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Concise Total Synthesis of (-)-Affinisine Oxindole, (+)-Isoalstonisine, (+)-Alstofoline, (-)-Macrogentine, (+)-N_a-Demethylalstonisine, (-)-Alstonoxine A, and (+)-Alstonisine

Michael Rajesh Stephen,[a] M. Toufiqur Rahman,[a] V.V.N. Phani Babu Tiruveedhula,[a] German O. Fonseca,[a] Jeffrey R. Deschamps,[b] and James M. Cook[a,*]

[a]Department of Chemistry & Biochemistry, University of Wisconsin—Milwaukee, 3210 North Cramer Street, Milwaukee, Wisconsin 53211, United States

[b]Center for Biomolecular Science and Engineering, Naval Research Laboratory, Code 6930, Washington, DC 20375, United States

Abstract:

A highly enantio- and diastereoselective strategy to access any member of the sarpagine/macroline family of oxindole alkaloids via internal asymmetric induction was developed from readily available D-(+)-tryptophan. At the center of this approach was the diastereospecific generation of the spiro[pyrrolidine-3,3'-oxindole] moiety at an early stage via a *tert*-butyl hypochlorite-promoted oxidative rearrangement of a chiral tetrahydro-β-carboline derivative. This key branching point determined the spatial configuration at the C-7 spiro center to be entirely 7*R* or 7*S*. Other key stereospecific processes were the asymmetric Pictet-Spengler reaction and Dieckmann cyclization, which were scalable to the 600 gram and 150 gram levels, respectively. Execution of this approach resulted in first enantiospecific total synthesis of (+)-isoalstonisine and (-)-macrogentine from the chitosenine series (7*R*), as well as (+)-alstonisine, (+)-alstofoline, (-)-alstonoxine A and (+)-N_a-demethylalstonisine from the alstonisine series (7*S*).

Key words: Enantiospecific total synthesis; Sarpagine and Macroline; Spirooxindole Alkaloids; Alstonisine and Chitosenine.

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Introduction

Oxindole alkaloids form an important group of monoterpene alkaloids that contain the spirocyclic oxindole nucleus (see Figure 1, **1-11** for some examples).[1],[2] It is still not clear whether oxindole alkaloids serve a specific function in plant species or are simply present as indole alkaloid catabolites, but biogenetic considerations of Le Quesne 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 (**6**) and alkaloid I (**8**) exhibit short-lived inhibitory activity *in vivo* of ganglionic transmission in both rats and rabbits.[4b] The spirocyclic oxindole **9**, prepared by Sakai and co-workers as an analogue of **8**, has been employed in a formulation known to inhibit ulcers.[5] The bisindole gardmultine (**10**), which was isolated from *Gardneria multiflora*, displayed antitumor activity.[5a, 6] The alkaloids **6** and **8** are the two monomeric bases that comprise the structure of bisindole **10**.[6]

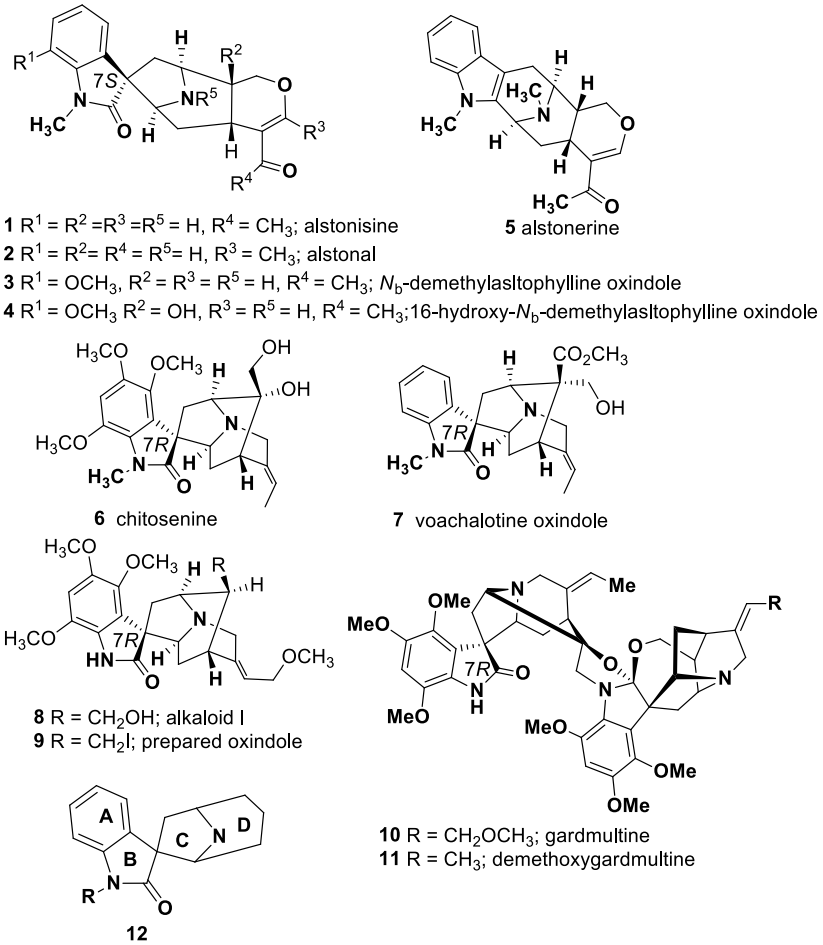

Figure 1. Representative oxindole alklaloids

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A number of alkaloids from *Alstonia angustifolia* have been reported to possess potent antimalarial activity;[4c-g] 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 reported macroline-related oxindole alkaloid, was isolated by Elderfield and Gilman from *Alstonia muelleriana* Domin in 1972.[7] The original structure and relative configuration of this alkaloid were established through single-crystal X-ray analysis by Nordman *et al*.[8] 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**).[8] The structures of alstonisine (**1**) and N_b-demethylalstophylline oxindole (**3**) illustrated by Wong *et al*. would on this basis, presumably, also be incorrect.[4c] The absolute configuration of alstonisine (**1**) was later determined by a biomimetic transformation of alstonisine (**1**) into talpinine by Le Quesne *et al*.[3] However, direct confirmation of the configuration at the spirocenter had not been reported. After this initial report, alstonisine (**1**) was also found in the plant species, *Alstonia angustifolia* and *A. macrophylla*.[4c],[9] Other macroline-related oxindole alkaloids have been isolated from *A. macrophylla* Wall, including alstonal (**2**),[4c] N_b-demethylalstophylline oxindole (**3**),[10] and 16-hydroxy-N_b-demethylalstophylline oxindole (**4**).[11] All of these macroline-related oxindole alkaloids **1-4** contain the 8-azabicyclo[3.2.1]nonane substructure represented in oxindole **12**. The structures of oxindole alkaloids **2** and **3** were determined by NOE spectroscopic experiments and are believed to be correct, since they correlate well with previously reported biogenetic proposals.[3, 10-11] The *Gardneria* alkaloids **6-11** also contain the spirocyclic oxindole system present in **12**, but the configuration at the spirocyclic C(7) carbon atom is opposite [C-7(*R*)] to the proposed structure of alstonisine (**1**). The structure of gardmultine (**10**) was deduced by chemical and spectroscopic evidence[5a, 5c] and was confirmed by single-crystal X-ray analysis.[5b] The structure of alstonisine (**1**) [especially the configuration at the spirocenter C(7)], however, had not been unambiguously established previous to the report of Wearing *et al.* as mentioned above.[2c, 8, 12]

The enantiospecific total synthesis of **1** via the asymmetric Pictet-Spengler reaction was used to establish the absolute configuration of all chiral centers in (+)-alstonisine. This was confirmed as C-7(*S*) by NOE spectroscopic experiments and further verified by single-crystal X-ray analysis at low temperature with a Cu source.[2d] Once the

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structure and optical rotation were found to be the same as (+)-alstonisine from *A. muelleriana* isolated by Elderfield, a sample of synthetic **1** (2 mg) was admixed with a sample of natural alstonisine **1** (2 mg) from *A. muelleriana*, kindly provided by Professor Le Quesne. The ^{13}C NMR spectrum of this material contained only one set of carbon signals, which were identical to those found in the spectrum of the natural alkaloid (+)-alstonisine (**1)** from *A. muelleriana.* This confirmed unambiguously the structure of **1** and the absolute configuration at C(7) as *S*. The original structure of alstonisine reported by Nordman (X-ray crystallography) in 1963 was drawn incorrectly and actually was the enantiomer of natural alstonisine (**1**). In addition, the structures of the two oxindoles in the report of Wong *et al*.[4c] were illustrated incorrectly. This work stimulated interest in the synthesis of other macroline-related oxindole alkaloids in our laboratory.

A general retrosynthetic strategy is depicted in Scheme 1. The common intermediate for those oxindole alkaloids in the [C-7(*S*)]-series (the top of Scheme 1) would be the N_b-H-tetracyclic ketone oxindole (**16**). The later intermediate would arise from the *tert*-butyl hypochlorite-promoted oxidation-rearrangement sequence of the important N_b-H-tetracyclic ketone (**15**). The asymmetry of this tetrahydro-β-carboline would be constructed by means of the modified Pictet-Spengler reaction followed by a Dieckmann cyclization in a two-pot process from D(+)-tryptophan, as reported earlier.[12a, 13] An analogous reasoning applies to those natural oxindole alkaloids in the C-7(*R*)-series (bottom of Scheme 1). In this case, the N_b-benzyl-tetracyclic ketone oxindole (**14**) would be the common oxindole precursor. The presence of a bulky protecting group on the N_b-nitrogen atom in the N_b-benzyl-tetracyclic ketone (**13**) is a key structural feature that determines the diastereoselective generation of the (*R*)-configuration at the C-7 spiro center during the oxidation-rearrangement reaction.[14]

Finally, although it was not part of the present study, it is important to mention two features in regard to the generality of the approach proposed here: (1) the sarpagine/macroline imino-ether alkaloids could also be accessed by the use of this strategy given their closely-related chemical structure with the oxindole group; and (2) those natural spirooxindole alkaloids bearing a substituted-benzene A-ring oxindole moiety (the methoxyl group is the only type of substituent that has been found other than hydrogen, to date, in this series) could be prepared through the proposed strategy from the corresponding enantiopure methoxy-substituted tryptophan.[15]

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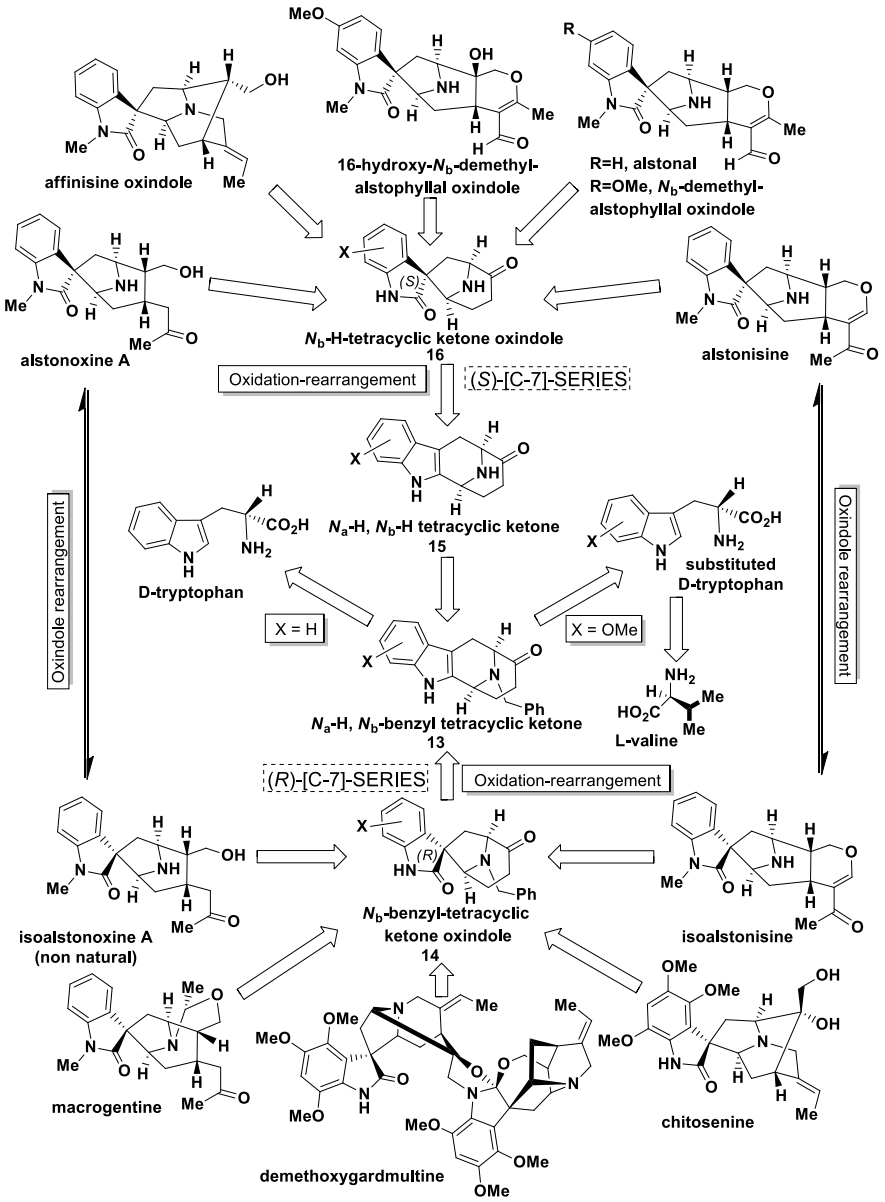

Scheme 1. Retrosynthetic strategy

Results and Discussion

The sarpagine-related (-)-affinisine oxindole was first isolated from the leaf extract of *Alstonia angustifolia var. latifolia* by Kam *et al*. and its structure was assigned in 2004.[16] The original structure and relative configuration of this alkaloid were established via analysis by IR, UV/VIS, NMR, and mass spectroscopy.[16] The configuration of the spirocyclic center was determined to be (*S*) from the NOE interaction observed between H(9) and H(16) and the geometry of the C(19),C(20)-double bond was determined to be (*E*) from the NOE interaction observed between the H(18) (methyl group) and H(15) (Figure 3).[16] Unfortunately there was a typographical

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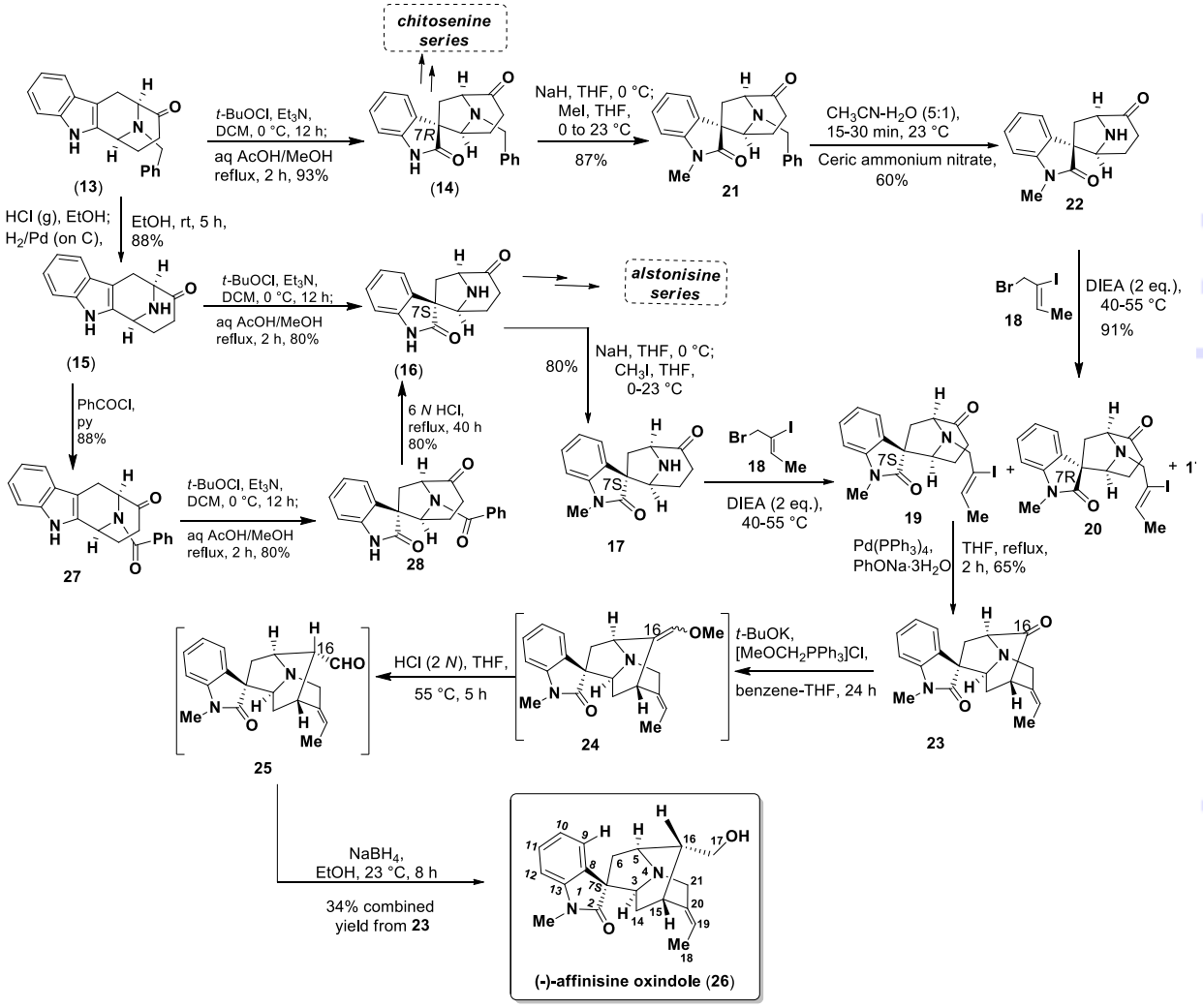
error on page 3052 of the Tetrahedron Letters, 2015, 56, 3052[17] which mislabelled the configuration at C-7 as *R*; however, the synthesis of the correct stereochemistry 7*S* and the properties of synthetic (-)-affinisine oxindole (**26**) are in good agreement with the structure reported by Kam *et al*.[18] The first enantiospecific total synthesis of (-)-affinisine oxindole (**26**), was carried out in 2015 (see Scheme 2 and later section),[17] which confirmed the absolute configuration at C(7) and C(16) proposed by Kam *et al*.[18] Later the absolute configuration of compounds **14**, **19**, **20**, and **23** were further confirmed by X-ray crystallographic analysis (Figure 2).[14a] This stereospecific approach provided entry into either the spirocyclic oxindole of the chitosenine-series **6** [C-7(*R*)] or the opposite configuration at C(7) in the alstonisine-series **1-4** (Figure 1). The utilization of this diastereomeric difference (synthetically) at C-7 is a key objective of the present work.



Scheme 2: Total synthesis of affinisine oxindole (**26**)[17]

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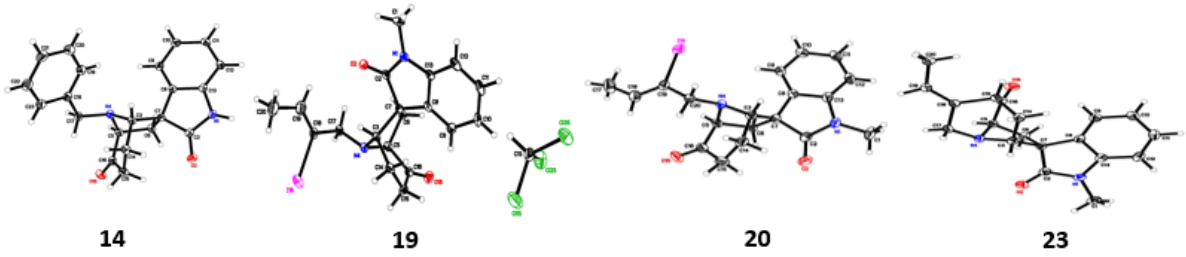

Figure 2. ORTEP drawing of **14, 19** (with $CHCl_3$ solvent), **20** and **23** (Please see SI for the X-crystal details)

The enantiospecific synthesis of alstonisine[2d] and affinisine oxindole[17] promoted further interest in the synthesis of other spiro oxindole alkaloids diastereomeric at the spiro juncture at C-7 via this strategy of internal asymmetric induction. Interestingly, Yu *et al*.[12a] also demonstrated that when the N_a-H, N_b-benzoyl tetracyclic ketone (**27**) was employed in the oxidation-rearrangement process, N_b-benzoyl oxindole (**28**), which was structurally (7*S*) related to alstonisine, was diastereospecifically formed in 80% yield (Scheme 2). This observation is of importance for the synthesis of other members of the sarpagine/macroline oxindole alkaloids. Removal of the benzoyl group was achieved in high yield under acidic conditions (6 *N* aq. HCl/reflux/40 hours, 80% yield).[14a] This could also be carried out under basic conditions, if required.

The 100% diastereoselectivity obtained during these transformations was a result of the difference in stereochemical attack of *tert*-butyl hypochlorite on the N_b-benzyl versus N_b-H tetracyclic ketone. The N_b-benzyl group in the N_a-H, N_b-benzyl tetracyclic ketone (**13**), presumably, occupied the equatorial position (Scheme 3) and, therefore, blocked one face of the 2,3-indole double bond.[14b] This promoted attack by the "Cl^+" species from the concave face of the molecule. In the subsequent pinacol-type rearrangement, the migrating group must attack from the face opposite the C-Cl bond in (**32**) to provide oxindole (**14**). Meanwhile, in the case of the N_a-H, N_b-H ketone (**15**), the concave face was more hindered when compared to the N_b-benzyl ketone (**13**, Scheme 3). In the tetrahydro-β-carboline (**15**), the 2,3-indole double bond was presumably attacked from the convex face to form oxindole (**16**), with the alstonisine **(1)** stereochemistry. In the case of the N_b-benzoyl oxindole (**28**), it is believed that the planar character of the C=O(N) amide bond rendered the position of the benzoyl moiety in a more planar conformation away from the double bond of the carboline system. Again, as in the N_b-

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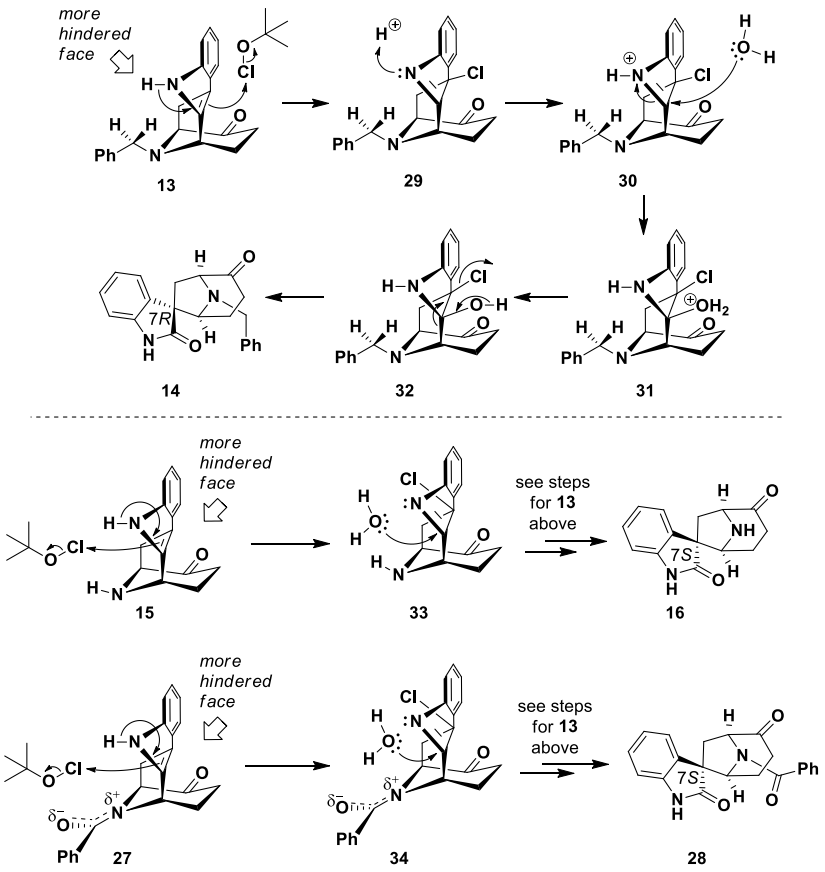
H ketone (**15**) case, the concave face of the molecule would be the more hindered to attack by *tert*-butyl hypochlorite (Scheme 3) which provided the 7(*S*) oxindole **16**.[12a, 12b]



Scheme 3. Proposed mechanism for the formation of the two diastereomeric spirooxindoles

Finally, Yu *et al*.[12a] attempted to perform the *tert*-BuOCl oxidation on the corresponding N_a-methyl derivatives of ketones (**13**) and (**15**) but these failed under these conditions, presumably, because these N_a-methyl analogs would not readily undergo oxidation of the indole 2,3-double bond. Presumably, formation of the indolenine intermediate iminium ion at the N_a-methyl position, similar to (**30**) in Scheme 3, was too high in energy in this series under these conditions.[19]

To complete the synthesis of (–)-affinisine oxindole (**26**), ketone (**19**) was converted into the desired pentacyclic ketone (**23**) in 65% yield (Scheme 4) *via* an intramolecular palladium-catalyzed enolate-mediated cross-coupling reaction, under the conditions developed by Solé and Bonjoch *et al*. (10 mol%) $Pd(PPh_3)_4$/$PhONa{\cdot}3H_2O$ (2.5 equivalents) in THF (previously freeze-pump-thaw, 3-5 cycles, to remove all the oxygen from the solution) at reflux for 2 hours.[20] The use of a weaker base than *t*-butoxide was

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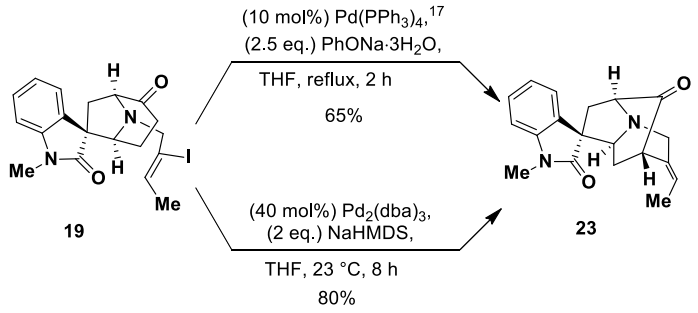
thought to be of critical importance to gain access to the desired pentacyclic oxindole (**23**). The steric outcome of this reaction was again confirmed by X-ray analysis. Especially important was the fact that no oxindole isomerization occurred during this process (see SI). Gratifyingly, during studies on the total synthesis of isoalstonisine described in later sections, it was found that the use of (40 mol%) of $Pd_2(dba)_3$ as a palladium source with sodium bis(trimethylsilyl)amide [(NaHMDS, 2 equivalents) in freeze-pump-thaw,THF] at room temperature (23 °C) significantly improved the yield of the reaction to 80% of the pentacyclic ketone (**23**) after purification by chromatography. This was the best yield we could obtain. The formation of the privileged intermediate pentacyclic ketone **23** (80% yield) at room temperature via the intramolecular enolate- mediated palladium cross coupling process is an important key step in the total synthesis of affnisine oxindole (**26**) and of importance in alkaloid total synthesis (Scheme 4). The reported palladium catalyst, $Pd_2(dba)_3$ is a better air stable catalyst and easier to handle than the previously reported catalyst, $Pd(PPh_3)_4$.[21] The mild reaction conditions of this reaction at room temperature has the advantage of limiting the possibility of an E2 elimination of the vinyl iodide. An increase from 65% to 80% yield in a total synthesis which requires several steps is significant.



Scheme 4. The improved **s**ynthesis of pentacyclic ketone **23**

The first example of such an important palladium-catalyzed coupling process involving vinyl halides were reported by Piers *et al*.[22] in an alicyclic system at the beginning of the 1990s, when he described the intramolecular alkenylation of ketone enolates and then applied the reaction to the synthesis of the diterpenoid crinipellin B. Some years later another example of this coupling process was reported in the heterocyclic series by Wang *et al*. in the context of the total synthesis of the alkaloid (+)-vellosimine.[13c] Bonjoch, Solé *et al*. reported their studies on the synthesis of nitrogen heterocycles by the Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides and ketone

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enolates at about the same time.[20] Buchwald also described the intermolecular vinylation of ketone enolates during this period.[23] The final steps in the first total synthesis of (-)-affinisine oxindole have been reported.[17]

The first stereospecific total synthesis of the sarpagine-related (–)-affinisne oxindole (**26**) was successfully accomplished in 8 reaction vessels in a 10% overall yield from commercially available D-(+)-tryptophan.[17] The ^{1}H NMR (see SI Table 1) and ^{13}C NMR (see SI Table 2) spectral data, as well as the IR spectrum (dry film on KBr) 3375, 1711 cm^{-1} [literature[16] IR (dry film) 3384, 1712 cm^{-1} were in excellent agreement with the natural product.[16-17] In addition, the physical properties including the optical rotation $[\alpha]^{23}_{D}$ = –66° (*c* 0.3, $CHCl_3$) [literature[16] $[\alpha]^{23}_{D}$ = –70° (*c* 0.06, $CHCl_3$)]; and HRMS were in excellent agreement with those published by Kam *et al*.[16-17]

Finally, selected NOE NMR experiments were then carried out on synthetic (–)-affinisine oxindole (**26**), as shown in Figure 3. NOE studies of the synthetic material confirmed the configuration of the spirocyclic center, the configuration at C(16), and the geometry of the C(19),C(20)-double bond to be the same as those reported by Kam *et al*.[16],[18]

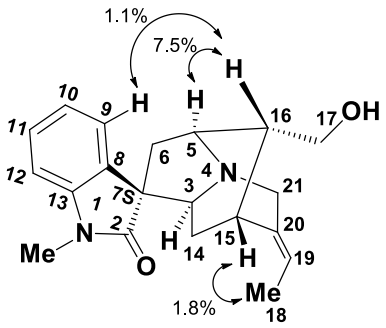

Figure 3. 1D NOE NMR data, C-7(*S*) series, (-)-affinisine oxindole (**26**)

As further structural proof, the oxindole epimeric at C-7 [*i.e.*, C-7(*R*)] of (–)-affinisine oxindole (**26**) i.e., isoaffinisine oxindole was also synthesized in enantiospecific fashion during these studies, and its structure was fully characterized and confirmed by X-ray crystallography (see later section) which permitted the correlation of some of the same signals to (-)-affinisine oxindole (**26**) here.[17]

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Enantionspecific total synthesis in the C-7(*R*) series, the oxindole alkaloid (+)-isoalstonisine (35)

The successful first enantiospecific, diastereospecific total synthesis of the sarpagine related **C-7(*S*) series** (–)-affinisine oxindole (**26**) from D-(+)-tryptophan, *via* the reported synthetic approach discussed in Scheme 1, prompted the extension of this application to the synthesis of the **C-7(*R*) series** oxindole alkaloid (+)-isoalstonisine (**35**) also from commercially available D-(+)-tryptophan.

The macroline related oxindole alkaloid (+)-isoalstonisine (**35**) was first isolated from the ground leaves of the Malayan medicinal plant *Alstonia angustifolia* var. *latifolia* in 2000 by Kam *et al*.[16, 24] It represented the first time that a C7-(*R*) series sarpagine/macroline oxindole alkaloid was isolated from plants; [C7-(*R*) (–)-macrogentine (**57**, see later) was also isolated during this work]. The structure elucidation by Kam *et al*. was performed on the basis of mass spectrometry; IR and UV spectroscopic studies as well as ^{1}H, ^{13}C, and NOE NMR spectral techniques. In order to confirm the assigned relative spatial arrangement of atoms in the structure of isoalstonisine (**35**), computational studies were carried out by Kam *et al*. (MM2, CS Chem3D Pro) in which the major and diagnostic differences in the observed NOE's of alstonisine (**1**, used for comparison) and isoalstonisine (**35**) were consistent with the predicted distances in the energy minimized structures.[24] The configuration of the spirocyclic center C-7 was, initially, incorrectly determined to be (*S*). Later, Kam *et al*. corrected the C-7 configuration and labeled it (*R*).[18]

The synthetic route, which was envisaged in order to diastereospecifically functionalize the C-15 position of the key oxindole intermediate (**14**, retrosynthetic analysis in Scheme 1), was based on the successful stereospecific synthesis of (-)-affinisine oxindole (**26**) during the course of these studies.[17]

Consequently, the chemistry described before for the preparation of (-)-affinisine oxindole (**26**)[17] could be employed starting with the N_a-H, N_b-benzyl tetracyclic ketone oxindole (**14**) instead of the ketone oxindole (**16**, compare Scheme 1 *versus* Scheme 5). Thus, the E-ring in isoalstonisine (**35**) would be generated from tetracyclic oxindole (**36**) through a modified Wacker-oxidation sequence which would be followed by regioselective removal of the N_b-protecting group (R^1).[25] In turn, oxindole (**36**) could be prepared with the execution of a base-promoted retro-Michael process on an N_b-alkyl

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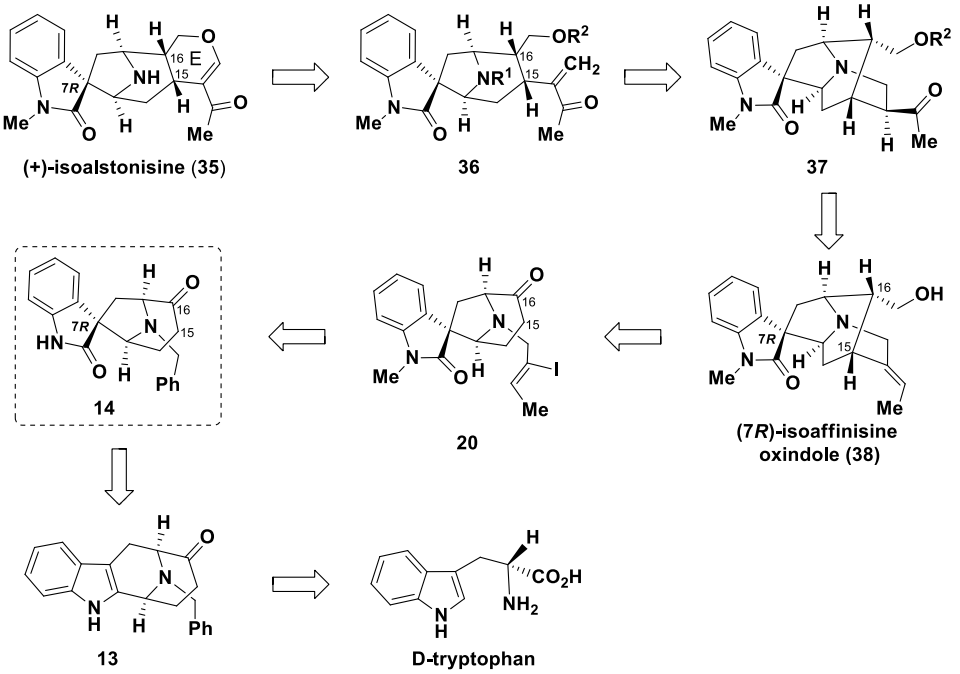
quaternary ammonium salt of pentacyclic oxindole (**37**).[25],[26] The construction of the *β*-methyl ketone moiety in (**3**) would be feasible from oxindole (**38**) by a highly regiospecific (*anti*-Markovnikov), stereospecific (*syn*) hydroboration-oxidation sequence to provide an alcohol which then could be oxidized by different methods.[25],[26]



Scheme 5. Retrosynthetic analysis for (+)-isoalstonisine (**35**)

It is important to note here that intermediate oxindole (**38**) is the [(*R*)-C-7] epimeric isomer of the natural affinisine oxindole (**26**). Therefore, the synthesis of oxindole (**38**) would also contribute to the structural proof of affinisine oxindole (**26**). Finally, the primary-hydroxy oxindole (**38**) would be prepared from tetracyclic ketone (**14**), and D-(+)-tryptophan as the initial starting material, by an analogous application of the chemistry discussed in earlier sections. In agreement with the retrosynthetic analysis depicted in Scheme 5, the N_a-methyl, N_b-allyl tetracyclic ketone oxindole (**20)**, was functionalized at the C-15 position in a stereospecific fashion through a modified palladium-catalyzed enolate-driven cross-coupling reaction.[17, 20] The conditions of which, were developed during these studies (Scheme 4 and 6).

Treatment of oxindole (**20**) with 40 mol% of $Pd_2(dba)_3$, NaHMDS (2 equivalents) in THF (freeze-pump-thaw, 3-5 cycles, to remove all the oxygen from the solution) at ambient temperature (23 °C) for 8 hours provided the desired pentacyclic ketone

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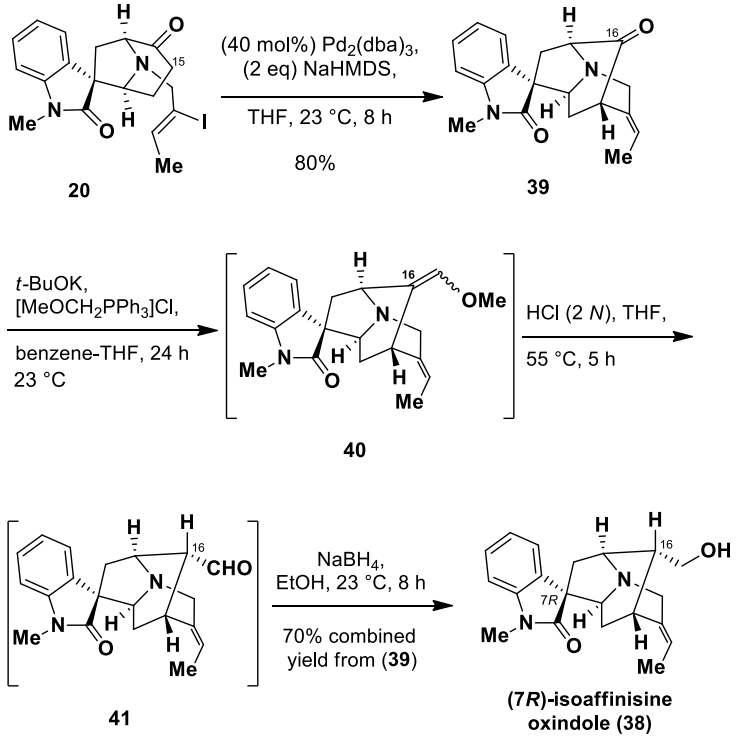
oxindole (**39**), diastereospecifically and in high yield (80%). In a similar manner as the preparation of [(*S*)-C-7] affinisine oxindole (**26**, Scheme 1) from oxindole (**23**),[17] the N_a-methyl pentacyclic ketone (**39**) was also carried through a one-reaction-vessel (3 steps) homologation process of the carbonyl group at C-16 to give the C-17 functionalized aldehyde, which was subsequently reduced to the corresponding hydroxy methyl moiety. This was easily executed by a successive Wittig-olefination reaction with (methoxymethyl)triphenyl-phosphonium chloride and anhydrous *tert*-BuOK in dry benzene. Then the mixture of stereoisomeric enol ethers (**40**) was hydrolyzed under acidic conditions to afford the thermodynamically more stable α-epimeric aldehyde (**41**) as a single diastereomer. Finally, the crude aldehyde product (no purification was required) was converted into its corresponding primary alcohol by reduction with $NaBH_4$ in EtOH at room temperature to provide the [C-7(*R*)] (-)-isoaffinisine oxindole (**38**) in 70% overall yield from ketone **39 (**Scheme 6).[17]



Scheme 6. Synthesis of (7*R*)-isoaffinisine oxindole **(38)**

The synthesis of oxindole (**38**) was of importance because the X-ray crystal structure on this material served as additional proof of the correct stereochemical assignment of (-)-isoaffinisine oxindole as the epimer with the [(*R*)-C-7] spirocenter (see all ORTEP drawings in the reference[14a] and in the SI).

In the next stage of the synthesis, directed toward the construction of **42**, the primary hydroxyl group of isoaffinisine oxindole (**38**) was protected with the bulky

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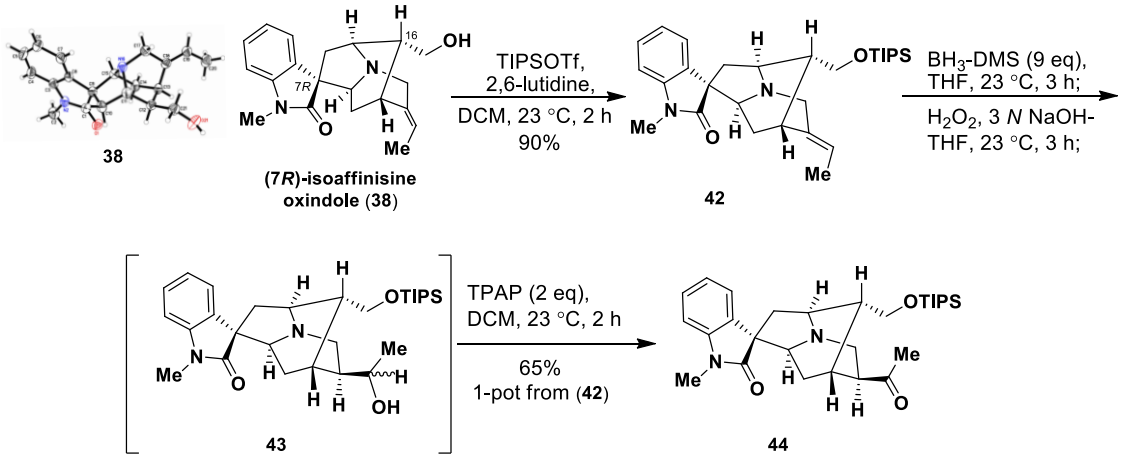
triisopropylsilyl moiety in 90% yield by reaction of oxindole (**38**) with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 1.6 equivalents) and 2,6-lutidine (2 equivalents) in DCM at room temperature for 2 hours. The TIPS protecting group was used successfully in the parent system for a similar transformation and had better stability than smaller silyl groups such as TBDMS, as expected.[25, 27] The above protection with a bulky group set the stage for the following hydroboration-oxidation sequence. Therefore, the hydroboration process was executed on **42** in THF at ambient temperature using a 9-fold excess of BH_3-DMS complex over 3 hours (Scheme 7).



Scheme 7. Synthesis of methyl ketone **44**

After careful quenching of the reaction mixture with water at 0 °C, an aqueous solution of NaOH (3 *N*) was added with stirring and this was followed by the addition of hydrogen peroxide (H_2O_2, 35% in water) in the usual fashion. The solution which resulted was allowed to stir for 3 hours at 23 °C to provide a mixture of secondary alcohols (**43**) which were easily purified through a very short column (wash column) to remove highly polar material (also <5% tertiary alcohol had formed and was removed). The diastereomeric mixture was inconsequential since they would be converted into the corresponding methyl ketone in **44**.

Interestingly, the N_b-BH_3 complex of oxindole (**43**) was never detected after the hydroboration-oxidation protocol. This observation is consistent with the reactivity of the N_b-nitrogen atom for in the oxindole system it is significantly lower than that of the N_b-nitrogen atom in the parent system due to steric hindrance, as was also observed before in the N_b-allylation of oxindoles.[14, 28] The diastereomeric mixture of secondary alcohols (**43**) was then subjected to oxidation conditions to generate the corresponding methyl ketone (**44**). Although many different oxidants were employed to execute this

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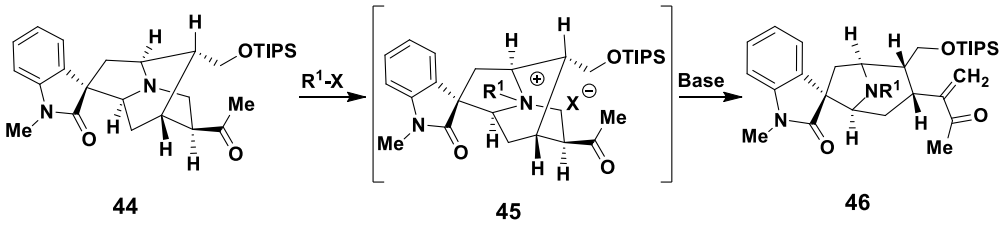
conversion with poor results,[14a] gratifyingly the use of 2 equivalents of organic-media stable tetra-*n*-propylammoniumperruthenate (TPAP, $[RuO_4]^{-1}$, Ru-oxidation state: +7) [29] in dry DCM afforded the desired methyl ketone in a very clean, mild process at 23 °C in 2 hours. The combined yield of the 1-reaction-vessel transformation from alkene oxindole (**42**) into the corresponding *β*-methyl ketone (**44**) was an acceptable 65% (Scheme 7). Interestingly, it was found that the blocking effect of the bulky TIPS protecting group on the C-16 hydroxyl was greater on the oxindole system than that in the parent (indole) case, since only the *β*-diastereomer was observed at C-20, the *α*-epimer was not detected. The high diastereospecificity occurred because the *β*-face (top face) of the tertiary olefin was sterically more hindered than the *α*-face (bottom face) towards the borane addition to the double bond.

Table 1. Retro-Michael reaction



44 **45** **46**

Entry	Alkylation step			retro-Michael step		Result
	R^1-X (eq.)	additive (eq.)	solvent/temp. (°C)/ 24 h	base (eq.)	solvent/temp (°C)/30 min	
1	Bn-Br (1.5)	$NaHCO_3$	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
2	Bn-Br (10)	$NaHCO_3$ (10)	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
3	Bn-Br (10)	$NaHCO_3$ (10)	MeOH/64	K_2CO_3 (20)	THF/66	decomposition
4	Bn-Br (10)	$NaHCO_3$	MeOH/64	K_2CO_3 (2)	THF/66	decomposition
5	Bn-Br (10)	$NaHCO_3$	ACN/82	K_2CO_3 (2)	THF/66	decomposition
6	Bn-Br (10)	$NaHCO_3$	DMF/100	K_2CO_3 (2)	THF/66	decomposition
7	Allyl-Br (10)	$NaHCO_3$ (10)/AgOTf	THF/66	K_2CO_3 (2)	THF/66	decomposition
8	Allyl-Br (10)	$NaHCO_3$ (10)/AgOTf	DMF/100	K_2CO_3 (2)	THF/66	decomposition
9	Allyl-Br (10)	$NaHCO_3$ (10)/AgOTf	neat/70	K_2CO_3 (2)	THF/66	decomposition
10	Allyl-Br (10)		neat/70	K_2CO_3 (2)	THF/66	decomposition, 20% (**45**)
11	Me-I		neat/70	*t*-BuOK (2)	THF/23	(**46**) 30%
12	**Me-I**		**neat/70**	**NaHMDS (2)**	**THF/23**	**(46) 80%**

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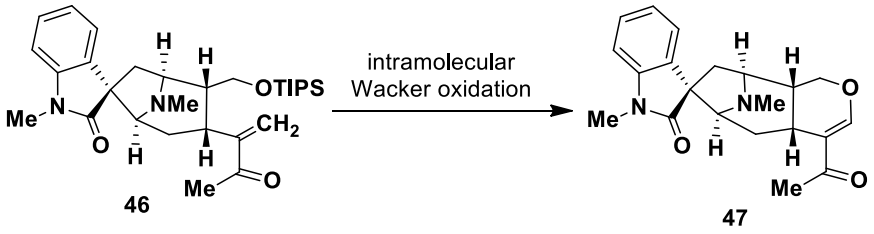
Table 2. Wacker-Cook oxidation[30] (termed the Wacker-Cook reaction by Moldanado)[30]



Entry	Catalyst (mol%)	Reoxidant/additive	Solvent system	Temp (°C)/ time (h)	Result
1	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)/ NaOAc (1 eq)	AcOH/dioxane/H_2O (1:3:3)	80/6	decomposition
2	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)/ NaOAc (1 eq)	AcOH/dioxane/H_2O (1:3:3)	80/2	decomposition
3	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	AcOH/dioxane/H_2O (1:3:3)	80/6	decomposition
4	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	AcOH/*t*-BuOH/H_2O (1:3:3)	80/6	decomposition
5	Na_2PdCl_4 (40)	*t*-BuOOH (1.5 eq)	dioxane/H_2O (6:1)	40/3	(**47**) 20%
6	**Na_2PdCl_4 (40)**	***t*-BuOOH (1.5 eq)**	**dioxane/H_2O (6:1)**	**85/6**	**(47) 65%**

With access to pentacyclic ketone (**44**), the next step rested on the ring-opening of **44** (or **37** in Scheme 5) through a base-promoted retro-Michael reaction of an N_b-alkylated quaternary ammonium salt of oxindole (**44**). Since natural isoalstonisine (**35**) possessed an N_b-H functionalized nitrogen atom, it was advantageous to install an alkylating agent that could be removed easily from the secondary N_b-nitrogen at a later stage. It was known, however, that the steric access to the N_b-nitrogen position in these types of sarpagine/ macroline oxindole systems was highly hindered.[14b, 28] Thus, initially, it was decided to use benzyl bromide (b.p. = 201°C) to achieve the N_b-alkylation, which would in turn leave an N_b-benzyl functional group after the retro-Michael reaction.[31],[32],[33],[34] The benzyl group would later be removed by known deprotection protocols (e.g. reductive hydrogenation or radical debenzylation as seen before in related systems). However, all attempts to execute this alkylation with either benzyl bromide or benzyl iodide[14a] met with less than promising results and complex mixtures.[14a]

At this point it was decided to treat oxindole (**44**) with methyl iodide (b.p. = 42.4 °C), which was successfully used for similar transformations in the parent system (indole).[25-26] In this vein, MeI was heated at 70 °C, neat, in the presence of oxindole (**44**, in a sealed tube) for one day. After removal of the excess MeI under reduced pressure, the

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crude solid, which resulted, was dissolved in dry THF in the presence of 2 equivalents of potassium *tert*-butoxide for 30 minutes at room temperature.

The desired α,β-unsaturated methyl ketone (**46**, Table 1, entry 11) was detected albeit in low yield (30%). The use of NaHMDS (2 equivalents) under similar conditions improved the olefin yield to 80% (Table 1, entry 12). The next stage in the synthesis of (+)-isoalstonisine (**36**) by the route depicted in Scheme 5, required the formation of a carbon-oxygen bond that would close the E-ring of the molecule. To this end, a modified Wacker-related process, used in the parent system by Liao *et al*. seemed promising. [25] The execution of the intramolecular Wacker oxidation which worked in the Liao *et al*. synthesis of (–)-alstonerine (Table 2, entry 1) failed to provide the expected product (complex mixtures of byproducts were recovered each time). Modification of these reaction conditions: shorter reaction time (entry 2); removal of the NaOAc additive (entry 3); and use of *tert*-butanol instead of dioxane did not improve the outcome of the reaction.

It was hypothesized that the acidic media was the cause of the problem, presumably by promoting the equilibration of epimeric oxindoles at C-7, through a retro-Mannich type of process, that was operational under these acidic reaction conditions. Consequently, since the acidic media was not required for the transformation, it was decided to remove the acetic acid and execute the protocol under neutral conditions. Gratifyingly, the pentacyclic ketone oxindole (**47**) was found in the reaction mixture, after heating at 40 °C for 3 hours, in 20% yield. The yield was later improved to 65% by exposing the starting materials to a higher temperature (85 °C) and a longer reaction time (6 hours).

Although the mechanism has not been studied in detail, a proposed one is shown in Scheme 8.[25] It was believed that the process originally involved the fast and reversible coordination of the Pd(II) species to the alkene much like the earlier work of Trost and others. Under neutral conditions, the nucleophilic oxygen atom of the silyloxy functional group would attack the Pd(II) olefin complex. This event would be followed by cleavage of the silyl moiety in the presence of chloride ions; then β-hydride elimination; and finally reductive elimination would provide the desired enone (**47**). The Pd(0) was reoxidized to Pd(II) by *tert*-BuOOH (Scheme 8) analogous to the standard conditions.

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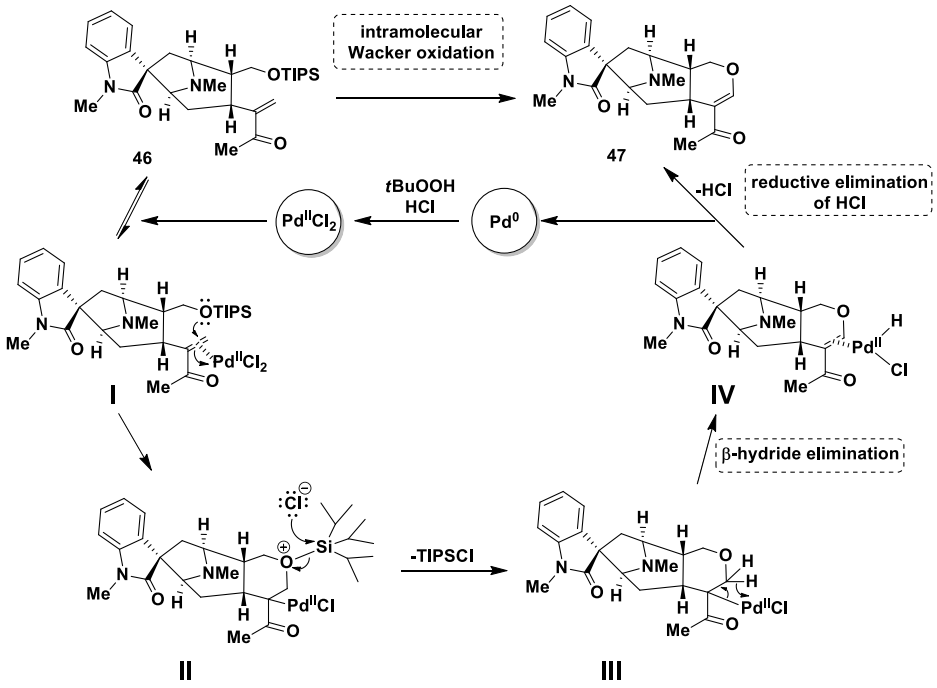

Scheme 8. Possible mechanism for the formation **47**

The best method found, to date, in the literature for the *N*-dealkylation of tertiary amines was the one introduced by Olofson *et al*. which involved the use of the inexpensive reagent α-chloroethyl chloroformate (ACE-Cl).[35] The cleavage of the α-chloroethyl carbamate ester was carried out by simply heating it in methanol (addition of H^+ was not needed). Accordingly, N_b-methyl pentacyclic oxindole (**47**) was exposed to the conditions of Olofson *et al*. with 10 equivalents of ACE-Cl in 1,2-dichloroethane [4.6 mmol (**47**)/mL] at 85 °C for 24 hours. The ammonium salt which formed was then treated with dry methanol at reflux for 5 hours. After basic work-up to neutralize the N_b-hydrochloride salt, the expected (+)-7*R*-isoalstonisine (**35**) was obtained in 80% yield (three steps in a 1-pot process, Scheme 9).

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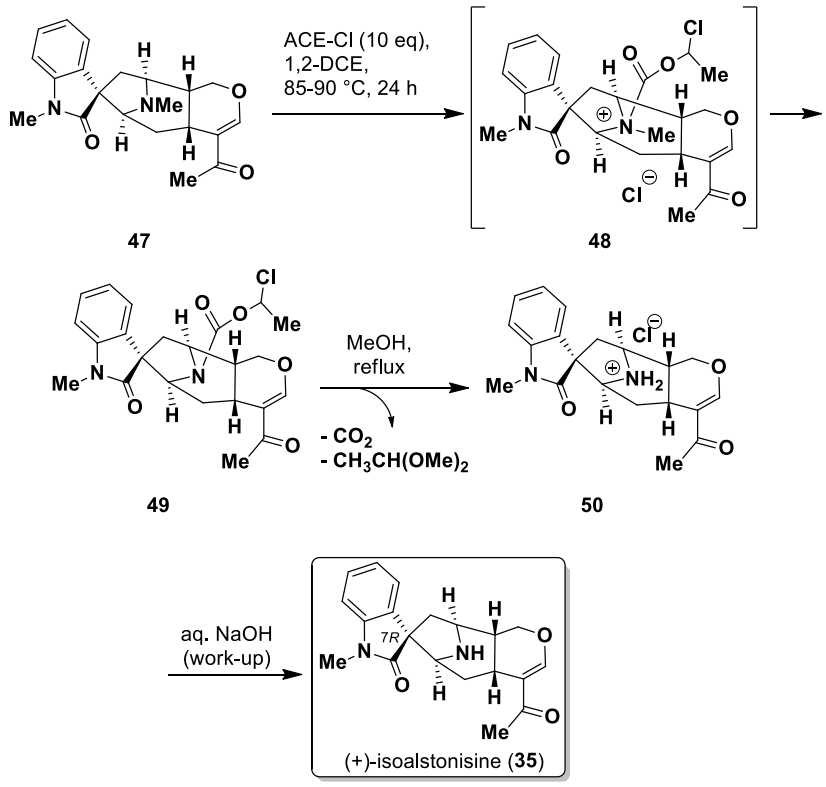

Scheme 9. Synthesis of (+)-isoalstonisine **(35)**

The ^{1}H NMR (see SI Table 3) and ^{13}C NMR (see SI Table 4) spectral data of synthetic (+)-isoalstonisine (**35**), as well as the IR spectrum [dry film on KBr: 1701 cm^{-1}, literature[24] IR (dry film) 1704 cm^{-1}] were in excellent agreement with that of the natural product.[24] In addition, the physical properties including the specific rotation {[α]$^{23}_{D}$ = +201° (*c* 0.15, $CHCl_3$), literature[24] [α]$^{23}_{D}$ = +207° (*c* 0.07, $CHCl_3$)]}, and HRMS were in excellent agreement with those published by Kam *et al*.[24]

Selected NOE-NMR experiments were then carried out on synthetic (+)-isoalstonisine (**35**, Figure 4) and compared to those of Kam *et al*.[24] on natural isoalstonisine and Wearing *et al*. on alstonisine.[14b] Irradiation of the diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 20% and *vice versa*, in synthetic alstonisine according to Wearing *et al*.[14b] Irradiation of H-9 in synthetic isoalstonisine (**35**) did not effect enhancement of H-15, thus confirming the correct assignment and also that there was no epimerization at C-7 during the last step.

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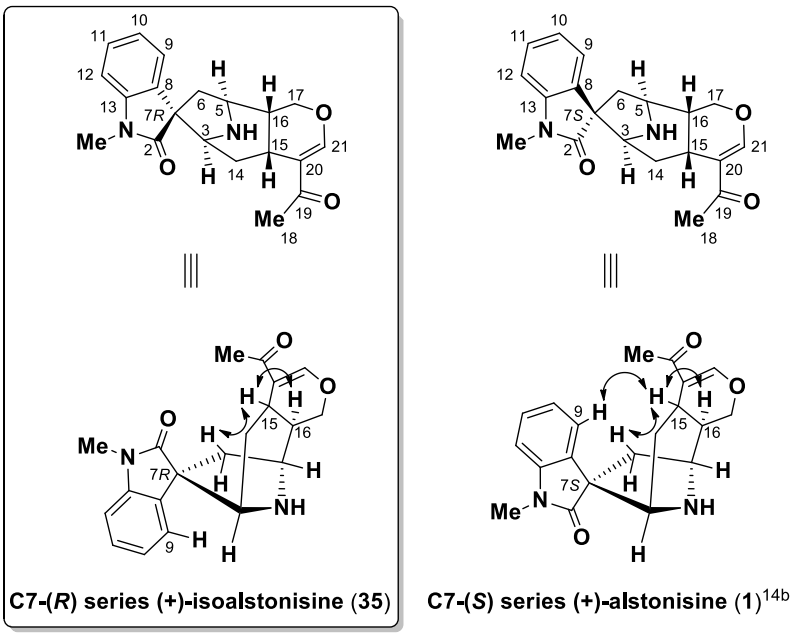

Figure 4. NOE NMR, Isoalstonisine (**35**)

Enantiospecific synthesis of (+)-alstonisine (1), (+)-N_a-demethylalstonisine (51), and (+)-alstofoline (52)

The oxindole alkaloids (+)-N_a-demethylalstonisine (**51**) and (+)-alstofoline (**52**) were first isolated by Kam and Choo *et al*. in 2000 from the Malayan *Alstonia angustifolia* var. *latifolia* K. and G.[24] The initial report incorrectly named the source of the plant as *Alstonia macrophylla* Wall but the authors then changed it in a later communication.[16] The alkaloidal content of *Alstonia macrophylla* Wall was studied by Kam and Choo *et al*. and appeared in published report in 2004.[36] The structures of these two oxindoles were determined using NMR spectral techniques, UV, IR, optical-rotation and analysis by mass spectroscopy. The corrected configuration at C-7, labeled (*S*), for both alkaloids was reported by Kam *et al*. in a recent article.[18]

With isoalstonisine (**35**) and the C-7-epimerization conditions developed for the tetracyclic oxindole system in hand,[14a, 37] it became of interest to explore the isomerization of 7*R*-isoalstonisine (**35**) into 7*S*-alstonisine (**1**). The successful execution of the epimerization protocol in good yield would represent an improved route to this important oxindole alkaloid alstonisine (**1**). Accordingly, a pure synthetic sample of isoalstonisine (**35**) was treated at 100-110 °C (in a sealed tube) in a dry pyridine-DCM (8:2) mixture for 60 hours. After separation and analysis of the mixture of diastereomers, it was found that alstonisine (**1**) was present in a gratifying 70% yield (Scheme 10). The

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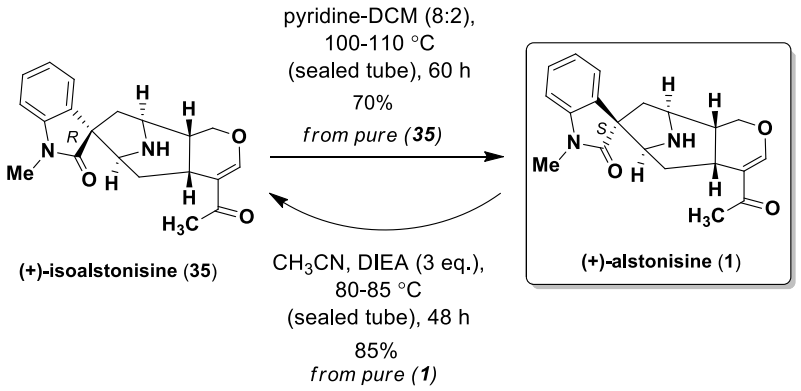
C-7 epimeric isoalstonisine (**35**) was detected in 18% yield and the rest (12%) of the material was a highly-polar unidentified mixture (baseline material on TLC analysis).



Scheme 10. C-7 epimerization

If the decomposition material was taken into account, the final mole ratio would be (**35**)/(**1**) = 4/1, approximately. On the other hand, heating alstonisine (**1**) in acetonitrile at 80-85°C (in a sealed tube) in the presence of 3 equivalents of Hünig's base (sodium carbonate can be used in place of Hünig's base) for 2 days gave, isoalstonisine (**35**) in 85% yield, and alstonisine (**1**) was recovered in 9% yield with 6% of decomposition, the mol% of the mixture would be approximately (**1**)/(**35**) = 1/9.

The ^{1}H NMR (see SI Table 5) and ^{13}C NMR (see SI Table 6) spectral data of (+)-alstonisine (**1**), as well as the IR spectrum [dry film on KBr: 1701 cm^{-1}, literature[24] IR (dry film) 1704 cm^{-1}] are in excellent agreement with the literature. In addition, the physical properties including the optical rotation {$[\alpha]^{23}$D = +195° (c 0.2, EtOH), literature: $[\alpha]^{23}$D = +197° (c 1.0, EtOH)[14b] and $[\alpha]^{23}$D = +200° (c 1.0, EtOH)[7]} and HRMS were in excellent agreement with those published in the literature by Elderfield *et al*. and Wearing *et al*.[7, 14b]

The transformation of (+)-alstonisine (1) into (+)-N_a-demethylalstonisine (51)

The 7*S*-series oxindole alkaloid (+)-N_a-demethylalstonisine (**51**) could be obtained from the corresponding (+)-N_a-methyl alstonisine (**1**), presumably, through a chemical transformation that removed the N_a-methyl functional group. In a search of the literature, attention was drawn to a communication by Hiemstra *et al*. on the total synthesis of (+)-gelsedine,[38] in which the removal of a methyl group from an oxindole was readily accomplished by using a procedure, which was known earlier for removal of an *N*-methyl group from an indole system (by Nakatsuka *et al*.).[39] It was decided to make

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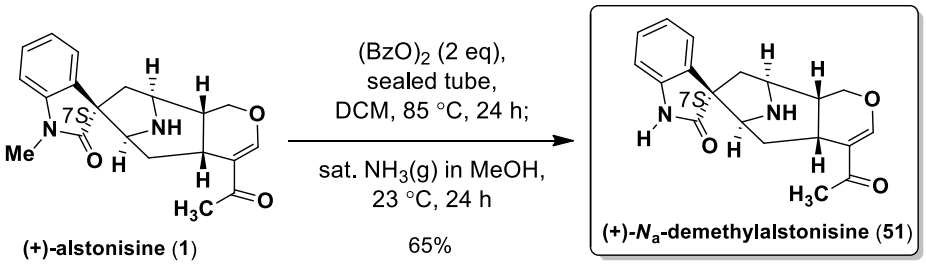
use of the conditions by Hiemstra *et al*. for the demethylation of alstonisine (**1**). A major souce of concern, however, was the presence of a secondary nitrogen atom (N_b-H) in the molecule. The reaction of dibenzoyl peroxide with secondary amines to provide *O*-benzoylhydroxylamines is well documented.[38]

Accordingly, a solution of alstonisine (**1**) and 2 equivalents of dibenzoyl peroxide in DCM was heated in a sealed tube for 24 hours at 85 °C (Scheme 11). After concentrating the reaction mixture, a solution of saturated NH_3(g) in methanol was added and the mixture was stirred for another 24 hours at ambient temperature to afford the expected (+)-N_a-demethylalstonisine (**51**) in moderate yield (65%). Attempts to increase the final yield by increasing the number of peroxide equivalents had the opposite effect, presumably for the reasons explained above, even though it could not be confirmed. A proposed mechanism for the demethylation of these oxindoles has been published.[14a],[38],[39]



Scheme 11. Synthesis of (+)-N_a-demethylalstonisine(**51**)

The ^{1}H NMR (see SI Table 7) and ^{13}C NMR (see SI Table 8) spectral data and HRMS for (+)-N_a-demethylalstonisine (**51**) were in excellent agreement with those published in the literature by Kam *et al*.[24] Selected NOE-NMR experiments were then carried out on synthetic (+)-N_a-demethylalstonisine (**51**, Figure 5). Again, irradiation of the diagnostic signal at the H-9 hydrogen atom effected enhancement of H-15 by 8% and *vice versa*, thus, confirming the 7*S* configuration of the spirocenter.

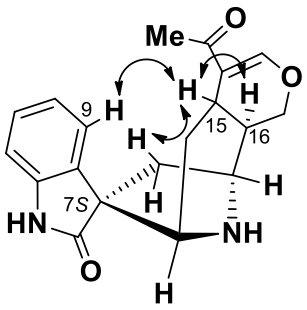


Figure 5. NOE NMR, N_a-demethylalstonisine (**51**)

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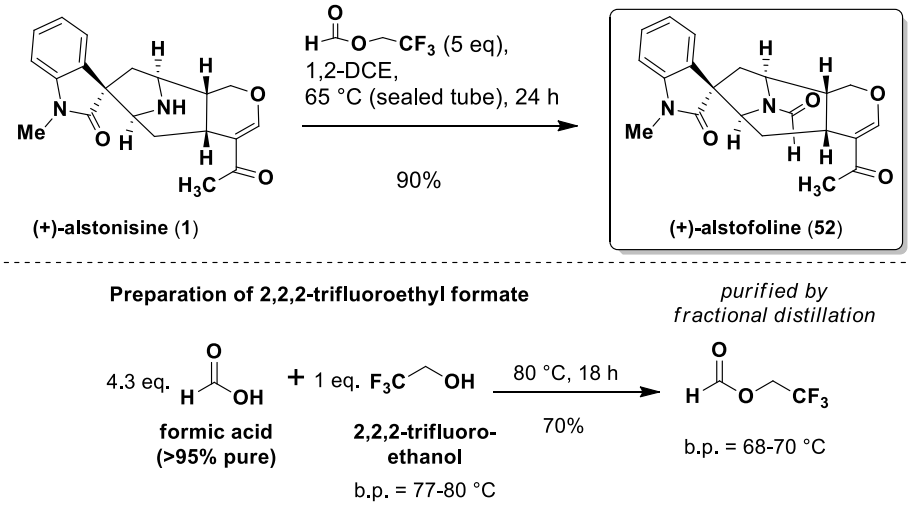
The transformation of (+)-alstonisine (1) into (+)-alstofoline (52)

Several different methods for formylation of amines could be found in the literature.[40] With all these precedents in mind, it was decided to employ conditions developed by Hill *et al*., that used a simple alkyl formate as the source of the formyl group.[40f] The reagent 2,2,2-trifluoroethyl formate (TFEF) can be used in a variety of reaction manifolds depending on the presence of other additives.[40f] Consequently, when applied to oxindole (**1**, Scheme 12), it was found that the reaction of alstonisine (**1**) with 2,2,2-trifluoroethyl formate (used as the solvent; either prepared (see SI) or from commercial sources) at 65 °C for 24 hours generated the expected N_b-formyl oxindole alstofoline (**52**) as a mixture of rotamers (in a 3:1 ratio, determined by ^{1}H NMR spectroscopy) in very high yield (90%). In order to reduce the amount of formate, a number of solvents were screened. Using a concentrated solution of 1,2-dichloroethane and as low as 5 equivalents of the trifluoroformate on stirring for 24 hours provided the same final yield of (+)-alstofoline (**52,** Scheme 12).



Scheme 12. Synthesis of (+)-alstofoline **(52)**

The ^{1}H NMR (see SI Table 9) spectral data of (+)-alstofoline (**52**), as well as the IR spectrum [dry film on KBr: 1713 cm^{-1}, literature[24] IR (dry film) 1706 cm^{-1}] were in good agreement with the natural product. In addition, the physical properties including the optical rotation {[α]$^{23}_D$ = +32° (*c* 0.10, $CHCl_3$), literature[24] [α]$^{23}_D$ = +39° (*c* 0.21, $CHCl_3$)]}, and HRMS were in good agreement with those published in the literature by Kam *et al*.[24] The irradiation of the diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 10% and *vice versa*, thus, confirming the 7*S* configuration of the spiro center (NOE-NMR) in (+)-alstofoline (**52**).

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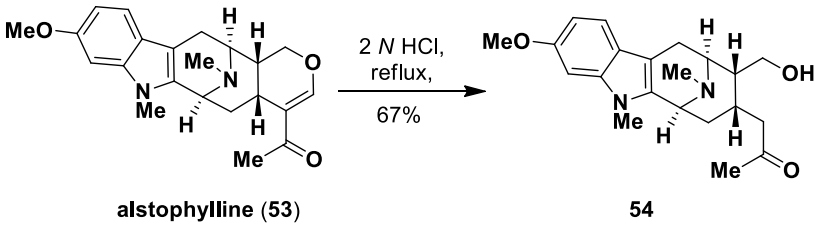
The enantiospecific synthesis of (–)-alstonoxine A (56) and (–)-macrogentine (57)

The oxindole alkaloids (–)-alstonoxine A (**56**) and (–)-macrogentine (**57**) were both isolated (by Kam *et al*.) from the stem-bark and leaf extract of a Malayan *Alstonia* species: *Alstonia angustifolia* var. *latifolia* K. G, but they were not found in the related Malayan *Alstonia macrophylla*.[16, 24, 36] The correct C-7 designation of configuration, which is 7*R* for macrogentine (**57**) and 7*S* for alstonoxine A (**56**), was recently published in a report in 2014.[18] The natural oxindole (–)-macrogentine (**57**) was the second sarpagine/ macroline oxindole isolated, after isoalstonisine (**35**), to possess the 7*R* configuration at the spirocenter.

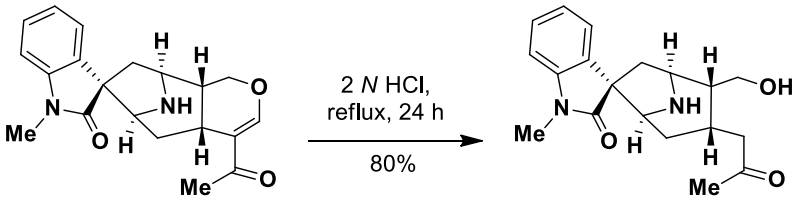
The structural characterization of both alkaloids was done by Kam *et al*. whom employed ^{1}H, ^{13}C, two-dimensional, and NOE NMR spectral techniques in conjunction with optical rotation measurements as well as UV, IR spectroscopy, and mass spectrometry. [16, 24, 36] Natural (–)-alstonoxine A (**56**) is an oxindole in which cleavage of the E-ring has occurred. In a study on the alkaloid alstophylline (**53**), Kishi *et al*. reported experimental conditions for the acidic hydrolysis of the E-ring in the indole system (which Kam *et al*. also used for structural confirmation, Scheme 13).[24, 41]



alstophylline (53) **54**

Scheme 13. Acidic hydrolysis of E-ring[41]

Thus, when isoalstonisine (**35**) was heated at reflux in 2 *N* aqueous HCl for 24 hours, cleavage of the E-ring was accomplished in 80% yield to provide (-)-isoalstonoxine A [**55**, C-7 epimer of alstonoxine A (**56**), Scheme 14].



(+)-isoalstonisine (35) **(-)-isoalstonoxine A (55)**

Scheme 14. Synthesis of (-)-isoalstonoxine A (**55**)

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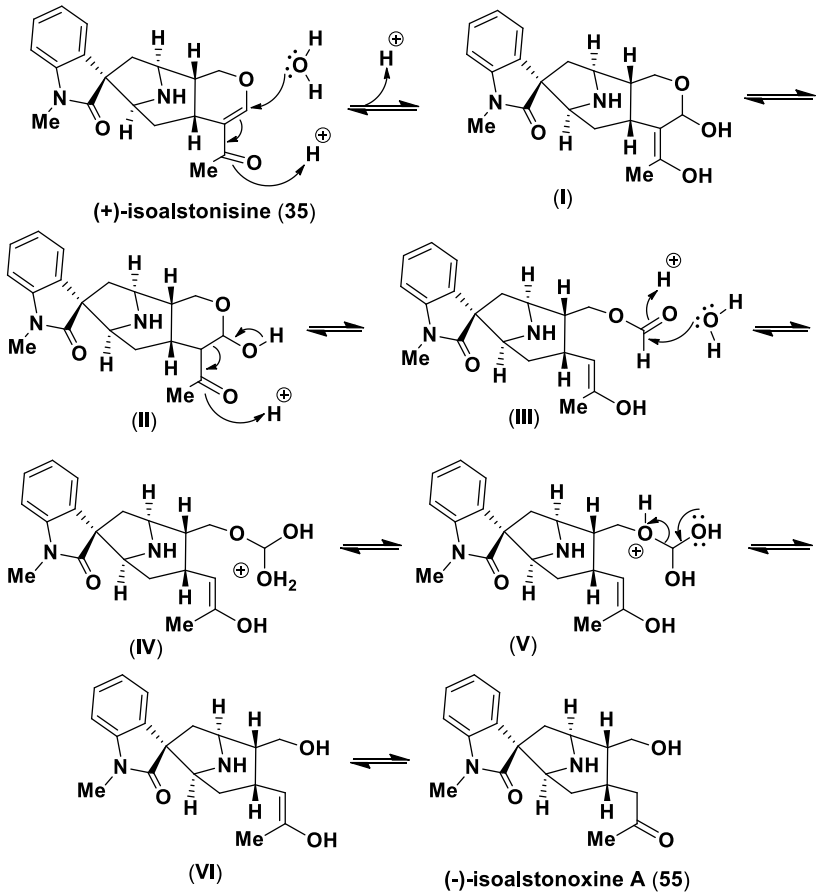
It is important to add that isomerization at the C-7 spiro center was not detected. Laus *et al*. observed that in acidic media the epimerization of oxindoles is remarkably slower due to protonation at the N_b-nitrogen atom.[37a, 42] The proposed mechanism for the opening of the E-ring is based on the studies of Kishi *et al*.[41] and is shown in Scheme 15.



Scheme 15. Possible mechanism for the opening of the E-ring

Epimerization at C-7 of isoalstonoxine A (55) into the natural oxindole (–)-alstonoxine A (56)

Since it was possible to achieve the hydrolysis of the E-ring in the C7-(*R*) series of (+)-isoalstonisine (**35**) into the non-natural (-)-isoalstonoxine A (**55**) in high yield, attention turned to access two more natural sarpagine/macroline oxindole alkaloids.

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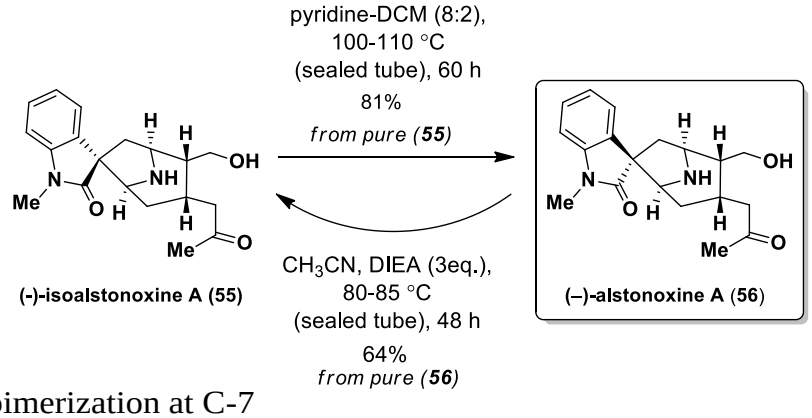
Consequently, when oxindole (**55**) was treated under the conditions for epimerization of the 7*R*-series to the 7*S*-series, *e.g*. pyridine-DCM (8:2) at 100-110 °C for 60 h, natural (–)-alstonoxine A (**56**) was obtained in 81% isolated yield, accompanied by 18% of the starting (-)-isoalstonoxine A (**55**). The mole ratio of **55**/**56** was 1:4 (Scheme 16). When the reverse epimerization, *e.g.* 7*S*-series to 7*R*-series, was executed utilizing a pure synthetic sample of alstonoxine A (**56**) in acetonitrile at 80-85 °C with 3 equivalents of DIEA for 2 days, a mixture was reached in which the mole ratio was 1.8:1 [**55**/**56** = 64:36, Scheme 16] of (-)-isoalstonoxine A (**55**) and natural (–)-alstonoxine A (**56**).



Scheme 16. Epimerization at C-7

The ^{1}H NMR (see SI Table 10) and ^{13}C NMR (see SI Table 11) data for (–)-alstonoxine A (**56**), as well as the IR spectrum [dry film on KBr: 3357, 3240, 1701 cm^{-1}, literature[24] IR (dry film) 3390, 3288, 1694 cm^{-1}] were in agreement with the literature.[24] In addition, the physical properties including the optical rotation value {[α]$^{23}_{D}$ = –40.0° (*c* 0.15, $CHCl_3$), literature[24] [α]$^{23}_{D}$ = –34° (*c* 0.19, $CHCl_3$)]}, and HRMS were in good agreement with those published in the literature by Kam *et al*.[24] A number of selected NMR-NOE experiments were then carried out on synthetic (–)-alstonoxine A (**56**). The diagnostic H-9 hydrogen-atom effected enhancement of H-15 by 5% and *vice versa* when irradiated in an NOE NMR experiment, thus, confirming the 7*S* configuration of the spiro center.

The diastereospecific synthesis of (–)-macrogentine (57) from (-)-isoalstonoxine A (55)

The oxindole alkaloid (-)-macrogentine (**57**) possesses a carbon skeleton in which rings A, B, C, and D of the macroline oxindole system are essentially intact, however, cleavage and rearrangement have occurred involving the E ring. More specifically, the

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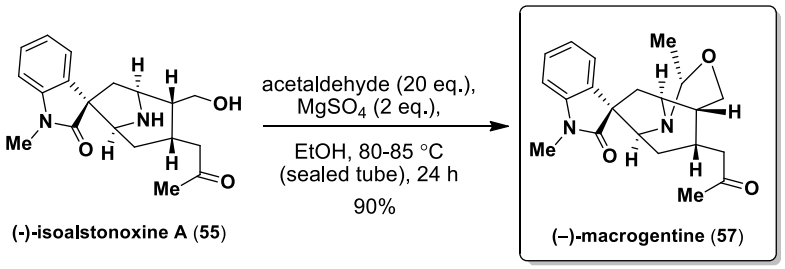
E-ring is a 6-member oxazolidine with the 2-position of the oxazolidine system substituted with a methyl group in the equatorial position.[24]

Oxazolidines can be synthesized by several routes with the direct route based on the condensation of amino alcohols with either aldehydes or ketones. There are many examples in the literature where amino alcohols are reacted with a ketone or aldehyde to form a 2-mono substituted oxazolidine.[43] The most common procedure for the formation of oxazolidines from amino alcohols involves the heating of the latter in the presence of an excess of aldehyde and a dehydrating agent. Thus, when (-)-alstonoxine A (**56**) was treated with 20 equivalents of acetaldehyde, in the presence of 2 equivalents of anhydrous $MgSO_4$ in absolute ethanol at 80-85 °C (in a sealed tube) for 24 hours (Hitchcock *et al*.[44]), the oxazolidine E-ring formed in a 90% yield, as shown in Scheme 17. The use of other solvents failed to provide a high yield under the same conditions: in DCM or $CHCl_3$ (traces of product detected); in toluene or benzene (<20% yield). When the $MgSO_4$ was replaced with, molecular sieves it did not change the above results.



Scheme17. Synthesis of (-)-macrogentine **(57)**

As was expected from previous studies of molecular models, the newly formed C-21 stereocenter (2-position in the oxazolidine ring) had an *S* configuration with the methyl group occupying the equatorial position of the 6-membered ring, as shown in Scheme 18. A proposed sequence of events, consistent with studies done by Wrackmeyer *et al*.;[43g] Rizk *et al*.;[43h] Jones *et al*.;[43i] Neelakantan *et al*.;[43j, 43k]and Hagopian *et al*.,[43l] is shown in Scheme 18. The stereospecific formation of the equatorial methyl group was rationalized principally by the two unfavorable 1,3-diaxial interactions between the methyl group and the protons at H-5 and H-17 in the epimeric oxindole (III, path a, Scheme 18). Such steric interactions are not present in the equatorial epimer (IV). Additionally, intermediate (I, Scheme 18) leading to intermediate (III), is more sterically

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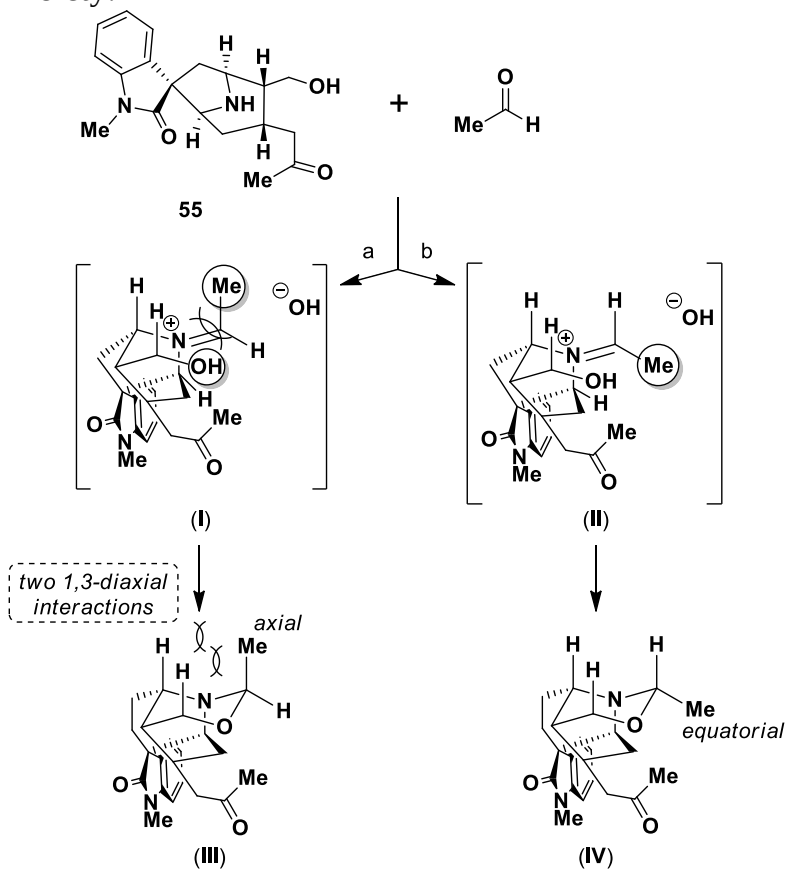
hindered than intermediate (II) where the methyl group is located far away from the hydroxy methyl moiety.



Scheme 18. Possible mechanism for the formation of (-)-macrogentine (**57**)

This hypothesis was confirmed by NOE NMR studies in which irradiation of the methyl group effected an increase in the H-14 signal by 13%; however, there was no enhancement in the intensity of the signals at H-5 or H-17 signals (Figure 6). The proton ^{1}H NMR (see SI Table 12) spectral data and ^{13}C NMR data (see SI Table 13) for (-)-macrogentine (**57**) were in agreement with the literature.[24]

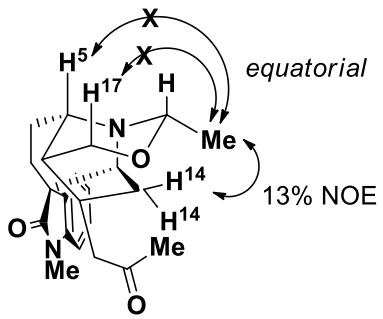


Figure 6. NOE NMR, (-)-macrogentine (**57**)

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Conclusions

The (7*R*)-sarpagine/macroline related oxindole alkaloids (+)-isoalstonisine (**35**) and (–)-macrogentine (**57**) together with the (7*S*)-sarpagine/macroline related oxindole alkaloids (–)-affinisine oxindole (**27**), (–)-alstonoxine A (**56**), (+)-alstonisine (**1**, second generation total synthesis), (+)-N_a-demethylalstonisine (**51**) and (+)-alstofoline (**52**) were synthesized in enantiospecific fashion; moreover, the key stereocenters at C(3) and C(5) were established in >98% *ee* by the asymmetric Pictet-Spengler reaction. The oxidation of the 2,3-indole double bond of the two different N_b-substituted analogs (N_b-CH_2Ph or N_b-H) of the tetracyclic ketone gave either the C-(7)*R* or C-(7)*S* stereochemistry respectively at the spiro junction in 100% *de*.

A highly enantio- and diastereoselective general strategy to access any member of the sarpagine/macroline family of oxindole alkaloids was developed from cheap, commercially-available and optically active D-(+)-tryptophan. This *chiral-pool* starting material was manipulated through successive enantioselective reactions, using achiral reagents, to obtain the desired target molecules. The built-in chirality in D-(+)-tryptophan was used and expanded, *via* intramolecular asymmetric induction, to form new enantio rich compounds. Although the routes were usually stereospecific any diastereomeric byproducts enabled their facile separation by methods such as column chromatography or crystallization. This only occurred in a few instances but was the reason the chirality was built in from the beginning.

At the heart of this approach was the diastereospacific generation of the spiro[pyrrolidine-3,3′-oxindole] moiety at an early stage of the route *via* a *tert*-butyl hypochlorite-promoted oxidative rearrangement of chiral tetrahydro-β-carboline derivatives. This key branching point determined the spatial configuration at the C-7 spiro center to be either 7*R* or 7*S* and on large scale. Other key enantiospecific initial reactions were the asymmetric Pictet–Spengler and Dieckmann cyclization which were scalable to the 600 and 150 gram levels, respectively. This early construction of the spiro oxindole moiety furnished an important advantage for there was no need to perform complex studies for every single target molecule at the end of the route which involved the optimization of reaction conditions to the particular system under study, *e.g.* finding the suitable oxindole-generating reaction or screening of chiral catalysts to obtain the desired stereochemistry at C-7. On the other hand, it was well-known that oxindoles at C-7 could equilibrate between 7*R* and 7*S* through a Mannich-retro-Mannich

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type process.[37] Consequently, the careful confirmation of the diastereomeric outcome of oxindole reactions had to be realized. As a consequence of the studies on this topic, one was able to find a set of two reaction conditions that enabled the 7*R*,7*S*-interconversion validated by X-ray crystallography in many cases as well as, 1D NOE-NMR studies. Others have observed this phenomenon.[37]

The utility of a mild Pd-promoted enolate-driven cross-coupling process at room temperature, that generated the correct chiral center at C-14, was demonstrated. Also, the application of the Wacker–Cook (termed this by Maldonado *et al.*)[30] oxidation process for the generation of the E-ring enol ether functionality of some oxindole systems was expanded.

Finally, the complete structural elucidation of all the final products corroborated the studies by Kam *et al.* who performed the alkaloid isolation process and initial structure determination from plant material in many cases confirmed by X-ray crystallography.

Experimental :

1.General methods

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane was distilled from calcium hydride prior to use. Methanol was distilled over magnesium sulfate prior to use. Benzene and toluene were distilled over sodium prior to use. Acetonitrile was distilled over CaH_2 prior to use. Reagents were purchased of the highest commercial quality and used without further purification unless otherwise stated. Thin layer chromatography (TLC) was performed using Dynamic Adsorbents Inc. UV active silica gel, 200 µm, plastic backed plates; Dynamic Adsorbents Inc. UV active alumina N, 200 µm, F-254 plastic backed. Flash and gravity chromatography were performed using silica gel P60A, 40-63 µm purchased from Silicycle. Basic alumina (Act I, 50-200 µm) for chromatography was purchased from Dynamic Adsorbents. Neutral alumina (Brockman I, ~150 mesh) for chromatography was purchased from Sigma-Aldrich. TLC plates were visualized by exposure to short wavelength UV light (254 nm). Indoles were visualized with a saturated solution of ceric ammonium sulfate in 50% sulfuric acid.[45] Alkynes were visualized by immersing the TLC plate in a permanganate solution,[45] followed by gentle heating with a heat gun; these compounds appeared as either

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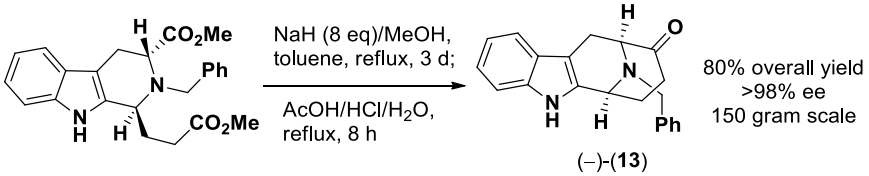
yellow or light brown spots on a light purple or pink background. Elemental analyses were performed on a Carlo Erba model EA-1110 carbon, hydrogen, and nitrogen analyzer. All samples submitted for CHN analyses were first dried under high vacuum for a minimum of six h using a drying pistol with isopropyl alcohol or benzene as the solvent with potassium hydroxide pellets in the drying bulb. Melting points were taken on a Stuart melting point apparatus SMP3 manufactured by Barloworld Scientific US Ltd. Proton (^{1}H NMR) and carbon high resolution nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker 300-MHz or a GE 500-MHz NMR spectrometer. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, td = triplet of doublets, qd = quartet of doublets, sex = sextet, m = multiplet), integration, and coupling constants (Hz). ^{13}C NMR data are reported in parts per million (ppm) on the δ scale. The low resolution mass spectra (LRMS) were obtained as electron impact (EI, 70eV), which were recorded on a Hewlett-Packard 5985B gas chromatography-mass spectrometer, while high resolution mass spectra (HRMS) were recorded on a VG Autospec (Manchester, England) mass spectrometer. HRMS recorded by electrospray ionization (ESI) methods were performed at the Laboratory for Biological Mass Spectrometery at Texas A&M University on an API QStar Pulsar model manufactured by MDS Sciex. Optical rotations were measured on a JASCO Model DIP-370 digital polarimeter. Infra-red spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR or a Perkin Elmer 1600 series FT-IR spectrometer.

1.1) Synthetic Procedures

One pot process for converting trans-(1*S*,3*R*)-(–)-2-benzyl-3-methoxy carbonyl-1-methoxycarbonylethyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole into (6*S*,10*S*)-(–)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*] indole (–)-(13).



(–)-(**13**)

The *trans* diester (26.0 g, 64 mmol) was dissolved in dry toluene (100 mL) in a round bottom flask (250 mL) which was equipped with a Dean Stark trap (DST) and a reflux condenser. The solution which resulted was heated to reflux for 3 h with stirring (magnetic stir). The above predried solution was cooled and added to a suspension of sodium hydride (7.6 g of 60% NaH, washed twice with dry hexane) and dry toluene (650 mL) in a round bottom flask (3 L) under

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an atmosphere of argon. Dry CH_3OH (8 mL) was added carefully (**a large amount of H_2 gas was evolved at this point**). The mixture was stirred at 23 °C for 0.5 h, and then heated to reflux for an additional 72 h. After analysis by TLC (silica gel, EtOAc/hexane, 1/4) indicated the disappearance of starting material, the reaction mixture was cooled to 0 °C and then quenched carefully with glacial acetic acid (15 mL). The solvent was removed under reduced pressure and glacial acetic acid (167 mL), aq hydrochloric acid (245 mL, conc.) and water (65 mL) were added to the above vessel. The mixture which resulted was heated at reflux for 8 h. After removal of the solvent under reduced pressure, the residue was brought to pH = 9 by addition of an aq solution of cold NaOH (3 *N*). The mixture which resulted was extracted with CH_2Cl_2 (4 x 250 mL) and the combined organic extracts were washed with a saturated aq solution of NH_4Cl (100 mL), brine (2 x 100 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded an oil which was chromatographed on silica gel with EtOAc/hexane (3:7) to provide the tetracyclic ketone (**13**, 16.4 g, 82%). This reaction was scalable up to 150 g scale in 80% overall yield.

Catalytic debenzylation of (6*S*,10*S*)-(–)-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (13) to provide (6*S*,10*S*)-(–)-9-oxo-12-H-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (15) over Pd/C, H_2.

The N_a-H, N_b-benzyl tetracyclic ketone (**13**, 10 g, 31.7 mmol) was suspended in anhydrous EtOH (100 mL), and saturated anhydrous ethanolic HCl (15 mL) was added dropwise to form a clear solution. The solvent was removed under reduced pressure. Then the residue was dissolved again in dry EtOH (80 mL), and the solvent was removed under vacuum. This process was repeated three times after which EtOH (50 mL) and Pd/C (10%, 2.0 g) were added. The mixture that resulted was allowed to stir at 23 °C under an atmosphere of hydrogen for 5 h. Analysis by TLC (silica gel) indicated the absence of starting material. The catalyst was removed by filtration and was washed with EtOH (3 x 50 mL). The solvent was removed under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 and aq NH_4OH (5:1, 100 mL). The aq. layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude product, which was purified by chromatography on silica gel [$CHCl_3$/MeOH (20:1)] to provide pure N_a-H, N_b-H tetracyclic ketone (**217**, 6.2 g, 88%): **FTIR** (NaCl) 3390, 3384, 1709 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.08-2.15 (2H, m), 2.39-2.50 (3H, m), 2.80 (1H, d, J = 16.4 Hz), 3.08 (1H, dd, J = 16.5, 6.8 Hz), 3.97 (1H, d, J = 6.7 Hz), 4.27 (1H, d, J

= 3.9 Hz), 7.10 (1H, d, *J* = 7.4 Hz), 7.16 (1H, d, *J* = 7.4 Hz), 7.29 (1H, d, *J* = 7.9 Hz), 7.44 (1H, d, *J* = 7.6 Hz), 8.06 (1H, bs); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 25.78, 31.96, 35.02, 46.06, 59.75, 107.50, 110.90, 118.14, 119.76, 122.09, 126.85, 133.95, 135.71, 210.95; This material was identical to an authentic sample.[14b]

Preparation of *tert*-butyl hypochlorite.

To around bottom flask (500 mL) which contained a stirred mixture of Clorox® (167 mL, 5.25% in NaOCl) and ice (30 g) was added a mixture of pure *tert*-butanol (12.3 mL) and concentrated AcOH (8.2 mL) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for an additional 10 min. The organic layer was then separated and washed quickly with an aq solution of cold $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4) to provide *tert*-butyl hypochlorite (7.9 g, 80%). It was directly employed for the next step. **This reagent must be kept cold**, **managed in dim light, and avoid contact with rubber. When stored in the refrigerator, it must be in a amber bottle at or below 0 °C.**[46]

Diastereospecific conversion of the N_a-H, N_b-benzyl ketone (13) into the N_a-H, N_b-benzyl ketooxindole (14) *via tert*-butyl hypochlorite oxidation.

To a round bottom flask (100 mL), which contained a stirred solution of N_a-H, N_b-benzyl ketone (**13**, 816 mg, 2.5 mmol) and Et_3N (0.28 g, 1.1 equivalents) in DCM (30 mL), was added the freshly prepared *tert*-butyl hypochlorite (0.36 g, 0.4 mL, 3 mmol) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure and the solid which resulted was dissolved in a solution of MeOH-10% AcOH (1:1, 20 mL). The reaction mixture which resulted 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 aq solution of $NaHCO_3$ (20 mL), brine (2 x 20 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (silica gel, EtOAc/hexane, 3/7) to provide the N_a-H, N_b-benzyl ketooxindole (**14**, 770 mg, 93%). **m.p.** = 203-204 °C; **$[\alpha]_D^{27}$** = +182.3° (*c* 0.95, in $CHC1_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.30-2.41(2H, m), 2.41-2.43 (1H, m), 2.43-2.56 (2H, m), 3.15 (1H, d, *J* = 2.56 Hz), 3.41 (1H, dt, *J* = 8.8, 10.4 Hz), 3.55 (1H, d, *J* = 7.20 H z), 3.89 (2H, dd, *J* = 4.1, 13.1 Hz), 6.89 (1H, d, *J* = 7.5 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 7.24 (1H, t, *J* = 7.5 Hz), 7.26-7.42 (5H, m), 7.77 (1H, d, *J* = 7.5 Hz), 8.66 (1H, s); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 23.67, 34.27, 39.61 , 51.67, 55.71, 65.26, 67.51, 109.05, 122.87, 123.96, 127.33, 127.88, 128.38, 128.80, 137.49,

137.65, 139.14, 179.56, 212.59; **IR** (KBr) 3236, 1707, 1676,1466 cm^{-1}; This material was identical to an authentic sample.[12a]

Diastereospecific conversion of the N_a-H, N_b-H, ketone (15) into the N_a-H, N_b-H ketooxindole (16) *via tert*-butyl hypochlorite oxidation.

To a round bottom flask (50 mL) which contained a stirred solution of N_a-H, N_b-H ketone (**15**) (113 mg, 0.5 mmol) and Et_3N (0.1 g, 1.2 equivalents) in DCM (20 mL) was added the freshly prepared *tert*-butyl hypochlorite (72 mg, 80 µL, 0.6 mmol) at 0 °C. The reaction mixture which resulted was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure and the solid which resulted was dissolved in a solution of MeOH-10% AcOH (1:1, 15 mL). The solution which resulted 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 aq solution of $NaHCO_3$ (10 mL), brine (2 x 10 mL) and dried (Na_2SO_4). After removal of the solvent under reduced pressure, the crude oxindole was purified by flash chromatography (silica gel, EtOAc/hexane, 3/5) to provide the N_a-H, N_b-H ketooxindole (**16**, 97 mg, 80%). $[\alpha]_D^{27}$ = –65.9° (*c* 1.0, $CHC1_3$); **IR** (KBr): 3400-3100,1700,1610 cm^{-1}. This material was identical to an authentic sample.[2d]

Synthesis of N_a-methyl, N_b-H tetracyclic ketone oxindole (17) from oxindole (16).

To a round bottom flask (1000 mL) which contained a solution of pure N_a-H, N_b-H tetracyclic ketone oxindole (**16**, 3 g, 12.4 mmol) in dry THF (300 mL) under argon at 0 °C, was added NaH (0.545 g, 13.6 mmol, 60% dispersion in mineral oil). The slurry which resulted was allowed to stir at 0 °C for 5 min and then CH_3I (2.1 g, 14.8 mmol) was added to the reaction flask through a syringe. The reaction solution was allowed to reach rt and this was followed by TLC analysis (Silica gel, EtOAc-hexanes = 3:1) until disappearance of starting material (**16**). The solution was quenched by careful addition of cold water (10 mL) and then concentrated under reduced pressure to a third of its volume. Then CH_2Cl_2 (500 mL) was added to the mixture and the solution was successively washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). Removal of the solvent under reduced pressure afforded the crude solid, which was purified by flash chromatography (Silica gel, EtOAc-hexanes = 1:1) to provide the pure oxindole (**17**) as an amorphous pale yellow solid (2.54 g, 80% yield): **m.p.** = 80-82 °C; $[\alpha]_D^{27}$ = +26.4° (*c* 0.25, $CHCl_3$); **IR** (KBr) 3300, 2937, 1695, 1611, 1493, 1471, 1374, 1349, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 (td, *J* = 7.5, 1 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 3.95 (d, *J* = 8 Hz, 1H), 3.48

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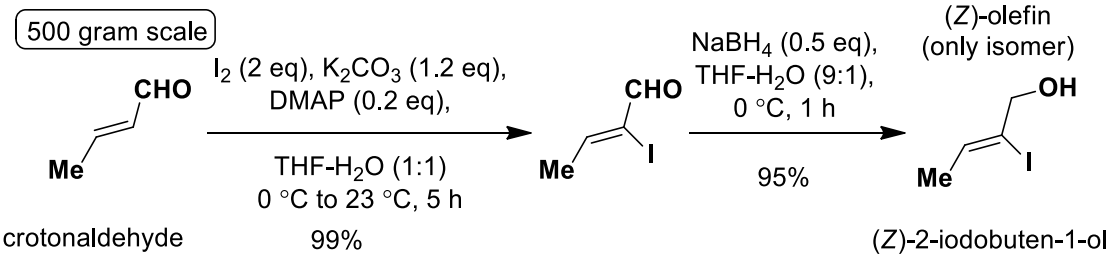
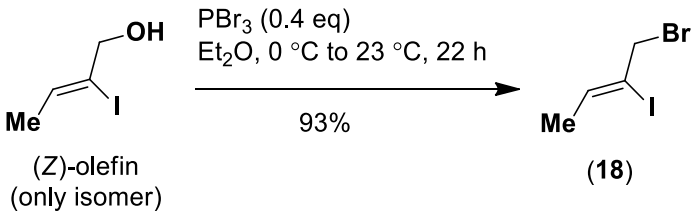
(d, *J* = 5.3 Hz, 1H), 3.25 (s, 3H), 2.62 (m, 3H), 2.11 (m, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 207.1, 182.1, 154.6, 144.3, 128.4, 123.6, 122.7, 108.5, 60.1, 40.5, 32.4, 26.4, 24.8; This material was employed in a later experiment.

Large scale one-pot synthesis of (*Z*)-2-iodobuten-1-ol from crotonoaldehyde.



To a cold (using dry ice) stirred solution of crotonaldehyde (200 g, 234 mL, 2.85 mol) in 1:1 THF-H_2O (10 L) was added K_2CO_3 (480 g, 3.47 mol), I_2 (1095 g, 4.31 mol) and DMAP (70 g, 0.57 mol) successively. The reaction mixture was gradually allowed to come to rt and stirred for a total of 5 h. Upon completion by TLC, the reaction mixture was again cooled (using dry ice). Small portions of $NaBH_4$ (54 g, 1.43 mol) were gradually added to the reaction mixture and the reaction was constantly monitored for completion. The mixture was subsequently extracted with EtOAc and dried over Na_2SO_4, before concentration and purification by flash column chromatography (EtOAc-hexanes, 1:4) afforded 530 g (95%) of the (*Z*)-2-iodobuten-1-o1. The ^{1}H and ^{13}C NMR data were identical to those reported in the literature.[47]

Synthesis of (*Z*)-1-bromo-2-iodo-2-butene (18) from (*Z*)-2-iodobuten-1-ol.



To a cold, stirred solution of alcohol (52 g, 0.26 mol) in dry diethyl ether (1000 mL at 0 °C) was added PBr_3 (0.4 equivalents, 28.5 g) slowly. After the addition was complete the reaction solution was slowly allowed to reach rt and stirred for a total of 22 h. Cold water (200 mL, 0 °C) was then slowly added to the solution to quench the reaction. The layers were separated and the aq layer was further extracted with diethyl ether (3 x 200 mL). The organic layers were combined and dried (Na_2SO_4). The solvent was later removed under vacuum to afford 62 g (93% yield) of (*Z*)-1-bromo-2-iodo-2-butene (**18**) as a light yellow clear oil. No further

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purification was needed. The ^{1}H and ^{13}C NMR data were identical to those reported in the literature.[48]

Synthesis of N_b-allyl-tetracyclic ketone oxindole (19) from oxindole (17).

The N_a-methyl, N_b-H ketooxindole (**17**, 2 g, 7.8 mmol), (*Z*)-1-bromo-2-iodo-2-butene (**18**, 16.3 g, 62.5 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 1.31 g, 10.1 mmol) were added to a 1-neck round-bottom flask with a stir bar such that the flask was half full. The flask was closed with a rubber septum and the air evacuated using a stream of argon. The reaction flask was then placed inside an oil bath at 50 °C and the reaction progress monitored by TLC [Silica gel, EtOAc-hexanes = 1:1 to check for the disappearance of (**17**); EtOAc-hexanes = 1:3 to check for the formation of oxindole (**19**)]. After the starting material (**19**) was completely consumed, the reaction mixture was allowed to cool to rt. The crude mixture was then directly subjected to flash chromatography [(Silica gel, hexanes + 1% Et_3N was used first to recover unreacted excess of (**18**)], then the solvent was switched to CH_2Cl_2 + 1% Et_3N to recover the pure oxindole **19**). The expected pure allyl oxindole (**19**) was obtained as an amorphous yellow solid (3.1 g, 90% yield): **m.p.** = 58-60 °C; **$[\alpha]^{26}_D$** = +39.7° (*c* 2.3, $CHCl_3$); **IR** (KBr) 2933, 1700, 1611, 1471, 1374, 1349, 754 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.04 (td, *J* = 7.5, 1 Hz, 1H), 6.99 (dd, *J* = 7.5, 1 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.04 (qt, *J* = 6.4, 1 Hz, 1H), 4.00 (dt, *J* = 14, 1 Hz, 1H), 3.75 (brd, *J* = 7.3 Hz, 1H), 3.68 (dt, *J* = 14, 1 Hz, 1H), 3.62 (brd, *J* = 6.9 Hz, 1H), 3.21 (s, 3H), 2.90 (m, 1H), 2.81 (q, *J* = 7.4 Hz, 1H), 2.46 (ddd, *J* = 17.4, 8.9, 3.6 Hz, 1H), 2.24 (m, 1H), 2.13 (d, *J* = 13.5 Hz, 1H), 1.82 (d, *J* = 6.4 Hz, 3H), 1.69 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.7 (C), 181.4 (C), 143.7 (C), 132.6 (CH), 130.2 (C), 128.1 (CH), 124.0 (CH), 122.4 (CH), 109.8 (C), 107.9 (CH), 71.2 (CH), 66.4 (CH), 62.6 (CH_2), 58.2 (C), 41.2 (CH_2), 34.2 (CH_2), 26.4 (CH_3), 23.1 (CH_2), 21.7 (CH_3); HRMS (ESI, m/z, relative intensity) calcd for $C_{19}H_{21}IN_2O_2$ $(M+H)^+$ = 437.0721, found 437.0713. This compound was further confirmed by X-ray crystallographic analysis. CCDC reference number 1547266 (please see SI for further details). This indicates the structures of the previous intermediates were correct.

Synthesis of N_a-methyl, N_b-benzyl tetracyclic ketone oxindole (21) from oxindole (14).

To a round bottom flask (3000 mL) which contained a solution of pure N_a-H, N_b-benzyl tetracyclic ketone oxindole (**14**, 29 g, 87.2 mmol) in dry THF (1000 mL) under argon at 0 °C,

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NaH (3.7 g, 91.6 mmol, 60% dispersion in mineral oil) was slowly added in portions. The slurry which resulted was allowed to stir at 0 °C for 5 min and then CH_3I (13.6 g, 95.8 mmol) was added to the reaction flask through a syringe. The reaction solution was allowed to reach rt and this was followed by analysis on TLC (SiO_2 gel, CH_2Cl_2) until disappearance of starting oxindole (**14**) was realized. The solution was then quenched by careful addition of cold water (50 mL) and then concentrated under reduced pressure to a third of its volume. The CH_2Cl_2 (2000 mL) was added to the mixture and the solution was successively washed with 10% aq $NaHCO_3$ (2 x 500 mL), brine (500 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography (SiO_2 gel, CH_2Cl_2 + 1% Et_3N) to provide the pure oxindole (**21**) as an amorphous pale yellow solid (25.4 g, 87% yield): **m.p.** = 86-88 °C; **[α]$^{24}_{D}$** = +112.4° (*c* 0.93, CH_2Cl_2); **IR** (KBr) 2926, 1701, 1610, 1491, 1469, 1374, 1351, 1123, 1084, 749, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.4, 1H), 7.42-7.26 (m, 6H), 7.13 (td, *J* = 7.5, 1 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 3.92 (dd, *J* = 18.3, 13 Hz, 2H), 3.58 (d, *J* = 7 Hz, 1H), 3.52 (m, 1H), 3.25 (s, 3H), 3.14 (d, *J* = 2.5 Hz, 1H), 2.48-2.44 (m, 2H), 2.39 (m, 1H), 2.34-2.24 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.6 (C), 177.2 (C), 142.1 (C), 137.5 (C), 137.1 (C), 128.1 (CH), 128.4 (CH), 127.9 (CH), 127.3 (CH), 123.5 (CH), 122.9 (CH), 107.5 (CH), 67.5 (CH), 65.1 (CH), 55.3 (C), 51.7 (CH_2); 39.6 (CH_2); 34.3 (CH_2); 26.4(CH_3); 23.7 (CH_2); HRMS (ESI, m/z, relative intensity) calcd for $C_{22}H_{23}N_2O_2$ (M+H)+ = 347.1760, found 353.1772.

Synthesis of *N*$_a$-methyl, *N*$_b$-H tetracyclic ketone oxindole (22) from oxindole (21).

Pure *N*$_a$-methyl, *N*$_b$-benzyl tetracyclic ketone oxindole (**21**, 1 g, 2.89 mmol) was dissolved in a mixture of MeCN-H_2O (5:1, 200 mL) at rt. Ceric ammonium nitrate (CAN, 3.49 g, 6.36 mmol) was then added portion wise to the above solution and the reaction progress was monitored by TLC (Silica gel, EtOAc-hexanes = 1:1). Once the starting material, oxindole (**21**), was completely consumed (do not keep the product in the reaction mixture for a longer time otherwise the yield decreases), the reaction solution was quenched by addition of saturated aq $NaHCO_3$ solution (50 mL) and stirred vigorously for 10 min. The solution was concentrated to a third of its initial volume and then brine (300 mL) was added to the mixture. The solution was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried (K_2CO_3). The removal of the solvent afforded a crude solid which was purified by flash chromatography (Silica gel, EtOAc-hexanes = 1:4) to provide pure oxindole (**22**) as a white crystalline solid (0.44 g, 60% yield): **m.p.** = 98-101°C; **[α]$^{23}_{D}$** = +112.0° (*c* 0.1, $CHCl_3$); **IR** (KBr) 3288, 2944,

1695, 1610, 1493, 1470, 1352, 1085, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.5, 1 Hz, 1H), 7.31 (td, *J* = 7.5, 1 Hz, 1H), 7.09 (td, *J* = 7.5, 1 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 3.91 (brt, *J* = 4 Hz, 1H), 3.47 (dt, *J* = 17, 9.6 Hz, 1H), 3.36 (d, *J* = 4.3 Hz, 1H), 3.28 (s, 3H), 2.49-2.41 (m, 3H), 2.33 (dd, *J* = 14, 9.4 Hz, 1H), 2.00-1.88 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.7 (C), 177.0 (C), 142.0 (C), 136.9 (C), 127.9 (CH), 122.9 (CH), 122.6 (CH), 107.7 (CH), 65.6 (CH), 63.8 (CH), 56.1 (CH), 40.3 (CH_2), 33.7 (CH_2), 30.5 (CH_2), 26.4 (CH_3); This material was employed in a later experiment.

Synthesis of N_b-allyl-tetracyclic ketone oxindole (20) from oxindole (22):

The N_a-methyl, N_b-H ketooxindole (**22**, 3.7 g, 14.4 mmol), (*Z*)-1-bromo-2-iodo-2-butene (**18**, 30 g, 115.5 mmol) and *N*,*N*-diisopropylethylamine (DIEA, 2.2 g, 17.3 mmol) were added to a 1-neck round-bottom flask with a stir bar such that the flask was half full. The flask was closed with a rubber septum and the air evacuated using a stream of argon. The reaction flask was placed inside an oil bath at 50 °C and the reaction progress was monitored by TLC [Silica gel, EtOAc-hexanes = 1:1 to check for the disappearance of (**22**); EtOAc-hexanes = 1:3 to check for the formation of oxindole (**20**)]. After the starting material (**22**) was completely consumed, the reaction mixture was allowed to cool to rt. The crude mixture was then directly subjected to flash chromatography [Silica gel, CH_2Cl_2 was used first to recover unreacted excess of (**18**); then was switched to CH_2Cl_2-EtOAc = 7:3 + 1% Et_3N to recover pure product]. The expected pure oxindole (**20**) was recovered as an amorphous yellow solid (5.7 g, 91% yield). **m.p.** = 73-75 °C; **$[\alpha]^{26}_D$** = +58.7° (*c* 0.15, $CHCl_3$); **IR** (KBr) 2946, 1704, 1611, 1471, 1374, 1351, 753 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.4, 1 Hz, 1H), 7.31 (td, *J* = 7.4, 1 Hz, 1H), 7.12 (td, *J* = 7.4, 1 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 5.87 (qt, *J* = 6.4, 1 Hz, 1H), 3.61 (m, 3H), 3.58 (d, *J* = 1.5 Hz, 1H), 3.27 (s, 3H), 3.18 (d, *J* = 4 Hz, 1H), 2.50 (d, *J* = 7.8 Hz, 1H), 2.43 (d, *J* = 1 Hz, 1H), 2.37 (m, 1H), 2.32 (d, *J* = 8.2 Hz, 1H), 2.27 (d, *J* = 9.4 Hz, 1H), 1.80 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 212.0 (C), 177.2 (C), 141.9 (C), 136.8 (C), 134.1 (CH), 127.9 (CH), 125.1 (CH), 123.1 (CH), 107.3 (CH), 105.5 (C), 66.7 (CH), 65.6 (CH), 59.4 (CH_2), 55.4 (C), 39.6 (CH_2), 34.3 (CH_2), 26.4 (CH_3), 24.6 (CH_2), 21.7 (CH_3); This compound was further confirmed by X-ray crystallographic analysis. CCDC reference number 1547268 (please see SI for further details). This indicates the structures of the previous intermediates were correct.

Synthesis of pentacyclic ketone oxindole (23) from oxindole (19).

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Method A: A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**19**, 1.0 g, 2.3 mmol), $Pd(PPh_3)_4$ (0.265 g, 0.23 mmol) and $PhONa•3H_2O$ (0.975 g, 5.7 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles). The solution was then heated to reflux under argon for 2 h. Analysis by TLC (Silica gel, EtOAc-hexanes = 4:1) indicated the disappearance of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**19**) and the presence of a new oxindole component of lower *Rf* value. The solution was allowed to warm to rt and then was concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and then dried (K_2CO_3). Removal of the solvent provided a mixture which was subjected to flash chromatography (Silica gel, EtOAc-hexanes = 4:1) to afford the expected oxindole (**23**) as an amorphous pale yellow solid (0.46 g, 65% yield).

Method B: A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**19**, 1.0 g, 2.3 mmol), Pd_2dba_3 (0.842 g, 0.92 mmol) and NaHMDS (2 equivalents, 0.843 g, 4.6 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution). The solution was then stirred under argon for 8 h at rt. Analysis by TLC (Silica gel, EtOAc-hexanes = 4:1) indicated the absence of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**19**) and the presence of a new oxindole component of lower *Rf* value. The solution was then concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure provided a mixture which was subjected to flash chromatography (Silica gel, EtOAc-hexanes = 4:1) to afford the expected pure oxindole (**23**) as an amorphous pale yellow solid (1.84 mmol, 567 mg, 80% yield): **m.p.** = 61-64 °C; $\mathbf{[\alpha]^{27}_D}$ = –6.12° (*c* 8.5, $CHCl_3$); **IR** (KBr) 2923, 1716, 1610, 1493, 1373, 1345, 1197, 1119 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.26 (td, *J* = 8, 2 Hz, 1H), 7.02 (td, *J* = 8, 2 Hz, 1H), 6.89 (brd, *J* = 8 Hz, 1H), 6.79 (brd, *J* = 8 Hz, 1H), 5.44 (qt, *J* = 7, 2 Hz, 1H), 3.73 (brd, *J* = 1.5 Hz, 2H), 3.69 (brd, *J* = 8 Hz, 1H), 3.51 (brd, *J* = 8 Hz, 1H), 3.44 (d, *J* = 4.5 Hz, 1H), 3.18 (s, 3H), 2.75 (ddd, *J* = 13, 8, 1.5 Hz, 1H), 2.23 (ddd, *J* = 14, 4.5, 1.5 Hz, 1H), 1.97 (d, *J* = 13 Hz, 1H), 1.84 (dd, *J* = 14, 9 Hz, 1H), 1.64 (dt, *J* = 7, 2 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) *δ* 216.4 (C), 180.7 (C), 143.9 (C), 133.8 (C), 129.4 (C), 128.5 (CH), 125.9 (CH), 122.1 (CH), 120.6 (CH), 108.0 (CH), 69.0 (CH), 62.4 (CH), 55.6 (C), 48.4 (CH_2), 43.9 (CH), 38.5 (CH_2), 26.5 (CH_3), 25.4 (CH_2), 12.4 (CH_3); HRMS (ESI, m/z, relative intensity)

calcd for $C_{19}H_{21}N_2O_2$ (M+H)+ = 347.1603, found 353.1605.This compound was further confirmed by X-ray crystallographic analysis. CCDC reference number 1547269 (please see SI for further details). This indicates the structures of the previous intermediates were correct.

Synthesis of (–)-affinisine oxindole (26) from oxindole (23).

A mixture of anhydrous *tert*-BuOK (0.292 g, 2.6 mmol) and (methoxymethyl)triphenyl-phosphonium chloride (0.881 g, 2.57 mmol) in dry benzene (10 mL) was allowed to stir at rt for 45 min. The pentacyclic ketone oxindole (**23**, 0.113 g, 0.367 mmol) was dissolved in dry THF (4 mL) and was then added to the above orange solution dropwise at rt (23 °C). The mixture that resulted was stirred at rt for 1 d. The mixture was diluted with EtOAc (50 mL) then washed with 10% aq $NaHCO_3$ (2 x 10 mL), brine (10 mL) and dried (K_2CO_3). The solution was concentrated under reduced pressure and the baseline materials were removed by a quick wash column on silica gel. The solvent was removed under reduced pressure and the residue [containing a mixture of enol ethers (**24**)] was dissolved (without further purification) in a solution of aq HCl (2 *N*)-THF (1:1, 10 mL). The solution which resulted was stirred at 55 °C (oil bath temperature) under an argon atmosphere for 5 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc (20 mL) and brought to pH = 8 with an ice cold solution of aq NaOH (1 *N*). The aq layer was then extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with 10% aq $NaHCO_3$ (2 x 10 mL), brine (10 mL) and then dried (K_2CO_3). The removal of the solvent under reduced pressure provided a crude mixture [containing aldehyde (**25**)] which was dissolved in EtOH (200 proof, 25 mL) and then $NaBH_4$ (0.015 g, 0.4 mmol) was added to the above solution in one portion at 0 °C. The mixture was then allowed to reach rt and was stirred for a total of 8 h. The reaction mixture was concentrated under reduced pressure (not to dryness) and the residue was diluted with CH_2Cl_2 (150 mL) and poured into ice cold water (20 mL). The aq layer was extracted with additional CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine (10 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a crude mixture which was chromatographed (Silica gel, EtOAc) to provide (–)-affinisine oxindole (**26**) as a clear oil (0.040 g, 34% yield over three steps): $\mathbf{[\alpha]^{23}_D}$ = –66.0° (*c* 0.3, $CHCl_3$) [literature[16] $[\alpha]^{23}_D$ = –70° (*c* 0.06, $CHCl_3$)]; **IR** (KBr) 3375, 2933, 1711, 1610, 1470 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 (brd, *J* = 8 Hz, 1H), 7.31 (td, *J* = 8, 1 Hz, 1H), 7.09 (td, *J* = 8, 1 Hz, 1H), 6.83

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(brd, *J* = 8 Hz, 1H), 5.32 (qt, *J* = 7, 2 Hz, 1H), 3.78 (m, 2H), 3.62 (m, 2H), 3.37 (dd, *J* = 10, 2 Hz, 1H), 3.31 (dd, *J* = 6, 3 Hz, 1H), 3.21 (s, 3H), 2.88 (brs, 1H), 2.77 (dd, *J* = 13, 6 Hz, 1H), 2.18 (ddd, *J* = 14, 4, 2 Hz, 1H), 2.05 (m, 1H), 1.82 (d, *J* = 13 Hz, 1H), 1.61 (dt, *J* = 7, 2 Hz, 3H), 1.56 (ddd, *J* = 14, 10, 2 Hz, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 181.8 (C), 144.4 (C), 136.0 (C), 130.4 (C), 128.1 (CH), 126.6 (CH), 121.5 (CH), 114.8 (CH), 107.8 (CH), 65.7 (CH_2), 62.8 (CH), 59.1 (CH), 56.7 (C), 48.8 (CH_2), 47.9 (CH), 44.6 (CH_2), 28.8 (CH_2), 26.5 (CH_3), 26.1 (CH), 12.4 (CH_3); **HRMS** (ESI, *m/z*, relative intensity) calcd for $C_{20}H_{25}N_2O_2$ $(M+H)^+$ = 325.1916, found 325.1912.

Synthesis of pentacyclic ketone oxindole (39) from tetracyclic ketone oxindole (20).

A mixture of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**20**, 1.0 g, 2.3 mmol), Pd_2dba_3 (0.842 g, 0.92 mmol) and NaHMDS (2 equivalents, 0.843 g, 4.6 mmol) was dissolved in THF (previously distilled over Na/benzophenone ketyl, 250 mL), and then the system was degassed (freeze-pump-thaw degassed, 3-5 cycles, to remove all the oxygen from the solution). The solution was then stirred under argon for 8 h at rt. Analysis by TLC (Silica gel, EtOAc-hexanes = 4:1) indicated the absence of N_b-(*Z*)-2′-iodo-2′-butenyl tetracyclic ketone oxindole (**20**) and the presence of a new oxindole component of lower *Rf* value. The solution was then concentrated to a third of its original volume under reduced pressure. The residue was dissolved in CH_2Cl_2 (500 mL) and washed with 10% aq $NaHCO_3$ (2 x 100 mL), brine (100 mL) and dried (K_2CO_3). The removal of the solvent under reduced pressure provided a mixture which was subjected to flash chromatography (Silica gel, EtOAc-hexanes = 4:1) to afford the expected pure oxindole (**39**) as an amorphous pale yellow solid (1.84 mmol, 567 mg, 80% yield). **m.p.** = 68-70 °C; **$[\alpha]^{26}_D$** = +9.1° (*c* 0.11, CH_2Cl_2); **IR** (KBr) 2932, 1731, 1705, 1610, 1491, 1375, 1349, 753, 731 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 1H), 7.29 (t, *J* = 8 Hz, 1H), 7.07 (t, *J* = 8 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 5.40 (m, 1H), 3.68 (brm, 3H), 3.45 (m, 1H), 3.30 (d, *J* = 9 Hz, 1H), 3.22 (s, 3H), 3.08 (dt, *J* = 14, 2 Hz, 1H), 2.48 (dd, *J* = 14, 9 Hz, 1H), 2.31 (brd, *J* = 14 Hz, 1H), 1.74 (m, 1H), 1.67 (m, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 216.0 (C), 176.8 (C), 142.2 (C), 136.8 (C), 135.6 (C), 127.9 (CH), 124.0 (CH), 122.9 (CH), 119.5 (CH), 107.5 (CH), 68.1 (CH), 64.7 (CH), 54.3 (C), 48.6 (CH_2), 43.7 (CH), 39.7 (CH_2), 26.4 (CH_3), 22.0 (CH_2), 12.5 (CH_3); This material was employed in a later experiment.

Synthesis of (-)-isoaffinisine oxindole (38) from pentcyclic ketone oxindole (39).

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A mixture of anhydrous *tert*-BuOK (0.584 g, 5.2 mmol) and (methoxymethyl)triphenyl phosphonium chloride (1.76 g, 5.14 mmol) in dry benzene (20 mL) was allowed to stir at rt for 45 min. The pentacyclic ketone oxindole (**39**, 226 mg, 0.734 mmol) was dissolved in dry THF (10 mL) and was then added to the above orange solution dropwise at rt (23 °C). The mixture which resulted was allowed to stir at rt for 1 d. The mixture was diluted with EtOAc (100 mL) then washed with 10% aq $NaHCO_3$ (2 x 20 mL), brine (20 mL) and dried (K_2CO_3). The solution was concentrated under reduced pressure and baseline materials were removed by a quick wash column on silica gel (EtOAc/hexanes 1:1). The solvent was removed under reduced pressure and the residue [containing a mixture of enol ethers (**40**)] was dissolved (without further purification) in a solution of aq HCl (2 *N*)-THF (1:1, 20 mL). The solution which resulted was stirred at 55 °C (oil bath temperature) under an argon atmosphere for 5 h. The reaction mixture was cooled to 0 °C, diluted with EtOAc (40 mL) and brought to pH = 8 with an ice cold solution of aq NaOH (1 *N*). The aq layer was then extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with 10% aq $NaHCO_3$ (2 x 20 ml), brine (20 mL) and then dried (K_2CO_3). The removal of the solvent under reduced pressure provided a crude mixture [containing aldehyde (**41**)] which was dissolved in EtOH (200 proof, 50 mL) and then $NaBH_4$ (0.030 g, 0.8 mmol) was added to the above solution in one portion at 0 °C. The mixture was stirred and allowed to warm to rt and was stirred for a total of 8 h. The reaction mixture was concentrated under reduced pressure (not to dryness) and the residue was diluted with CH_2Cl_2 (300 mL) and poured into cold water (50 mL). The aq layer was extracted with additional CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (20 mL) and dried (K_2CO_3). The solvent was removed under reduced pressure to afford a crude mixture which was chromatographed (Silica gel, EtOAc) to provide (-)-isoaffinisine oxindole (**38**) as a yellowish solid (167 mg, 0.514 mmol, 70% yield). **m.p.** = 71-74 °C; **$[\alpha]^{23}_D$** = –54.0° (*c* 0.10, $CHCl_3$); **IR** (KBr) 3390, 2941, 1710, 1465 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8 Hz, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.04 (t, *J* = 8 Hz, 1H), 6.80 (d, *J* = 8 Hz, 1H), 5.27 (brq, *J* = 7 Hz, 1H), 3.58 (m, 4H), 3.23 (s, 3H), 3.14 (m, 2H), 2.81 (brm, 1H), 2.75 (dt, *J* = 14, 3 Hz, 1H), 2.42 (dd, *J* = 13, 7 Hz, 1H), 2.16 (m, 1H), 2.07 (d, *J* = 12 Hz, 1H), 1.62 (d, *J* = 7 Hz, 3H), 1.42 (m, 1H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 178.3 (C), 142.1 (C), 138.4 (C), 137.6 (C), 127.4 (CH), 123.4 (CH), 122.8 (CH), 114.2 (CH), 107.2 (CH), 66.2 (CH_2), 65.8 (CH), 59.1 (CH), 55.4 (C), 49.0 (CH_2), 48.1 (CH), 46.3 (CH_2), 26.8 (CH), 26.4 (CH_3), 26.1 (CH_2), 12.4 (CH_3); This compound was further confirmed by X-ray crystallographic analysis. CCDC reference

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number 1547265 (please see SI for further details). This indicates the structures of the previous intermediates were correct.

Synthesis of triisopropylsilyl ether oxindole (42) from (-)-isoaffinisine oxindole (38).

A solution of (-)-isoaffinisine oxindole (**38**, 1.5 g, 4.6 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C, after which 2,6-lutidine (4 equivalents, 2.1 mL, 18.4 mmol) was added, and this was followed by addition of TIPSOTf (2 equivalents, 2.5 mL, 9.2 mmol) to the stirred solution. The mixture was then allowed to stir for an additional 2 h at rt, after which ice cold water (5 mL) was added to quench the reaction mixture. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and poured into cold water (50 mL). The aq 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 under vacuum to remove the excess 2,6-lutidine before the solid was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:4] to provide oxindole (**42**, 4.14 mmol, 1.99 g, 90%). $\mathbf{[\alpha]^{23}_D}$ = –84.0° (*c* 0.15, $CHCl_3$); **IR** (KBr) 2937, 1713, 1488, 1120 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8 Hz, 1H), 7.24 (td, *J* = 8, 1 Hz, 1H), 7.03 (td, *J* = 8, 1 Hz, 1H), 6.79 (d, *J* = 8 Hz, 1H), 5.24 (m, 1H), 3.58 (m, 4H), 3.24 (s, 3H), 3.10 (m, 2H), 2.80-2.71 (brm, 2H), 2.41 (dd, *J* = 13, 7 Hz, 1H), 2.14 (m, 1H), 2.07 (d, *J* = 12 Hz, 1H), 1.59 (dt, *J* = 7, 2 Hz, 3H), 1.39 (m, 1H), 1.07 (s, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 178.3, 142.2, 138.7, 137.5, 127.3, 123.5, 122.7, 113.9, 107.1, 66.3, 65.9, 59.3, 55.4, 49.2, 48.5, 46.5, 26.6, 26.4, 18.1, 17.7, 12.5, 12.3; This material was employed in a later experiment.

Synthesis of pentacyclic ketone oxindole (44) from pentacyclic olefin oxindole (42).

To a solution of triisopropylsilyl ether oxindole (**42**, 500 mg, 1.04 mmol) in dry THF (30 mL) was added BH_3-DMS complex (1 *M* in THF, 9.4 mL, 9.36 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 (5 mL) at 0 °C. At this point aq NaOH (3 *N*, 18 mL, 57 mmol) was added to the mixture, followed by addition of H_2O_2 (30% in water, 5.0 mL, 43 mmol). The mixture which resulted was allowed to stir at rt for 3 h after which EtOAc (500 mL) and H_2O (80 mL) were added. The organic layer was separated and dried (Na_2SO_4). The EtOAc was then removed

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under reduced pressure and the residue was purified on a short flash column (wash column) with EtOAc/hexanes (4:6) to provide a mixture of *sec*-ol diastereomers which was used directly in the next step.

The mixture of isomers was dissolved in CH_2Cl_2 (30 mL) and the tetrapropylammonium perruthenate (2 equivalents, 2.08 mmol, 731 mg) was quickly added to the solution. The reaction was stirred at rt for approximately 2 h. Water (30 mL) was then added and the layers were separated. The organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide pentacyclic oxindole (**44**, 0.676 mmol, 336 mg, 65%). **$[\alpha]^{23}_D$** = –53.0° (*c* 0.25, $CHCl_3$); **IR** (KBr) 2941, 1720, 1711, 1355, 1206 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8 Hz, 1H), 7.24 (t, *J* = 8 Hz, 1H), 7.03 (t, *J* = 8 Hz, 1H), 6.78 (d, *J* = 8 Hz, 1H), 3.87 (dd, *J* = 11, 7 Hz, 1H), 3.77 (t, *J* = 10 Hz, 1H), 3.62 (dd, *J* = 14, 5 Hz, 1H), 3.21 (s, 3H), 3.05 (dd, *J* = 10, 2 Hz, 1H), 2.94-2.86 (m, 2H), 2.77-2.70 (m, 1H), 2.45-2.33 (m, 4H), 2.14 (s, 3H), 2.10-2.05 (m, 1H), 2.10 (d, *J* = 13 Hz, 1H), 1.12-1.10 (m, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 210.7, 178.1, 142.1, 138.2, 127.4, 123.6, 122.8, 107.2, 64.8, 64.7, 58.1, 55.2, 46.7, 46.1, 42.9, 41.0, 29.7, 28.8, 26.4, 25.7, 21.2, 18.1, 11.9; This material was employed in a later experiment.

Synthesis of tetracyclic enone oxindole (46) from pentacyclic ketone (44).

Oxindole (**44**, 100 mg, FW = 496.76, 0.20 mmol) was mixed with MeI (employed as the solvent, 5 mL) and the solution which resulted was heated at 70 °C (external temperature, oil bath) in a closed round bottom flask (screw-cap) for 24 h. The solution was then allowed to cool to rt and the MeI was removed under reduced pressure (inside the hood!), to provide the methyl ammonium salt of **45** as a crude solid, which was used without further purification: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.19 (t, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 4.81-4.73 (m, 1H), 4.41 (t, *J* = 10 Hz, 1H), 4.28 (dd, *J* = 14, 7 Hz, 1H), 4.06-4.00 (m, 1H), 3.89 (s, 3H), 3.80 (m, 1H), 3.71-3.65 (m, 1H), 3.60-3.52 (m, 2H), 3.47-3.42 (m, 1H), 3.24 (s, 3H), 2.93 (dd, *J* = 14, 6 Hz, 1H), 2.74 (brs, 1H), 2.47 (dd, *J* = 14, 6 Hz, 1H), 2.24 (s, 3H), 1.82 (dd, J = 15, 9 Hz, 1H), 1.19-0.95 (brs, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 205.7, 176.5, 143.2, 130.3,129.9, 124.2, 124.1, 109.3, 68.0, 61.8, 55.9, 54.8, 51.0, 43.0, 42.0, 41.8, 29.7, 28.1, 27.2, 24.1, 23.6, 18.0, 11.9.

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The crude salt of **45** was dissolved in dry THF and NaHMDS (2 equivalents, 0.40 mmol, 74 mg) were quickly added under a stream of argon. The solution was stirred an additional 30 min at rt. The solution was concentrated to a third of its original volume and the ice cooled water was added to the solution. Ethyl acetate was used to extract the aq layer (3 x 50 mL) and the combined organic layers were washed once with brine and dried (K_2CO_3). The solvent was removed under reduced pressure and the crude material was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:3] to provide tetracyclic oxindole (**46**, 0.16 mmol, 82 mg, 80%). **[α]$^{23}_{D}$** = +95.0° (*c* 0.12, $CHCl_3$); **IR** (KBr) 2942, 2865, 1709, 1645, 1125, 1096 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7 Hz, 1H), 7.25 (t, *J* = 7 Hz, 1H), 7.02 (t, *J* = 7 Hz, 1H), 6.78 (d, *J* = 7 Hz, 1H), 6.04 (s, 1H), 5.64 (s, 1H), 3.93 (brm, 1H), 3.69 (t, *J* = 9 Hz, 1H), 3.45 (m, 1H), 3.24-3.18 (m, 4H), 3.07 (s, 1H), 2.81 (s, 3H), 2.41 (d, *J* = 4 Hz, 1H), 2.35 (s, 3H), 2.18 (m, 1H), 2.06 (m, 1H), 1.69-1.61 (m, 1H), 1.37-1.31 (m, 1H), 1.13-0.85 (m, 21H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 198.8, 177.9, 151.4, 141.9, 139.1, 127.3, 123.4, 122.6, 122.4, 106.9, 68.3, 64.1, 58.6, 55.3, 44.1, 42.9, 35.5, 30.1, 29.7, 26.3, 20.66, 18.1, 11.9; HRMS (ESI, m/z, relative intensity) calcd for $C_{30}H_{47}N_2O_3Si$ (M+H)+ = 511.3356, found 511.3347. This indicates the structures of the previous intermediates were correct.

Synthesis of pentacyclic enone oxindole (47) from enone oxindole (46)

To a solution of enone oxindole (**46**, 50 mg, FW = 510.78, 0.098 mmol) in a dioxane/water (6:1) mixture (7 mL) were added Na_2PdCl_4 (40 mol%, 0.039 mmol, 12 mg) and *tert*-butyl hydroperoxide (70% in water, 1.5 equivalents, 0.147 mmol) at rt and the mixture was stirred at 85 °C for approximately 6 h. After the mixture was cooled to rt, ice-cooled water (3 mL) and a saturated solution of aq $NaHCO_3$ (10 mL) were added to the mixture and this was followed by addition of EtOAc (50 mL). After separation, the aq layer was extracted with additional EtOAc (2 x 30 mL). The combined organic layers were washed with a saturated solution of aq $NaHCO_3$, then brine, and dried (K_2CO_3). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide the pentacyclic oxindole (**47**, 0.064 mmol, 22 mg, 65%). **[α]$^{23}_{D}$** = +184° (*c* 0.10, $CHCl_3$); **IR** (KBr) 2933, 1713, 1695, 1357, 1233 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.16 (td, *J* = 8, 1 Hz, 1H), 7.00 (dd, *J* = 8, 1 Hz, 1H), 6.86 (td, *J* = 8, 1 Hz, 1H), 6.73 (dd, *J* = 8, 1 Hz, 1H), 4.19 (t, *J* = 12 Hz, 1H), 3.94 (ddd, *J* = 12, 4, 1 Hz, 1H), 3.70 (m, 1H), 3.45 (brd, *J* = 6 Hz, 1H), 3.22 (s, 3H), 2.89 (brs, 1H),

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2.81 (s, 3H), 2.49 (d, *J* = 11 Hz, 1H), 2.37 (dd, *J* = 14, 8 Hz, 1H), 2.17 (s, 3H), 1.98 (m, 1H), 1.81 (m, 1H), 1.42-1.53 (m, 1H).; **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 196.0 (C), 177.7 (C), 155.4 (CH), 141.7 (C), 136.7 (C), 127.0 (CH), 121.7 (C), 119.8 (CH), 117.9 (CH), 106.9 (CH), 70.9 (CH_2), 62.3 (CH), 55.4 (C), 49.5 (CH), 41.6 (CH_2), 36.9 (CH), 34.4 (CH_3), 31.7 (CH_2), 26.7 (CH_3), 25.6 (CH_3), 22.4 (CH); This material was employed in a later experiment.

Procedure for the *N*$_b$-demethylation of oxindole (47) to provide (+)-isoalstonisine (35).

Oxindole (**47**, 5 mg, 0.014 mmol) was dissolved in dry 1,2-dichloroethane (3 mL) in a vessel that was sealed with screw cap. ACE-Cl (from a new bottle, 20 mg, 0.14 mmol) was added to the solution at 0 °C under argon. The reaction vessel was closed and was heated in an oil bath at 85-90 °C (external temperature) for 24 h with stirring. The mixture was then allowed to reach ambient temperature and the solvent was removed under vacuum. Distilled, dried methanol (5 mL) was added to the residue and the mixture was heated to reflux for 5 h with stirring. The solvent was removed in vacuo and distilled EtOAc was added to the residue and then cold aq 1 *N* NaOH (5 mL) was added to neutralize the HCl salt which had formed. The layers were separated and the aq layer was washed with EtOAc (3 x 5 mL). The combined organic layers were washed with brine until neutrality (pH = 7) and dried (K_2CO_3). After the solvent was removed under reduced pressure, the residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:3] to provide (+)-isoalstonisine (**35**, 4 mg, 80%). **[α]$^{23}_D$** = +201° (*c* 0.15, $CHCl_3$), [lit.[24] **[α]$^{23}_D$** = +207° (*c* 0.07, $CHCl_3$)]; **IR** (KBr) 3411 (weak), 2933, 1701, 1690, 1257 cm^{-1}, [lit.[24] **IR** (dry film) 1704 cm^{-1} (C=O, lactam, ketone)]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.25 (td, *J* = 8, 1 Hz, 1H), 7.13 (dd, *J* = 8, 1 Hz, 1H), 6.98 (td, *J* = 8, 1 Hz, 1H), 6.80 (dd, *J* = 8, 1 Hz, 1H), 4.24 (t, *J* = 11 Hz, 1H), 4.14 (ddd, *J* = 11, 4, 1 Hz, 1H), 3.99 (m, 1H), 3.73 (brd, *J* = 7 Hz, 1H), 3.22 (s, 3H), 3.11 (brt, *J* = 3 Hz, 1H), 2.58 (dd, *J* = 14, 2 Hz, 1H), 2.34 (m, 2H), 2.22 (s, 3H), 1.96 (brm, 1H), 1.47 (brdt, *J* = 12, 4 Hz, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 197.0 (C), 177.4 (C), 155.9 (CH), 142.3 (C), 137.5 (C), 127.7 (CH), 122.2 (CH), 121.8 (C), 120.6 (CH), 107.6 (CH), 67.6 (CH_2), 66.8 (CH), 57.1 (C), 56.8 (CH), 42.2 (CH_2), 37.6 (CH), 32.5 (CH_2), 26.3 (CH_3), 25.6 (CH_3), 23.7 (CH); The spectral data for (+)-isoalstonisine (**35)** was in excellent agreement to that reported by Kam *et al*.[24] This indicates the structures of the previous intermediates were correct.

Synthesis of (+)-isoalstonisine (35) by epimerization at C-7 of (+)-alstonisine (1).

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In a 10 mL screw-cap glass tube with a magnetic sitrrer, alstonisine (**1**, 7 mg, FW = 338.40, 0.021 mmol) and diisopropylethylamine (DIEA, 3 equivalents, 0.062 mmol, 8 mg) were placed into acetonitrile (5 mL). The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and allowed to run for 48 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide (+)-isoalstonisine (**35**, 0.018 mmol, FW = 338.40, 6 mg, 85%). *Note*: see the latter procedure for the complete characterization data of this oxindole.

Synthesis of (+)-alstonisine (1) by epimerization at C-7 of (+)-isoalstonisine (35).

In a 10 mL screw-cap glass tube with a magnetic sitrrer, (+)-isoalstonisine (**35**, 8 mg, FW = 338.40, 0.024 mmol) was placed into a pyridine-DCM (8:2, 5 mL) mixture. The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 100-110 °C [external temperature (or oil bath temperature)] and allowed to run for 60 h with vigorous magnetic stirring. The vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide (+)-alstonisine (**1**, 0.015 mmol, FW = 338.40, 5.6 mg, 70%). **$[\alpha]^{23}_D$** = +195° (*c* 0.2, EtOH) [literature: $[\alpha]^{23}D$ = +197° (c 1.0, EtOH)[14b] and $[\alpha]^{23}D$ = +200° (c 1.0, EtOH)[7]]; **IR** (KBr) 1692, 1643, doblets at 1616 and 1611 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7, 1 Hz, 1H), 7.64 (s, 1H), 7.36 (td, *J* = 7, 1 Hz, 1H), 7.32 (td, J = 7, 1 Hz, 1H), 6.89 (dd, *J* = 7, 1 Hz, 1H), 4.56 (t, *J* = 11 Hz, 1H), 4.29 (ddd, *J* = 11, 4, 1 Hz, 1H), 3.77 (brd, *J* = 7 Hz, 1H), 3.41 (m, 1H), 3.22 (s, 3H), 3.20 (m, 1H), 2.56 (dd, *J* = 13, 7 Hz, 1H), 2.28 (m, 1H), 2.26 (s, 3H), 2.20 (d, *J* = 13 Hz, 1H), 2.06 (brm, 1H), 1.67 (m, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 197.0 (C), 182.9 (C), 158.0 (CH), 144.4 (C), 129.6 (C), 128.4 (CH), 126.0 (CH), 123.7 (CH), 122.2 (C), 108.4 (CH), 68.7 (CH_2), 64.2 (CH), 57.3 (C), 56.7 (CH), 42.3 (CH_2), 37.4 (CH), 31.4 (CH_2), 26.6 (CH_3), 25.3 (CH_3), 24.6 (CH); This spectral

data and optical rotation were in excellent agreement with that of Wearing *et al*.[14b] and Elderfield *et al*.[7] This indicates the structures of the previous intermediates were correct.

Synthesis of (+)-N_a-demethylalstonisine (51) from (+)-alstonisine (1).

A solution of alstonisine (**1**, 17 mg, FW = 338.40, 0.05 mmol) and benzoylperoxide (>98% Aldrich, 0.1 mmol, 24 mg) in CH_2Cl_2 (3 mL) was heated in a sealed tube (the inside air was removed under vacuum and then filled with an argon atmosphere) for 24 h at 85 °C. After concentrating the reaction mixture under vacuum, a saturated solution of NH_3 (g) in methanol (8 mL) was added, and the mixture was stirred for 24 h at rt. After concentrating the reaction mixture under vacuum, a saturated aq solution of $NaHCO_3$ was added. The mixture was then extracted with EtOAc and the combined organic layers were washed with brine and dried (Na_2SO_4). The removal of the solvent under reduced pressure afforded a crude product, which was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 2:1] to provide (+)-N_a-demethylalstonisine (**51**, 0.033 mmol, FW = 324.37, 10 mg, 65%). $\mathbf{[\alpha]^{23}_D}$ = +176° (*c* 0.15, MeOH), [lit.[24]: not reported]; **IR** (KBr) 3260 (weak), 1703, 1689 cm^{-1}, [lit.[12]: not reported]; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.28 (dd, *J* = 7, 3 Hz, 1H), 7.68 (s, 1H), 7.31 (td, *J* = 6, 1 Hz, 1H), 7.24 (td, J = 6, 1 Hz, 1H), 6.92 (dd, *J* = 7, 3 Hz, 1H), 4.51 (t, *J* = 11 Hz, 1H), 4.25 (ddd, *J* = 10, 4, 2 Hz, 1H), 3.74 (brd, *J* = 6 Hz, 1H), 3.40 (m, 1H), 3.27 (brs, 1H), 2.63 (dd, *J* = 13, 7 Hz, 1H), 2.32 (ddd, *J* = 14, 6, 2 Hz, 1H), 2.30 (s, 3H), 2.23 (d, *J* = 12 Hz, 1H), 2.01 (brm, 1H), 1.65 (m, 1H); ^{13}**C NMR** (75.5 MHz, $CDCl_3$) δ 197.2 (C), 184.6 (C), 158.1 (CH), 141.4 (C), 129.9 (C), 128.5 (CH), 126.5 (CH), 123.7 (CH), 122.4 (C), 109.8 (CH), 69.1 (CH_2), 64.3 (CH), 57.8 (C), 56.6 (CH), 42.4 (CH_2), 37.5 (CH), 31.3 (CH_2), 25.3 (CH_3), 24.6 (CH); The spectral data (^{1}H and ^{13}C NMR) were in excellent agreement to that reported by Kam *et al*.[24] This indicates the structures of the previous intermediates were correct.

Synthesis of (+)-alstofoline (52) by N_b-formylation of (+)-alstonisine (1).

In a 10 mL screw-cap glass tube with a magnetic stir bar, oxindole (**1**, 10 mg, FW = 338.40, 0.029 mmol) and 2,2,2-trifluoroethyl formate (TFEF, 5 equivalents, 0.145 mmol, 19 mg, *free of formic acid, please see below for the preparation*) were placed into dry 1,2-dichloroethane (3 mL). The vessel was capped with a rubber septum and then the inside air was removed under

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vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 65 °C [external temperature (or oil bath temperature)] and allowed to run for 24 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and the mixture was allowed to cool to rt. The solvent was removed under vacuum. The residue was directly purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide alstofoline as a mixture of rotamers (**52**, 3:1 ratio by ^{1}H NMR, 0.026 mmol, FW = 366.41, 9.6 mg, 90%). **[α]^{23}$_D$** = +32.0° (*c* 0.10, $CHCl_3$), [lit[24]: **[α]^{23}$_D$** = +39.0° (*c* 0.21, $CHCl_3$)]; **IR** (KBr) 2945, 1713, 1705, 1651 cm^{-1}, [lit.[24] **IR** (dry film) 1706, 1662 cm^{-1}]; **^{1}H NMR Major conformer**,(300 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 7, 1 Hz, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 7.44 (td, *J* = 8, 1 Hz, 1H), 7.35 (td, *J* = 8, 1 Hz, 1H), 6.91 (dd, *J* = 7, 1 Hz, 1H), 4.97 (brd, *J* = 6 Hz, 1H), 4.50 (ddd, *J* = 10, 4, 1 Hz, 1H), 3.93 (t, *J* = 10 Hz, 1H), 3.84 (brs, 1H), 3.63 (td, *J* = 12, 6 Hz, 1H), 3.19 (s, 3H), 2.72 (dd, *J* = 13, 7 Hz, 1H), 2.56 (ddd, *J* = 13, 6, 2 Hz, 1H), 2.28 (s, 3H), 2.23 (m, 2H), 1.61 (m, 1H); **^{1}H NMR Minor conformer**,(300 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7, 1 Hz, 1H), 8.11 (s, 1H), 7.63 (s, 1H), 7.44 (td, *J* = 8, 1 Hz, 1H), 7.35 (td, *J* = 8, 1 Hz, 1H), 6.89 (dd, *J* = 7, 1 Hz, 1H), 4.33 (brd, *J* = 6 Hz, 1H), 4.27 (ddd, *J* = 10, 4, 1 Hz, 1H), 4.01 (t, *J* = 10 Hz, 1H), 4.53 (s, 1H), 3.63 (dt, *J* = 12, 6 Hz, 1H), 3.17 (s, 3H), 2.81 (dd, *J* = 13, 7 Hz, 1H), 2.46 (ddd, *J* = 13, 6, 2 Hz, 1H), 2.28 (s, 3H), 2.23 (m, 2H), 1.51 (m, 1H). The spectral data and optical rotation were in excellent agreement to that reported by Kam *et al*.[24] This indicates the structures of the previous intermediates were correct.

Preparation of 2,2,2-trifluoroethyl formate (TFEF).

In a 50 mL jacketed flask fitted with a reflux condenser and temperature probe, 2,2,2,-trifluoroethanol (12 g, 0.12 mol, 0.10 equivalents) was combined with >95% formic acid (23.2 g, 0.48 mol, 4.0 equiv). The mixture was then heated at an internal temperature of 80 °C for 18 h. The analysis of a sample by NMR spectroscopy taken after 18 h indicated a 1.4:1 ratio of trifluoroethanol/trifluoroethyl formate. The mixture was then subjected to fractional distillation through a 10 inch Vigreux column and the fraction boiling at 55-70 °C (1 atmosphere) was collected. The distillate contained a 70% yield of trifluoroethyl formate: **^{1}H NMR** (300 MHz, CDCl3) δ 8.10 (s, 1H, HC=O), 4.55 (q, 2H, CH_2). The spectral data were in excellent agreement with that reported in the literature.[40f, 41]

Synthesis of (-)-isoalstonoxine A (55) by acidic hydrolysis of (+)-isoalstonisine (35)

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Isoalstonisine (**35**, 6 mg, 0.018 mmol) was heated to reflux (in a round bottom flask with condenser) in a solution of 2 *N* aq HCl (5 mL) for 24 h. The solution was allowed to reach rt and then was brougth to *p*H = 7.5 with an ice-cold solution of 2 *N* NaOH very slowly. The solution which resulted was then extracted with $CHCl_3$ (3 x 10 mL). The extract was dried (Na_2SO_4) and the solvent removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 3:1 then EtOAc] to provide (-)-isoalstonoxine A (**55**, 0.014 mmol, FW = 328.41, 4.7 mg, 80%). **[α]$^{23}_{D}$** = –28.0° (*c* 0.10, $CHCl_3$); **IR** (KBr) 3361, 3248, 1708, 1690, cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (td, *J* = 8, 1 Hz, 1H), 7.16 (td, *J* = 8, 1 Hz, 1H), 7.07 (brd, *J* = 8 Hz, 1H), 6.85 (brd, *J* = 8 Hz, 1H), 4.01 (d, *J* = 8 Hz, 1H), 3.78 (dd, *J* = 12, 1 Hz, 1H), 3.64 (dd, *J* = 12, 1 Hz, 1H), 3.51 (m, 1H), 3.26 (brm, 1H), 3.20 (s, 3H), 2.71 (dd, *J* = 18, 6 Hz, 1H), 2.63 (dd, *J* = 18, 6 Hz, 1H), 2.44 (dd, *J* = 13, 2 Hz, 1H), 2.31 (dd, *J* = 12, 8 Hz, 1H), 2.23 (s, 3H), 1.90 (m, 1H), 1.61-1.77 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.5 (C), 179.1 (C), 143.8 (C), 138.2 (C), 127.85 (CH), 122.9 (CH), 122.3 (CH), 108.3 (CH), 66.5(CH), 65.4 (CH_2), 62.5 (CH), 58.1 (C), 48.5 (CH_2), 42.2 (CH_2), 41.8 (CH), 33.7 (CH_2), 31.6 (CH_3), 26.5 (CH_3), 26.2 (CH); The spectral data of (-)-isoalstonoxine A (**55)** were in excellent agreement with that of the natural product.[24] This indicates the structures of the previous intermediates were correct.

Synthesis of (-)-isoalstonoxine A (55) by epimerization at C-7 of (–)-alstonoxine A (56).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**56**, 5 mg, FW = 328.41, 0.015 mmol) and diisopropylethylamine (DIEA, 3 equivalents, 0.045 mmol, 6 mg) were placed into acetonitrile (4 mL). The reaction vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and was allowed to run for 48 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 3:1] to provide isoalstonoxine A (**55**, 0.010 mmol, FW = 328.41, 3.2 mg, 64%). *Note*: see the latter procedure for the complete characterization data of this oxindole.

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Synthesis of (–)-alstonoxine A (56) by epimerization at C-7 of (-)-isoalstonoxine A (55).

In a 10 mL screw-cap glass tube with a magnetic stirrer, oxindole (**55**, 6 mg, FW = 328.41, 0.019 mmol) was placed into a pyridine-CH_2Cl_2 (8:2, 4 mL) mixture. The vessel was capped with a rubber septum, and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 100-110 °C [external temperature (or oil bath temperature)] and was allowed to run for 60 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The solvent mixture was removed under vacuum. The residue was purified by flash column chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 3:1] to provide (-)-alstonoxine A (**56**, 0.015 mmol, FW = 328.41, 4.8 mg, 81%). $\mathbf{[\alpha]^{23}_D}$ = –40.0° (*c* 0.15, $CHCl_3$), [lit.[24]: $\mathbf{[\alpha]^{23}_D}$ = –34.0° (*c* 0.19, $CHCl_3$)]; **IR** (KBr) 3357, 3240, 1701, 1694, cm^{-1}, [lit.[24]: **IR** (dry film) 3390, 3288, 1694, cm^{-1}]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (brd, *J* = 8 Hz, 1H), 7.31 (td, *J* = 8, 1 Hz, 1H), 7.17 (td, *J* = 8, 1 Hz, 1H), 6.84 (brd, *J* = 8 Hz, 1H), 4.00 (dd, *J* = 12, 1 Hz, 1H), 3.86 (d, *J* = 7 Hz, 1H), 3.76 (dd, *J* = 12, 1 Hz, 1H), 3.22 (brm, 1H), 3.19 (s, 3H), 3.00 (m, 1H), 2.74 (dd, *J* = 18, 6 Hz, 1H), 2.69 (dd, *J* = 18, 6 Hz, 1H), 2.40 (dd, *J* = 12, 8 Hz, 1H), 2.19 (s, 3H), 2.09 (dd, *J* = 13, 2 Hz, 1H), 1.85 (m, 1H), 1.66 (m, 2H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 208.7 (C), 182.7 (C), 144.5 (C), 129.6 (C), 128.5 (CH), 125.4 (CH), 123.7 (CH), 108.7 (CH), 66.1(CH_2), 63.4 (CH), 61.9 (CH), 57.8 (C), 47.7 (CH_2), 41.9 (CH), 41.1 (CH_2), 33.6 (CH_2), 30.9 (CH_3), 26.7 (CH_3), 26.3 (CH); The spectral data were in excellent agreement to that reported by Kam *et al*.[24] This indicates the structures of the previous intermediates were correct.

Synthesis of (–)-macrogentine (57) from (-)-isoalstonoxine A (55).

In a 10 mL screw-cap glass tube with a magnetic stir bar, oxindole (**55**, 12 mg, FW = 328.41, 0.037 mmol) and acetaldehyde (20 equivalents, 0.73 mmol, 32 mg) were placed into absolute ethanol (3 mL) and dry $MgSO_4$ (2 equivalents, 0.074 mmol, 9 mg). The reaction vessel was capped with a rubber septum and then the inside air was removed under vacuum and replaced with argon. The septum was quickly removed and the screw-cap was tightly placed. The reaction mixture was heated at 80-85 °C [external temperature (or oil bath temperature)] and was allowed to run for 24 h with vigorous magnetic stirring. The reaction vessel was then removed from the oil bath and it was allowed to cool to rt. The reaction mixture was gravity filtered to remove $MgSO_4$. The filtrate was collected and the solvent was removed under

vacuum. The residue was purified by flash chromatography [silica gel (washed with pure EtOAc), EtOAc-hexanes (distilled both), 1:1] to provide (-)-macrogentine (**57**, 0.033 mmol, FW = 354.44, 11 mg, 90%). **[α]$^{23}_{D}$** = –27.0° (*c* 0.10, $CHCl_3$), [lit.[24]: **[α]$^{23}_{D}$** = –21.0° (*c* 0.15, $CHCl_3$)]; **IR** (KBr) 2957, 1708, 1702, 1210, 1104 cm^{-1}, [lit.[24]: **IR** (dry film) 1704 cm^{-1}]; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8, 1 Hz, 1H), 7.30 (td, *J* = 8, 1 Hz, 1H), 7.05 (td, *J* = 8, 1 Hz, 1H), 6.86 (dd, *J* = 8, 1 Hz, 1H), 4.93 (q, *J* = 6 Hz, 1H), 4.22 (dd, *J* = 12, 1 Hz, 1H), 3.87 (dd, *J* = 12, 1 Hz, 1H), 3.77 (d, *J* = 7 Hz, 1H), 3.56 (d, *J* = 3 Hz, 1H), 3.43 (m, 1H), 3.25 (s, 3H), 2.57 (dd, *J* = 15, 7 Hz, 1H), 2.50 (dd, *J* = 15, 7 Hz, 1H), 2.43 (dd, *J* = 12, 2 Hz, 1H), 2.30 (dd, *J* = 13, 6 Hz, 1H), 2.25 (s, 3H), 1.89 (ddd, *J* = 13, 10, 3 Hz, 1H), 1.76 (dd, *J* = 13, 7 Hz, 1H), 1.50 (d, *J* = 5 Hz, 1H), 1.33 (d, *J* = 6 Hz, 3H); **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 209.4 (C), 177.7 (C), 142.3 (C), 138.7 (C), 127.8 (CH), 123.9 (CH), 122.7 (CH), 107.6 (CH), 85.6 (CH), 68.8 (CH_2), 63.1 (CH), 60.5 (CH), 55.4 (C), 49.1 (CH_2), 39.6 (CH_2), 35.2 (CH), 31.2 (CH_3), 30.3 (CH_2), 28.5 (CH), 26.6 (CH_3), 20.2 (CH_3); The spectral data was in excellent agreement to that reported by Kam *et al*.[24] This indicates the structures of the previous intermediates were correct.

2. X-ray crystal data: (Please see SI for more details)

Single-crystal X-ray diffraction data on 20, 14, 19, and 23 were collected at 296, 273, 100, and 100 °K respectively. All data were collected using MoKα radiation (λ = 0.71073 Å) and a Bruker APEX 2 CCD area detector.

The 0.79 x 0.55 x 0.36 mm^3 crystal of **20** was monoclinic in space group $P2_1/n$ with unit cell dimensions *a* = 12.7298(8) Å, *b* = 9.9647(6) Å, *c* = 14.7212(9) Å, and β = 106.790(2)°. Data were 100% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 3.89. The asymmetric unit contains a single molecule.

The 0.46 x 0.17 x 0.09 mm^3 crystal of **14** was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions *a* = 6.8433(4) Å, *b* = 8.3450(4) Å, and *c* = 29.1138(13. Data were 100% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 5.59. The asymmetric unit contains a single molecule.

The 0.51 x 0.13 x 0.01 mm^3 crystal of **19** was monoclinic in space group $P2_1$ with unit cell dimensions *a* = 10.4533(9) Å, *b* = 6.9333(6) Å, *c* = 15.6135(12) Å, and β = 106.712(3)°. Data were 98.7% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 3.97. The asymmetric unit contains a single molecule along with a co-crystallized solvent (chloroform) molecule.

The 0.41 x 0.38 x 0.19 mm^3 crystal of **23** was triclinic in space group *P*-1 with unit cell dimensions *a* = 9.6047(6) Å, *b* = 12.5723(9) Å, *c* = 14.8500(13) Å, α = 104.090(4)°, β = 103.346(4)°, and γ = 109.298(3)°. Data were 98.6% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 1.76. The asymmetric unit contains two molecules.

Full information on data collection, refinement, and results of the x-ray studies are given in Tables A1 to A25.

Atomic coordinates for **14**, **19**, **20** and **23** have been deposited with the Cambridge Crystallographic Data Centre). CCDC reference numbers are 1547267 (**14**), 1547266 (**19**), 1547268 (**20**), and 1547269 (**23**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

Single-crystal X-ray diffraction data on compound **38** was collected using CuKα radiation and a Bruker Platinum-135 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil. The oil-coated crystal was mounted on a micro-mesh mount (Mitergen, Inc.) and transferred to the diffractometer and data collected at 150°K. The 0.102 x 0.065 x 0.011 mm^3 crystal was monoclinic in space group P 2_1, with unit cell dimensions a = 11.7475(3), b = 6.0992(1), c = 11.9622(3) Å, and β = 97.397(2)°. Data was 86.8% complete to 68.10° θ (~ 0.83 Å) with an average redundancy of 2.58. The final anisotropic full matrix least-squares refinement on F^2 with 219 variables converged at R1 = 3.40%, for the observed data and wR2 = 9.18% for all data. Atomic coordinates for **38** have been deposited with the Cambridge Crystallographic Data Centre) and the CCDC reference number is 1547265 (**38)**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

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Notes

The authors declare no competing financial interest.

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