Tetrahedron 89 (2021) 132150

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tandem vinylogous Mannich and hetero Diels-Alder reactions: Concise total synthesis of (±)-Alstoscholarisine E☆

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ARTICLE INFO

Article history:
Received 8 March 2021
Received in revised form
1 April 2021
Accepted 2 April 2021
Available online 22 April 2021

Keywords:
Total synthesis
Indole alkaloid
Vinylogous Mannich reaction
Intramolecular hetero Diels-Alder reaction
Suzuki reaction
Reductive aminal formation

ABSTRACT

The shortest synthesis to date of (±)-alstoscholarisine E was accomplished in 15.2% overall yield requiring only seven linear steps from commercially available reagents. The approach features a tandem vinylogous Mannich reaction and an intramolecular hetero Diels-Alder reaction to access the *cis*-oxahydroisoquinolone core. Following the coupling of this *cis*-oxahydroisoquinolone subunit with a 3-methylindole derivative via a Suzuki reaction, a novel tactic to induce the challenging diastereoselective reduction of the cyclic vinyl ether moiety was discovered. Completion of the synthesis was achieved using a new procedure we developed for iridium-catalyzed, reductive formation of aminals from tertiary lactams, thereby expanding the utility of tertiary amides and lactams as surrogates for iminium ions.

1. Introduction

One of the hallmarks of Alzheimer's disease, Huntington's disease, Parkinson's disease and other neurodegenerative disorders is the gradual loss of brain functions that are manifested in cognitive deficits and physical impairments resulting in significant healthcare challenges [1]. Although palliative treatments have been developed to alleviate some symptoms associated with these debilitating diseases, there are no effective treatments that prevent or reverse the progressive neuronal decline common to these conditions [2]. New disease-altering approaches to address these unmet medical needs are required, and one promising option that has recently emerged is neural stem cell (NSC) therapy [3,4]. Because stem cell proliferation can be controlled using small molecules, there is considerable interest in the discovery of novel compounds that regulate stem cells and might serve as leads to treat neurodegenerative processes [5].

As part of their efforts to identify biologically active natural products, Luo et al. discovered that the crude alkaloid extracts from the leaves of *Alstonia scholaris*, an Asian tree used in traditional medicines for the treatment of a range of ailments, stimulated adult hippocampal NCS proliferation [6]. Ensuing phytochemical investigations resulted in the identification of alstoscholarisines A–E (**1**–**5**), which provided enhanced NSC proliferation (10 μg/mL) relative to the total alkaloid extracts (30 μg/mL), and alstoscholarisine A (**1**) and E (**5**), respectively, are among the most potent compounds (Fig. 1). Additional investigations determined that **1** improves NSC sphere formation and promotes NSC differentiation and neuronal fate commitment. As part of their ongoing work to identify novel indole alkaloids from *Alstonia scholaris*, Pan et al. also isolated alstoscholarisines H–J (**6**–**8**) and reported their syntheses, although **6**–**8** exhibited no effect on NSC proliferation or PC12 cell differentiation [7].

Among these structurally related alkaloids, **1**–**5** comprise a similar pentacyclic framework containing a *cis*-fused oxahydroisoquinolone ring system (highlighted in blue), a subunit common to a number of indole alkaloids. Notably, the tetrahydropyran ring is bridged by the indole moiety via a cyclic aminal with the piperidine ring to establish the caged structure bearing five contiguous stereocenters. Alstoscholarisines A–E are differentiated by the stereochemistry at C-19 with **1** and **2** possessing an equatorial methyl group, whereas this methyl group is in an axial orientation in **3**–**5**. The structures also differ in substitution at the C-16 bridgehead center, which is fully substituted in **2**–**4** and bears an ester or carboxylic acid group. The related alkaloids **6**–**8** possess

☆ Dedicated to our friend and former colleague Guangbin Dong in recognition of his being a recipient of the Tetrahedron Young Investigator Award for 2021.

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https://doi.org/10.1016/j.tet.2021.132150
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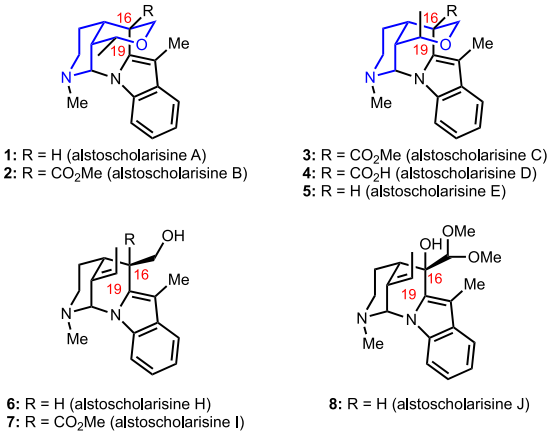


Fig. 1. Structures of alstoscholarisines A–E and H–J. The *cis*-fused oxahydroisoquinolone ring is highlighted in blue.

a similar structure with a ring-opened variant of the oxahydroisoquinolone ring.

The structural complexity of the alstoscholarisines **1**–**5** coupled with their interesting biological activity has motivated numerous synthetic endeavors and inspired varying strategies for forming the challenging *cis*-fused oxahydroisoquinolone and bridged aminal ring systems (Fig. 2) [8]. The synthesis of (±)–alstoscholarisine A was first achieved in 2016 by Bihelovic and Ferjancic using an approach that relied upon an enamine cascade initiated by condensation of amine **9** with aldehyde **10** to create the cyclic aminal **12**. After forming the tetrahydropyran to establish the bridged ring system, the synthesis of **1** was completed in 15 steps [9] in the longest linear sequence (LLS) from commercially available reagents [10]. A synthesis of (−)-alstoscholarisine A was reported in 2016 by Yang and coworkers [11]. Enantioselective construction of the fused indoyl lactam **13**, and subsequent elaboration led to the bridged tetrahydropyran **14**. Reductive amination of the aldehyde in **14** and partial reduction of the amide, followed by cyclization to form the bridged aminal ring completed the synthesis of (−)-**1** in 14-steps [9] (LLS) from commercially available reagents. Weinreb and coworkers developed a divergent strategy emanating from the *N*-sulfonylactam **15** that was applied to the syntheses of racemic alstoscholarisines A–E (**1**–**5**) [12,13]. In this approach, **15** was elaborated in a sequence that involved partial reduction of an intermediate lactam with DIBALH leading to the hemiaminal **16**. Treating **16** with trifluoroacetic acid cleaved the Boc-protecting group and triggered cyclization to produce the aminal ring in **17**. Subsequent formation of the bridged tetrahydropyran ring led to **1**–**5** by sequences requiring a total of 15–17 steps [9] (LLS) from commercially available starting materials.

Most recently, Liao and coworkers reported the enantioselective syntheses of **1** and **5** from a mixture of diastereomeric *cis*- and *trans*-oxahydroisoquinolones **18** and **19a,b** [14]. Elaboration of **18** by a Suzuki reaction gave **20** and stereoselective hydrogenation of the enol ether moiety led to **22**. The bridged aminal ring was formed via partial reduction of the lactam in **23** with tributyltin hydride in the presence of Tf_2O, followed by reductive *N*-methylation in a two-step, one-pot sequence that completed the synthesis of alstoscholarisine A (**1**) in 12 steps [9] (LLS) from commercially available materials. Toward alstoscholarisine E (**5**), epimerization of **19b** to give the corresponding *cis*-oxahydroisoquinolone and separation from **19a** was first required prior to the Suzuki coupling that would furnish **21**. The ensuing hydrogenation to provide **23** was only modestly selective, giving a mixture (2.2:1) of C-16 diastereomers. Then as before, the bridged aminal ring was formed

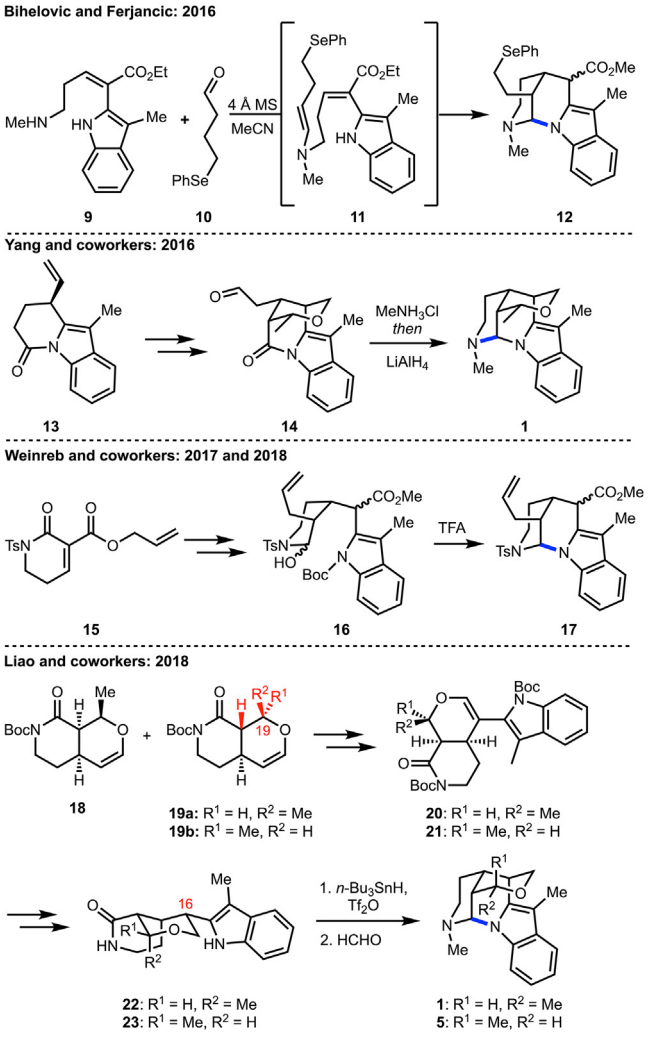
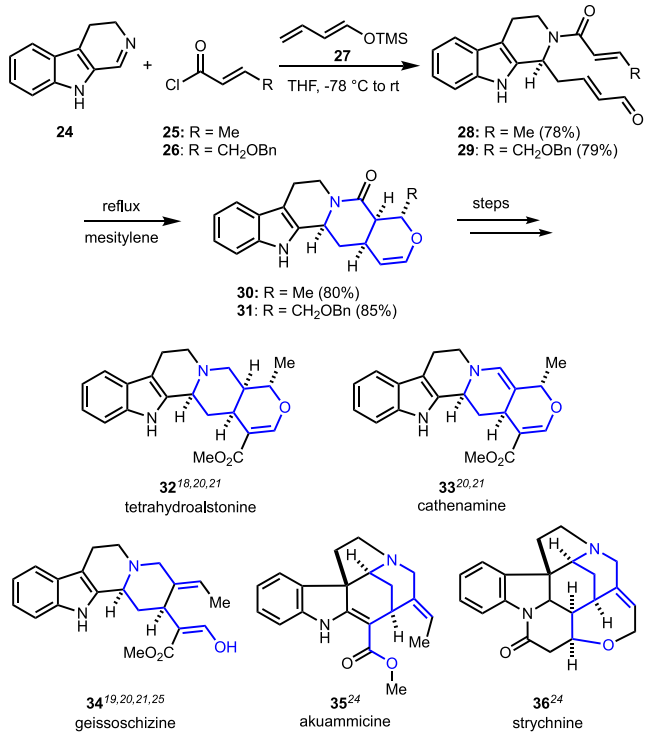


Fig. 2. Prior strategies for forming the bridging aminal ring of alstoscholarisines A-E.

via partial reduction of the lactam in **23** followed by reductive *N*-methylation to complete the synthesis of **5** in 13 steps [9] (LLS) from commercially available reagents.

We have had a longstanding program directed toward developing novel approaches for the syntheses of indole and other alkaloids [15,16]. Indeed, our interest in the heteroyohimboid alkaloid tetrahydroalstonine (**32**) led to the development of an intramolecular hetero Diels-Alder reaction to construct *cis*-fused oxahydroisoquinolones [15,17–22] and to the discovery and development of the vinylogous Mannich reaction [23]. In particular, we found that the vinylogous Mannich reactions of trimethylsilyloxydiene **27** with the readily available dihydrocarboline **24** in the presence of acyl chlorides **25** and **26** provided the heterodienes **28** and **29** (Scheme 1) [20–22]. Upon heating, **28** and **29** underwent intramolecular hetero Diels-Alder reactions to deliver the *cis*–fused oxahydroisoquinolones **30** and **31**, thereby enabling remarkably efficient access to various indole alkaloids **32**–**36** [18–21,24,25].

With this as background, we recognized that a tandem vinylogous Mannich reaction and an intramolecular hetero Diels-Alder reaction to form *cis*–fused oxahydroisoquinolones could be applied in the design of a concise approach to the alstoscholarisine alkaloids. At the outset of our work, the synthesis of alstoscholarisine E had not yet been achieved. Accordingly, we focused on the total synthesis of (±)–alstoscholarisine E (**5**), which we recently

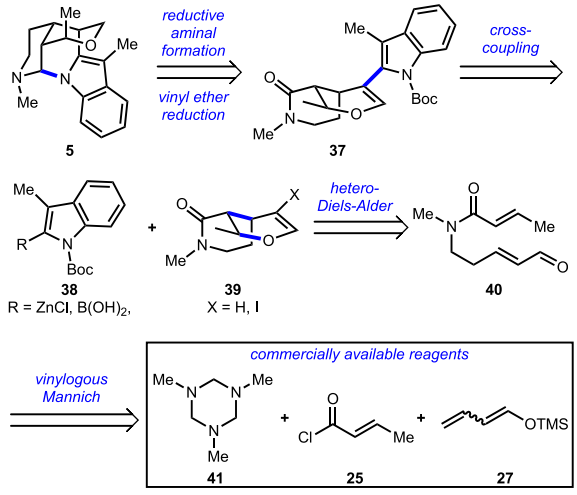


Scheme 1. General strategy for alkaloid synthesis via *cis*-fused oxahydroisoquinolones.

disclosed [26], and we now report the details of those studies.

2. Results and discussion

The retrosynthetic analysis of our convergent approach to (±)-alstoscholarisine E (**5**) is presented in Scheme 2. The final stage of the synthesis features transformation of the advanced intermediate **37** into **5** via stereoselective reduction of the enol ether group in **37**, followed by partial reduction of the tertiary lactam and spontaneous cyclization of the intermediate iminium ion to form the bridging aminal ring in **5**. The synthesis of **37** requires a Negishi or Suzuki cross-coupling reaction to join the *cis*-oxahydroisoquinolone **39** (X = I) with a 3-methylindole derivative such as **38** [R = ZnCl, $B(OH)_2$]. Based upon our previous work, we



Scheme 2. Retrosynthetic analysis of alstoscholarisine E.

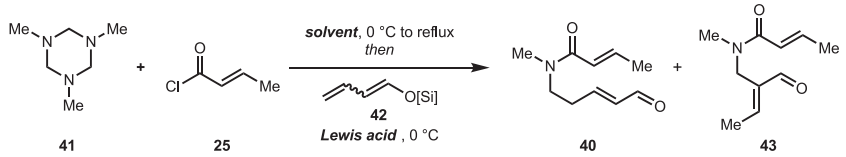
anticipated that the *cis*-oxahydroisoquinolone **39** (R = H) would be accessible via the intramolecular hetero Diels-Alder reaction of heterodiene **40**, which would be prepared via a vinylogous Mannich reaction using commercially available hexahydrotriazine **41**, crotonyl chloride (**25**), and trimethylsilyloxybutadiene **27**. Treating hexahydrotriazines such as **41** with an acyl chloride is known to induce fragmentation enabling nucleophilic capture with a variety of nucleophiles [27–30], including enol ethers in modest yield [28], but we are not aware of any such process involving a nucleophilic diene like **27**.

In accord with this plan, the first step in the synthesis of alstoscholarisine E (**5**) required the vinylogous Mannich reaction of **25**, **27**, and **41** to deliver the heterodiene **40**. Although a superficially straightforward transformation, considerable experimentation was required to optimize this process (Table 1). Acyl chloride-initiated fragmentations of hexahydrotriazines similar to **41** and capture of the intermediate *N*-α-chloroalkylamides have typically been performed in dichloromethane at 0 °C [27–31]. In analogy with these findings, we discovered that treating **41** with crotonyl chloride (**25**) at 0 °C, followed by heating the resulting mixture under reflux prior to adding trimethylsilyloxydiene **27** (ca 9:1 *E*/*Z*) at 0 °C delivered **40** in 29% yield together with the regioisomer **43** in 5% yield (entry 1). We queried whether a Lewis acid might be beneficial, but the presence of TMS–OTf offered no improvement (entry 2). Exchanging dichloromethane with acetonitrile provided lower yields in the absence of a Lewis acid (entry 3), but in the presence of TMS–OTf (0.1 eq), **40** and **43** were obtained in 62% and 10% yield, respectively. Slightly lower yields were obtained when the reaction was performed in dichloroethane, but yields were greatly diminished in THF and DMF (entries 5–7). Because including TMS–OTf in the reaction was important, other Lewis acids were evaluated. Although ethylaluminum dichloride ($EtAlCl_2$) was nearly as effective as TMS–OTf (entry 8), boron trifluoride etherate was clearly inferior (entry 9). Altering the stoichiometry of trimethylsilyloxydiene **27** relative to hexahydrotriazine **41** also had little effect (entries 10,11).

This simple operation delivered a mixture (6.2:1) of the isomeric heterodienes **40** and **43** by a process that is considerably shorter than our previous synthesis of a related heterodiene (Table 1, entry 4) [17]. However, based upon our varied experiences with vinylogous Mannich reactions [23], we were somewhat surprised by the formation of significant amounts of **43**, which results from reaction at the more hindered α-carbon atom of the silyl enol ether **27**. We wondered whether reaction at this carbon atom might be suppressed by increasing the steric bulk of the silyl group, thereby improving the ratio of **40** and **43**. Consistent with this hypothesis, when *tert*-butyldimethylsilyloxydiene **42** (R = TBS, 100% *E*) [32] was used as the nucleophile, **40** was obtained in 63% yield, and the ratio of isomers improved to 10.5:1 (Table 1, entry 12). Moreover, further increasing the size of the silyl group by using the known triisopropylsilyloxydiene **42** (R = TIPS, 100% *E*) [33] furnished **40** in 68% yield together with the isomeric diene **43** in a mere 2% yield (Table 1, entry 13). These improvements notwithstanding, we continued the synthesis using commercially available trimethylsilyloxydiene **27** and were thus able to prepare **40** in single step and on a gram scale to set the stage for the intramolecular hetero Diels-Alder reaction.

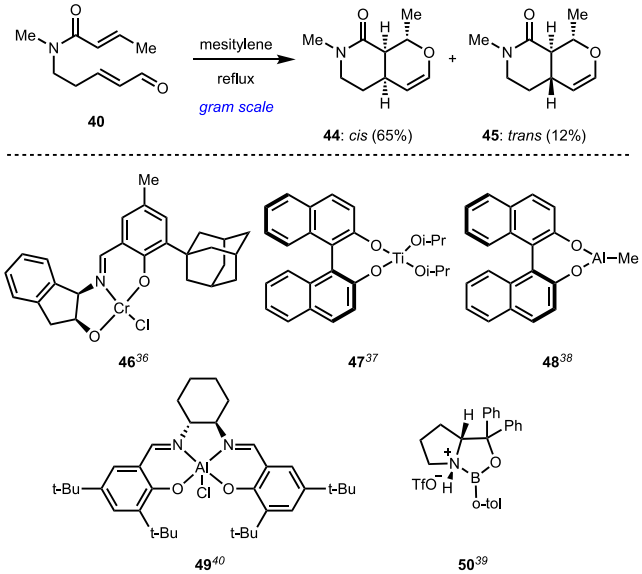
In accord with our previous studies [17,18,22], **40** underwent cyclization when heated under reflux in mesitylene to afford an easily separable mixture (5.4:1) of the *cis*- and *trans*-fused cycloadducts **44** and **45** in 77% combined yield (Scheme 3) [21]. Having formed the racemic *cis*-oxahydroisoquinolone **44**, we queried whether the cycloaddition might be catalyzed by a chiral Lewis acid to provide **44** in enantioenriched form. Given that both the diene and dieneophile in **40** are electron deficient and contain a Lewis-

Table 1
The vinylogous Mannich reaction of 1,3,5-trimethylhexahydrotriazine (**41**).



entry	[Si] (equiv)	Lewis acid (equiv)	solvent	yield **40** (%)[a]	yield **43** (%)[a]
1	TMS (4)	none	DCM	29	5
2	TMS (4)	TMSOTf (0.1)	DCM	29	6
3	TMS (4)	none	MeCN	7	3
4	TMS (4)	TMSOTf (0.1)	MeCN	62[b]	10[b]
5	TMS (4)	TMSOTf (0.1)	DCE	57	12
6	TMS (4)	TMSOTf (0.1)	THF	13	3
7	TMS (4)	TMSOTf (0.1)	DMF	0	0
8	TMS (4)	$EtAlCl_2$ (0.2)	MeCN	57	12
9	TMS (4)	$BF_3{\cdot}OEt_2$ (1.0)	MeCN	29	5
10	TMS (6)	TMSOTf (0.1)	MeCN	58	9
11	TMS (2.2)	TMSOTf (0.1)	MeCN	56	11
12	TBS (4)	TMSOTf (0.1)	MeCN	63 [b]	6 [b]
13	TIPS (4)	TMSOTf (0.1)	MeCN	68 [b]	2 [b]

[a] Yield determined by ^{1}H NMR spectroscopy with internal standard.
[b] Isolated yield determined after chromatographic purification.



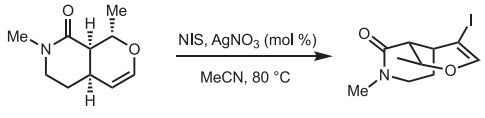
Scheme 3. Intramolecular hetero Diels—Alder reaction of heterodiene **40**.

basic carbonyl group that might interact with the catalyst, we were cognizant that realization of this goal was a significant challenge. Many of the known methods for promoting hetero Diels-Alder reactions with chiral Lewis acids utilize substrates that are more electronically predisposed to cyclization [34,35]. Moreover, we had previously tried, without success, to induce Lewis acid catalyzed [4 + 2] cycloadditions with substrates similar to **40** [17]. Undeterred by these precedents, we evaluated the chiral Lewis acids **46**–**50** [36–40], which are known to promote enantioselective Diels-Alder and hetero Diels-Alder reactions. However, treating **40** with each of these catalysts following the reported protocols [36–40] in a number of experiments failed to provide detectable quantities of cycloadducts **44** and **45**, even at elevated temperatures ranging from 25 to 140 °C. We were therefore relegated to using racemic **44** to complete the synthesis of (±)-alstoscholarisine E.

To set the stage for the cross-coupling of the cycloadduct **44** with a suitable indole derivative, it was first necessary to regioselectively introduce a halogen atom onto the enol ether moiety of **44**. Previous reports with structurally related glycals show that addition of *N*-iodosuccinimide (NIS) to enol ethers occurs readily to generate iodo succinimide adducts, whereas in the presence of catalytic amounts of silver nitrate (20 mol %), the vinyl iodide is produced in high yield [41,42]. In the event, treating **44** with NIS and silver nitrate (10–35 mol %) furnished **45** as the sole isolable product in yields ranging from 55 to 83% (Table 2). Lower quantities of silver nitrate generally provided improved yields, and the best results were obtained using 10 mol % of silver nitrate (entry 4).

We first explored Negishi couplings as a simple and direct approach to metallate and couple the indole **46** with the vinyl iodide **45** in a single operation. Following treatment of the known 3-methylindole **46** [43] with *tert*-butyllithium and subsequent transmetalation, the zincated intermediate **47** was subjected to several standard conditions for performing Negishi couplings (Table 3) [44]. Direct cross-coupling using catalytic $Pd(PPh_3)_4$, $Pd(PPh)_2Cl_2$, or $Pd(OAc)_2$ did not give detectable amounts of **37**, even when heated to 125 °C (entries 1–3). Subjecting **37** and **45** to a combination of $Pd(dba)_2$ and P(*o*-fur)$_3$ also failed to deliver **37** (entry 4). Use of RuPhos with either $Pd(dba)_2$ or $Pd(OAc)_2$ according

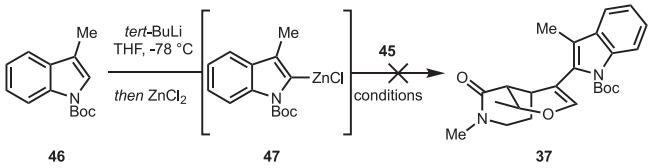
Table 2
Synthesis of the vinyl iodide **45**.



entry	$AgNO_3$ (mol %)	yield (%)[a]
1	35	55
2	30	67
3	20	79
4	10	83

[a] Isolated yields determined after chromatographic purification.

Table 3
Attempts at Negishi coupling of **45** and **47**.



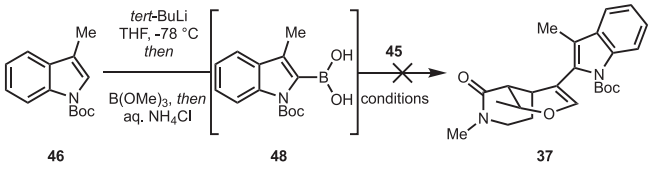
entry	catalyst	ligand	solvent	T (°C)
1	$Pd(PPh_3)_4$	none	THF	rt to 125
2	$Pd(PPh_3)_2Cl_2$	none	DMAc	80
3	$Pd(OAc)_2$	none	DMAc	80
4	$Pd(dba)_2$	P(*o*-fur)$_3$	THF	rt to 125
5	$Pd(dba)_2$	RuPhos	THF	80
6	$Pd(OAc)_2$	RuPhos	DMAc	80

Quantifiable formation of **37** was not observed via LCMS of the crude reaction mixtures.

to a protocol reported by Buchwald was also unsuccessful (entries 5,6) [45]. Each of these reactions provided significant quantities of returned **45,** and the only byproducts detected were **44** and 3-methylindole.

We then turned to the Suzuki-Miyaura reaction of **45** with the known indole boronic acid **48** as an alternative strategy [43,46]. However, competitive protodeboronation of 2-heterocyclic boronic acids is a well-known problem in Suzuki cross-couplings [47]. For example, **48** was reportedly only stable if kept in a diethyl ether solution after an aqueous work up, yet high yields were achieved in a Suzuki coupling with a related vinyl halide [46]. Encouraged by this report, we attempted a slightly modified protocol, wherein a solution of **46** in THF at −78 °C was treated with *tert*-butyllithium, followed by rapid addition of trimethyl borate (Table 4). After quenching the reaction mixture with a saturated solution of aqueous ammonium chloride, analysis (^{1}H NMR) revealed that the crude boronic acid **48** was obtained in near quantitative yield. Because of its instability, we tried to directly couple crude **48** with

Table 4
Suzuki-Miyaura coupling of **45** and **48**.



entry	**46** (equiv)	conditions	yield[a] (%)
1	1.2	$Pd(PPh_3)_4$ (10 mol %), $NaHCO_3$ THF/H_2O (2:1), 80 °C	0[b]
2	1.2	$Pd(OAc)_2$ (10 mol %) SPhos (12 mol %)Cs_2CO_3 dioxane/H_2O (5:1), 80 °C	0[b]
3	3	SPhos Pd G2 (5 mol %) K_3PO_4 PhMe/H_2O, 60 °C	18
4	4	SPhos Pd G2 (5 mol %) K_3PO_4 PhMe/H_2O, 60 °C	54
5	5	SPhos Pd G2 (5 mol %) K_3PO_4 PhMe/H_2O, 60 °C	51
6	4	SPhos Pd G2 (10 mol %) K_3PO_4 PhMe/H_2O, 60 °C	79

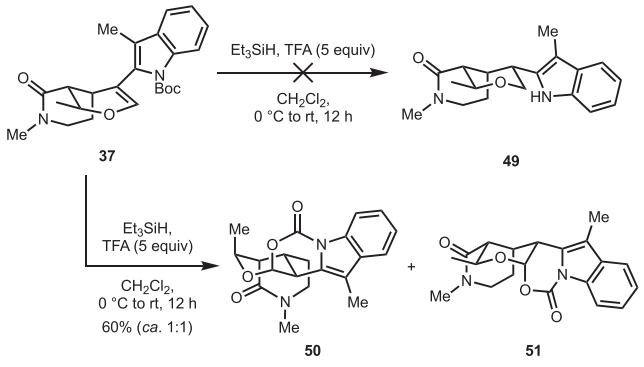
[a] Isolated yields determined after chromatographic purification.
[b] Quantifiable formation of **37** was not observed via LCMS of the crude reaction mixture.

the vinyl iodide **45** under several standard conditions (Table 3, entries 1,2), but no **37** was isolated.

We were aware that Buchwald and coworkers had overcome the challenges associated with cross-couplings of 2-heterocyclic boronic acids related to **48** using palladium precatalysts such as SPhos Pd G2 that are rapidly activated under mild conditions and exhibit high catalytic activity [48–50]. Indeed, contemporaneous with our efforts, Liao and coworkers reported a similar cross-coupling in their synthesis of (−)-alstoscholarisines A and E [14]. However, when we tried to apply the protocol reported by Liao using three equivalents of indole **46** and SPhos Pd G2 (5 mol %), the coupled product **37** was isolated in only 18% yield (entry 3). Increasing the number of equivalents of indole **46** led to improved yields (entries 4,5). Eventually we discovered that increasing the loading of SPhos Pd G2 to 10 mol % and using four equivalents of indole **46** delivered **37** in 79% yield on a gram scale (entry 6).

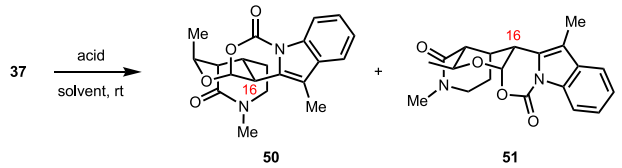
With **37** in hand, the stereoselective reduction of vinyl ether **37** was investigated. Although we had originally considered catalytic hydrogenation as a possible option, the related work of Liao and coworkers confirmed our concern regarding the lack of stereoselectivity of such a process [14]. We favored an alternative approach that would involve the diastereoselective, axial protonation of the enol ether moiety in **37** from the less hindered face, followed by hydride reduction of the intermediate carbocation to give **49** (Scheme 4). Toward this goal, a solution of oxahydroisoquinolone **37**, triethylsilane, and trifluoroacetic acid (TFA) (5 equiv) in dichloromethane was stirred for 12 h, but the desired deprotected, reduction product **49** was not observed. Rather, an unexpected mixture (ca. 1:1) containing two major products, which were tentatively assigned as being the two bicyclic acetals **50** and **51**, was isolated in 60% combined yield (Scheme 4). Although protonation of the enol ether occurred as anticipated, it was not stereoselective, and the intermediate carbocation was not captured by hydride, but rather by rapid cyclization with the *N*-carbamate group on the indole ring to give an acyloxy acetal that was stable to ionic reduction in the presence of TFA.

Despite the fact that the ionic reduction had not occurred as predicted, we were undeterred and explored this process further. Surprised by the rapid cyclization of the *tert*-butyl carbamate in the presence of acid, the concentration of TFA was increased (15 equiv) to assess whether removal of the Boc-protecting group might be faster. However, these conditions led to even more rapid cyclization and delivered a mixture (ca. 3.3:1) of the acyloxy acetal diastereomers **50** and **51** in 96% combined crude yield (Table 5, entry 1). This experiment suggested protonation and cyclization preferentially led to the undesired stereochemistry at *C*-16 in **50**. Furthermore, the results of the experiment depicted from Scheme 4 suggested that the acyloxy acetals might undergo equilibration



Scheme 4. Attempted ionic reduction of 37.

Table 5
Acid mediated acyloxy acetal formation from **37**.



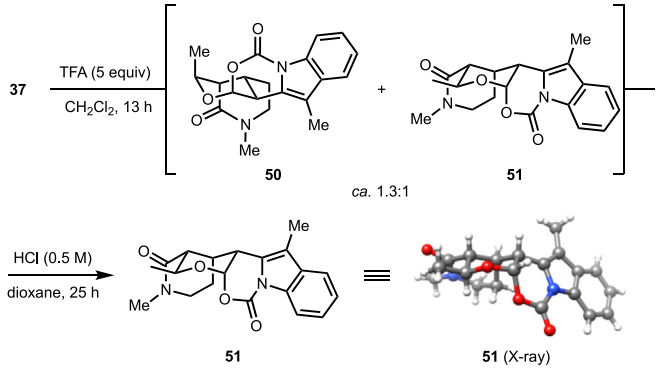
entry	acid/solvent	time (h)	yield (%)[a] (**50**:**51**)[b]
1	TFA (15 equiv)/CH_2Cl_2	1.5	96[c] (3.3:1)
2	HCl (2 M)/dioxane	3	59 (0:1)
3	HCl (1 M)/dioxane	5	69 (0:1)
4	HCl (0.4 M)/dioxane	31	77 (0:1)

[a] Isolated yields determined after chromatographic purification.
[b] The ratio of **50**:**51** was determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] The yield was determined after flash chromatography, but the products were contaminated with small amounts of impurities (see Supporting Information).

under the reaction conditions. Accordingly, we turned to other acids in hopes of achieving a stereoselective process that favored formation of **51**. Gratifyingly, when oxahydroisoquinolone **37** was treated with a solution of HCl (2 M) in dioxane, **51** was isolated in 59% yield as a single diastereomer (entry 2); the structure of **51** was established by X-ray crystallography [51]. Because loss of some of the Boc-group from **37** was observed (LCMS analysis) under these conditions, the concentration of HCl was reduced (1 M), and **51** was obtained in 69% yield as a single diastereomer (entry 3). Further reducing the concentration of HCl (0.4 M) and extending the reaction time to 31 h delivered **51** in 77% yield (entry 4).

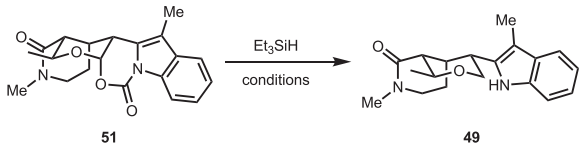
Suspecting that stereochemical outcome of the cyclization may have resulted from equilibration of the acyloxy acetal **50**, we performed an exploratory experiment to test this hypothesis. A solution of oxahydroisoquinolone **37** in dichloromethane was treated with TFA (5 equiv), and a mixture of diastereomeric acyloxy acetals **50** and **51** (ca. 1.3:1) was observed (^{1}H NMR analysis) (Scheme 5). This crude mixture was dissolved in dioxane containing HCl (0.5 M), and after stirring for 25 h, only **51** was observed. Because we did not determine the yield in this preliminary experiment, we cannot be certain that **50** was not lost to some unknown decomposition pathway rather than converted by equilibration to **51**. However, we presently believe that the results from this experiment and those gathered in Table 5 suggest that **51** is the thermodynamically favored product.

Having secured the correct stereochemistry at the *C*-16 center in



Scheme 5. Equilibration of a mixture of acyloxy acetal diastereomers.

Table 6
Reduction of the bicyclic acyloxy acetal **51**.



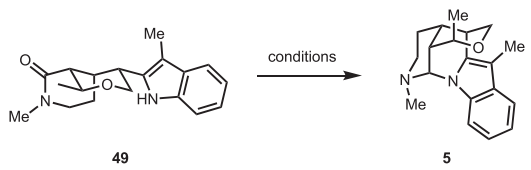
entry	conditions	yield (%)
1	$TiCl_4$ (20 equiv), CH_2Cl_2, −78 °C to rt	RSM[a]
2	TMSOTf (5 equiv), MeCN, −40 °C to rt	RSM[a]
3	$Sc(OTf)_3$ (1.5 equiv), CH_2Cl_2, 0 °C to rt	RSM[a]
4	$BF_3 \cdot OEt_2$ (10 equiv), CH_2Cl_2, 0 °C	RSM[a]
5	$EtAlCl_2$, CH_2Cl_2, −40 to 0 °C	97[b]

[a] Quantifiable formation of **49** was not detected via LCMS of the crude reaction mixture and only returned starting material (RSM) was observed.
[b] Isolated yield determined after chromatographic purification.

51, it was necessary to induce the reductive opening of the bicyclic acyloxy acetal. Triethylsilane in the presence of Lewis acids such as $TiCl_4$, TMS−OTf, $Sc(OTf)_3$, and $BF_3 \cdot OEt_2$ has been routinely used to reduce structurally related bicyclic lactone acetals, but applying these conditions to **51** only returned starting material (Table 6, entries 1–4) [52–54]. We eventually discovered that treating **51** with triethylsilane in the presence of excess $EtAlCl_2$ (7 equiv) resulted in clean reductive opening at the anomeric carbon atom and subsequent decarboxylation to provide **49** in 97% yield. Incomplete conversion was observed when fewer equivalents of $EtAlCl_2$ were used. The high diastereoselectivity achieved in this novel sequence of acyloxy acetal formation and reduction is notable given that a two-step process for removing the Boc-protecting group and hydrogenation of a similar indolyl oxahydroisoquinolone in Liao's synthesis of (−)-alstoscholarisine E proceeded with little selectivity [14].

To complete the synthesis of alstoscholarisine E (**5**), all that remained was the partial reduction of the lactam moiety of **49** followed by cyclization to form the bridging aminal ring. Related partial reduction strategies using DIBALH, Schwartz reagent [55], or Tf_2O in the presence of tributyltin hydride are known and were applied in prior syntheses of the alstoscholarisines [12–14] and some aspidosperma alkaloids [56,57], but applying these conditions to the indolyl oxahydroisoquinolone **49** failed to deliver significant quantities of **5** [26]. Hydrosilylation is another technique to induce partial reduction of amides and has recently emerged as a useful tactic for the reductive refunctionalization of amides via C–C bond formation [58–60]. However, lactam hydrosilylation followed by capture of the intermediate *N*,O-acetal with a nitrogen atom to generate an aminal was unknown, so we decided to evaluate the feasibility of extending reductive amide refunctionalizations to C–N bond formation. A preliminary experiment following a procedure reported by Buchwald for effecting the partial reduction of amides to aldehydes using Ph_2SiH_2 delivered only trace quantities of alstoscholarisine E (**5**) (Table 7, entry 1) [61]. We then discovered that treating **49** with 1,1,3,3-tetramethyldisiloxane (TMDS) and $Ti(O\textit{i}\text{-}Pr)_4$ at room temperature according to a protocol developed by Lemaire produced **5** in 36% yield, and when this reaction was heated at 50 °C, **5** was isolated in 56% yield (entries 2,3) [62]. These results were encouraging, but the reactions required excess amounts of $Ti(O\textit{i}\text{-}Pr)_4$, so we sought a superior method. We thus turned to a procedure disclosed by Nagashima using a catalytic amount of Vaska's complex (2 mol %) in toluene and obtained **5** in 56% yield (entry 4) [63]. Upon switching the solvent to dichloromethane, alstoscholarisine E was obtained in 77% yield (entry 5).

Table 7
Completion of the synthesis of (±)-alstoscholarisine E via lactam hydrosilylation and aminal formation.



49 5

entry	conditions	yield (%)
1	Ph_2SiH_2, Ti(O*i*-Pr)$_4$, THF, 50 °C	trace[a]
2	TMDS, Ti(O*i*-Pr)$_4$, PhMe, rt	36 [b]
3	TMDS, Ti(O*i*-Pr)$_4$, PhMe, 50 °C	56[b]
4	TMDS, IrCl(CO)$(PPh_3)_2$, PhMe, rt	56[c]
5	TMDS, IrCl(CO)$(PPh_3)_2$, CH_2Cl_2, rt	77[b]

[a] Small, non-quantifiable amounts of **5** were observed in the LCMS of the crude reaction mixture.
[b] Isolated yield after chromatographic purification.
[c] Yield determined by ^{1}H NMR spectroscopy with an internal standard.

Although partial reduction of amides using Vaska's complex and TMDS followed by nucleophilic trapping of the intermediate is known [64–69], to our knowledge the conversion of **49** to **5** represents the first example in which the intermediate is captured by a nitrogen nucleophile to generate an aminal. Accordingly, this represents a new and mild protocol for the iridium-catalyzed reductive aminal formation from tertiary lactams and amides that might be useful for the late-stage formation of other aminals.

3. Summary and conclusion

In summary, we have completed a concise and efficient synthesis of (±)-alstoscholarisine E (**5**) that proceeds in 15.2% overall yield and requires only seven chemical steps (LLS) from commercially available reagents. As such, it is considerably shorter than previous syntheses of structurally related alstoscholarisines. The approach features a number of interesting transformations. In particular, the synthesis commences with a unique variant of a tandem vinylogous Mannich reaction and an intramolecular hetero Diels-Alder reaction to deliver the *cis*-oxahydroisoquinolone **44** in just two steps. The challenging coupling of *cis*-oxahydroisoquinolone and indole subunits was achieved by a Suzuki reaction catalyzed by a precatalyst described by Buchwald. The stereochemistry at the *C*-16 bridging carbon atom was set by a novel, yet unplanned, sequence involving stereoselective, acid-mediated cyclization of the Boc-carbamate of **37** onto the vinyl ether moiety to furnish an acyloxy acetal that was converted to **49** by Lewis-acid promoted reduction and decarboxylation. To complete the synthesis of **5,** a new method for the iridium-catalyzed reductive aminal formation from a lactam was invented that may be more generally useful for late-stage formation of aminals from tertiary lactams and amides.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

We are grateful to the Robert A. Welch Foundation (F-0652) for funding. We also thank the UT Austin Mass Spectrometry Facility for high-resolution mass spectral data, the UT Austin X-ray diffraction lab for crystallographic data, and the NIH (Grant Number 1 S10 OD021508-01) for funding the Bruker AVANCE III 500 NMR spectrometer used for characterization of synthetic intermediates.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132150.

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