alstonia macrophylla* Wall by Rahman et al., including N_b-demethylalstophylline oxindole (**2**),[6] 16-hydroxy-N_b-demethylalstophylline oxindole (**3**),[7] and alstonal.[3] The structures of the oxindole alkaloids N_b-demethylalstophylline oxindole (**2**) and 16-hydroxy-N_b-demethylalstophylline oxindole (**3**) have been determined by NOE spectroscopic experiments and are believed to be correct, for they correlate well with the biogenetic proposals of Le Quesne.[6,7] The structure of alstonisine (**1**) [especially the configuration at C(7)], however, has not been unambiguously established to date.[4,8−10] Biogenetic considerations suggest that the indole alkaloid alstonerine (**4**) may serve as a precursor to alstonisine (**1**).[5] It is unclear whether oxindole alkaloids serve a specific function in plant species or are simply present as

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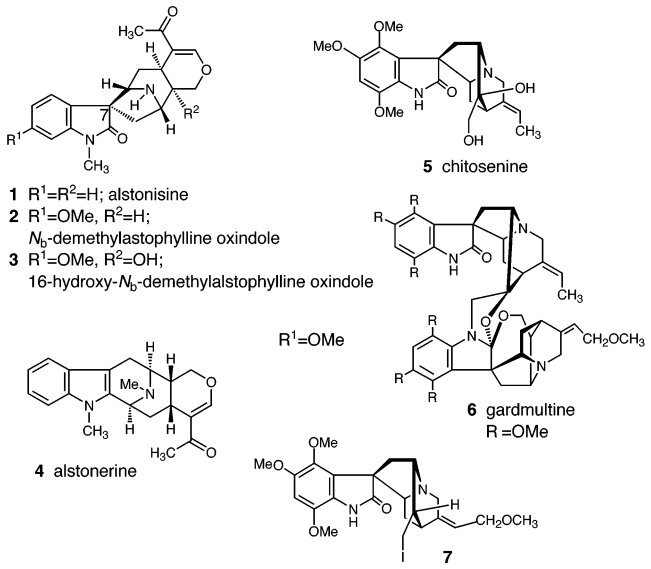
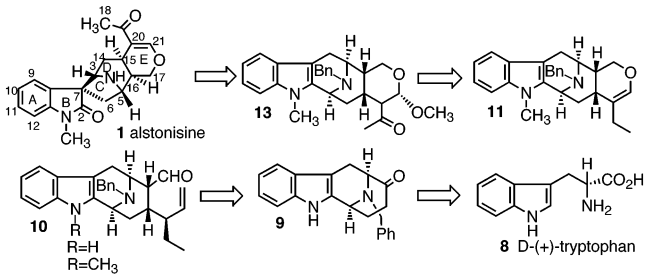


Figure 1.

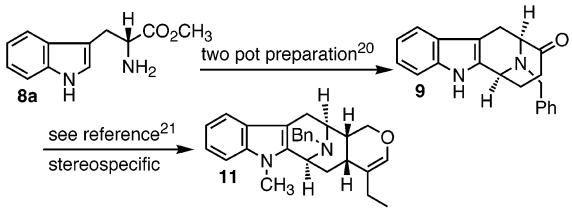
indole alkaloid catabolites. Although a number of alkaloids from *Alstonia angustifolia* were reported to possess potent antimalarial activity,[3,11−14] none of the *Alstonia* oxindoles have been evaluated biologically in detail because of the paucity of isolable material. However, chitosenine (**5**), a monomeric base isolated from *Gardneria multiflora* Makino with the configuration at the spirocyclic carbon C(7) atom opposite to that proposed here for alstonisine (**1**), was found to exhibit short-lived inhibitory activity of ganglionic transmission in vivo in both rats and rabbits.[15] Sakai and co-workers have employed spirocyclic oxindole (**7**), prepared from the bisindole gardmultine (**6**),[16−18] in a formulation known to inhibit ulcers.[19] Interestingly, this alkaloid was also diastereomeric at C(7) with respect to the proposed structure of alstonisine (**1**). Therefore, development of an efficient approach to the synthesis of both series of oxindole alkaloids would provide sufficient quantities of synthetic material for structure determination [i.e., for alstonisine (**1**)], as well as material for biological screening.

We wish to report here an enantiospecific, stereospecific total synthesis of alstonisine (**1**). This work has culminated in the establishment of the correct absolute configuration of alstonisine. It also confirmed the correct structure of alstonisine (**1**) in agreement with that proposed by Le Quesne based on biogenetic grounds.[5] In addition, a method that would provide entry into either spirocyclic oxindole, diastereomeric at C-7, has been developed in the course of this work. As shown in Scheme 1 (retrosynthetic analysis), the synthetic strategy rested on the readily available (−)-N_b-benzyl tetracyclic ketone **9**, prepared from ester **8a** in greater than 98% ee (Scheme 2).[20]

Scheme 1



Scheme 2



In agreement with the earlier work of Yu in the talpinine series,[21] **8a** was converted into **11**, via tetracyclic ketone **9** in a stereospecific fashion (Scheme 2). This sequence of reactions provided the first stereocontrolled entry into the correct chirality of alstonisine at C(3), C(5), C(15), and C(16). The regiospecific oxyselenation of the olefin **11** was carried out with *N*-phenylselenophthalimide,[22,23] in CH_2Cl_2−MeOH in the presence of *p*-TSA at 0 °C to provide a mixture of selenoacetals in high yield. This mixture was directly treated with $NaIO_4$ in THF−MeOH−H_2O solution at 0 °C for 10 h without separation to afford **12** in 90% yield as a 4:1 mixture of Z/E isomers (Scheme 3). Treatment of the mixture of olefins **12** with the BH_3·THF complex in THF at 0 °C for 14 h and H_2O_2 oxidation, followed by the modified Swern oxidation conditions of Zhang[24] (−78 to −10 °C, 1.5 h) gave the ketoacetal (**13**) in 80% yield. With the availability of intermediate **13**, it was decided to approach

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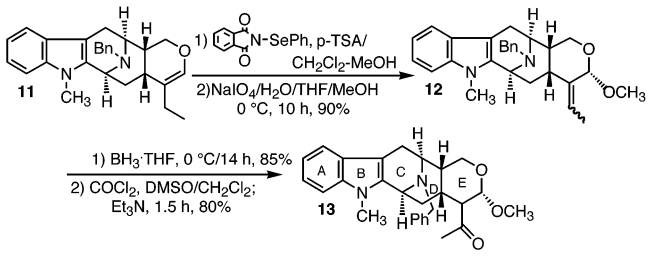
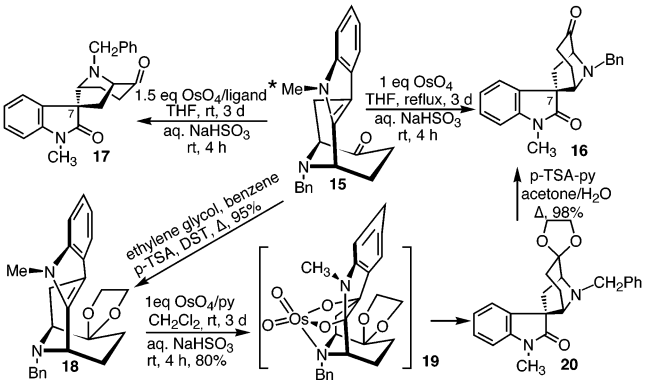
Scheme 3



the synthesis of alstonisine (**1**) in a stereocontrolled manner to establish the correct chirality at C(7).

Several approaches for the construction of spiro-annelated indolines have been reported recently. The key spirocyclic centers have been constructed principally through anionic routes,[25] aryl radical cyclizations,[26−33] intramolecular Heck reactions,[34−39] oxidations of indole double bonds,[40−43] osmylation,[10,24,44−48] and employment of NBS or *t*-BuOCl.[8,9] Esmond and Le Quesne had also observed formation of an oxindole during dihydroxylation of a key intermediate with OsO_4−pyridine in the biomimetic synthesis of macroline.[48] Initially, the conversion of tetracyclic ketone **15** into either diastereomeric N_b-benzyltetracyclic oxindole **16** (proposed alstonisine stereochemistry) or **17** (Scheme 4) with stoichiometric amounts of osmium tetraoxide in the presence or absence of the Sharpless ligands was executed by Peterson.[10] This was performed during approaches to the enantiospecific preparation of either the *Gardneria* and *Voacanga* oxindole

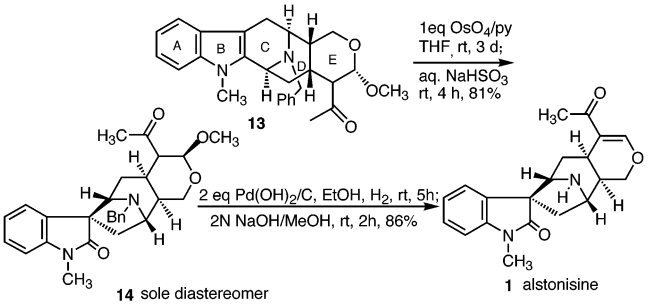
Scheme 4 [a]



[a] Ligands (*): quinuclidine, DHQ-CLB, DHQD-CLB, $(DHQ)_2$-PHAL, $(DHQD)_2$PHAL.

bases or the *Alstonia* oxindole alkaloids (**16**/**17**), as shown in Scheme 4. Excellent diastereoselectivity was obtained in this process. In the presence of OsO_4, **16** was the major diastereomer (91:9), but in the presence of OsO_4 with a Sharpless ligand the opposite diastereomer (**17**) was obtained (97:3). In the case of ketal **18**, only one diastereomer was formed and in 80% yield. With this information in hand, a solution of the ketoacetal **13** (as shown in Scheme 5) in

Scheme 5



THF−pyridine (5:1) was stirred with a premixed solution of osmium tetraoxide (1 equiv) in THF−pyridine (5:1) at room temperature for 72 h. This was followed by reductive workup with aqueous $NaHSO_3$. From this process the ketoacetal oxindole (**14**) was obtained as the sole diastereomer in 81% yield. It was believed that the osmium tetraoxide coordinated to the piperidine nitrogen atom, delivering the reagent from the convex face of the substrate intramolecularly (as shown in the model reactions in Scheme 4). This complexation was presumably favored because of the axial preference (with respect to ring D) of the benzyl group earlier observed by Peterson in the N_a-methyl, N_b-benzyl series.[10,49] Single-crystal X-ray analysis of a N_b-benzyltetracyclic derivative indicated that the benzyl group rested in the axial position of the D ring in the crystal as

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well.[50] The concomitant complexation of osmium at the equatorial position (with respect to ring D) facilitated intramolecular attack of the osmium reagent to furnish osmate ester **19**. The osmate ester (**19**) was then reduced by sodium bisulfite, and the cis-diol that resulted underwent a pinacol rearrangement to furnish the desired oxindole diastereospecifically.[10] Additional studies on the mechanism of this process are underway. Various attempts were made to execute the N_b-debenzylation process. A catalytic amount of 10% Pd/C in ethanol in the presence of hydrogen, or HCO_2NH_4 employed as the hydrogen source, or NBS/AIBN (upon heating) were attempted; however, they all have failed. The benzyl group was successfully removed by hydrogenolysis when 2 equiv of Pearlman's catalyst [$Pd(OH)_2$/C]/H_2 were used. Base-mediated elimination of the elements of methanol was then carried out to furnish alstonisine (**1**) in 86% yield (two steps). The spectral (IR, ^{1}H and ^{13}C NMR) and physical properties including the optical rotation $[\alpha]^{25}_D = +197°$ (*c* 1.0 in EtOH) [lit.[1] $[\alpha]^{25}_D = +200°$ (*c* 1.0 in EtOH)] of **1** were in excellent agreement with the published values (as shown in the table in Supporting Information) for the natural product alstonisine.[1,3,4,51] However, since the possibility existed that the sample from *A. macrophylla*[3] required for literature ^{13}C NMR comparisons may not be identical to that from *A. muelleriana* obtained much earlier by Elderfield et al.,[1] a mixed sample was employed for ^{13}C NMR 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* kindly provided by P. Le Quesne] contained only 20 signals, which indicated that the synthetic compound was unambiguously identical to the natural product and (vide infra) to that isolated from *A. macrophylla*.[3] Selected NOE experiments were carried out on synthetic alstonisine (**1**) (Figure 2). 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 by Le Quesne[5] and also found in N_b-demethylalstophylline oxindole by A-U. Rahman.[6] The other NOEs, shown in Figure 2, permitted the complete assignment of the stereochemistry of alstonisine (**1**). The structure of alstonisine was further confirmed by single-crystal X-ray analysis. The ORTEP (depicted in the Supporting Information) was in agreement with the structure of alstonisine proposed by Le Quesne on biogenetic grounds.[5]

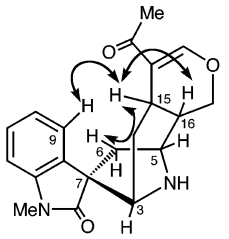

Figure 2. Selected NOEs of alstonisine (**1**).

In conclusion, ketone **9** was enantiospecifically and stereospecifically synthesized in a two-pot process from D-(+)-tryptophan methyl ester on large scale.[20] The enol ether **11** can be obtained from ketone **9** by following the steps employed in the improved synthesis of alstonerine.[21] The enol ether **11** can then be converted into oxindole **14** diastereospecifically via the osmylation process (OsO_4−pyridine). The N_b-benzyl group was successfully removed by adding 2 equiv of $Pd(OH)_2$/C in the presence of hydrogen. Therefore, the total synthesis of alstonisine was accomplished in enantiospecific fashion in an overall yield of 12% (from tryptophan methyl ester) in 17 reaction vessels. The structure of alstonisine (**1**) has been determined by NOE spectroscopic experiments and was 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.[3] were illustrated incorrectly. Future work now rests on the synthesis of N_b-demethylalstophylline oxindole and chitosenine [diastereomic at C-7 with respect to **1**].

Acknowledgment. We wish to acknowledge the Office of Naval Research, NIDA, and NIMH for support of this work. We thank Dr. P. Le Quesne for a gift of natural alstonisine.

Supporting Information Available: ^{13}C NMR comparisons, ORTEP drawing, and X-ray structural data for alstonisine (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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