RESEARCH ARTICLE

A Divergent Synthetic Route to the Vallesamidine, Strempeliopine and Schizozygine Alkaloids: Total Synthesis of (+)-Vallesamidine and (+)-14,15-Dehydrostrempeliopine

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Dedication ((optional))

Abstract: The total synthesis of representative members of the Schizozygine alkaloids (+)-vallesamidine and (+)-14,15-dehydrostrempeliopine were completed from a late stage divergent intermediate. The synthesis took advantage of efficient nitro group reactions with the A/B/C ring skeleton constructed concisely in gram scale through an asymmetric Michael addition, nitro-Mannich/lactamisation, Tsuji-Trost allylation and intramolecular C-N coupling reaction. Other key features of the synthesis are a novel [1,4]-hydride transfer/Mannich type cyclisation to build ring E and a diastereoselective ring closing metathesis reaction to construct ring D. This gave access to a late stage C-14,15 alkene divergent intermediate that could be simply transformed into (+)-vallesamidine, (+)-14,15-dehydrostrempeliopine and potentially other schizozygine alkaloids and unnatural derivatives.

Introduction

Vallesamidine (**1**) and strempeliopine (**2**) are monoterpene indole alkaloids isolated from *Vallesia dichotoma* Ruiz *et* Pav[1] and *Strempeliopsis strempelioides* K Schum[2] respectively, and are structurally related to similar, but more complex, schizozygine alkaloids **3**-**5**[3] that contain an additional C-14,15 alkene and oxygenated aromatic cores (Figure 1). Their potential bioactivities[4] and highly fused, polycyclic ring skeletons have attracted many efforts towards their total synthesis. Currently, the total syntheses of schizozygine alkaloids **3**-**5** have not been reported,[5] but the total synthesis of vallesamidine (**1**)[6] and strempeliopine (**2**)[7] have been completed. Heathcock's ingenious landmark racemic synthesis of vallesamidine (**1**) was completed in 8 steps in 19% overall yield.[6a,b] Asymmetric variants have relied upon formal syntheses[6c,d] from this, or new approaches[6e,f,h] and all vary in length from 15-23 steps. Strempeliopine (**2**) has been prepared using biomimetic[7a], racemic[7c] and asymmetric multi-step syntheses[7d] in similar step count. In all of these elegant approaches the opportunity to enable a divergent synthesis to the structurally related schizozygine alkaloids is denied because the C-14,15 single bond was present from the beginning and it would be synthetically challenging to introduce the required C-14,15 double bond. Hájíček and co-workers reported a study on 14,15-dehydrostrempeliopine (**6**), a model towards schizozygine (**3**), through a 15α-hydroxyl precursor, but the final dehydration failed.[8] We report here a distinctive synthetic strategy towards the schizozygine alkaloids based on a synthetically valuable late stage C-14,15 alkene divergent intermediate **7** (Scheme 1). Notable aspects of our synthesis include a novel [1,4]-hydride transfer/Mannich cyclisation, the exploitation of the nitro functional group for the synthesis of 3 of the 5 rings, the demonstration of a diastereoselective ring closing metathesis and the gram-scale synthesis of late stage intermediates in high stereoselectivity and yield. We show the divergence of this route by the total synthesis of (+)-vallesamidine (**1**) and (+)-14,15-dehydro-strempeliopine (**6**) in 2-3 simple transformations. Compound **6** is skelatally identical to schizozygine (**3**).[9] The strategy could deliver other schizozygine alkaloids **3**-**5** and we demonstrate the synthesis of analogous unnatural structures.

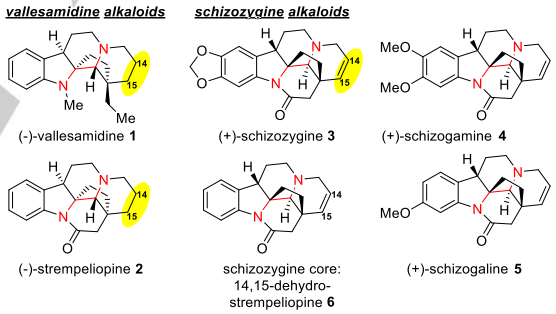

Figure 1. vallesamine and schizozygine alkaloids

Retrosynthetically access to both targets **1** and **6** would be by forming ring D by a diastereoselective ring closing metathesis[10a-c,g] of **8** to a common intermeduate **7** (Scheme 1). The *bis*-C-20 vinyl substituents would be derived from malonate **9**. For the formation of ring E we proposed a novel [1,4]-hydride transfer (HT)/Mannich cyclisation on the piperidine ring C of **10**. The synthesis of the precursor to this (**11**) relies upon the diverse chemistry of the nitro functional group and was guided by our studies on the stereoselective nitro-Mannich reaction[11] and the formation of indolines from the chemoselective cyclisation of 1,2-diamines.[12] The precursor to ring B (**12**) bearing a quaternary carbon (C-2) would be prepared through a Tsuji-Trost allylation of nitro lactam **13**, a known skeleton that could be assembled through nitro-Mannich/ lactamisation cascade from nitro malonate **14**.[13] Asymmetry would be introduced by an enantioselective Michael addition on nitro alkene **15** and the diastereoselectivity of the subsequent nitro-Mannich reaction dictated by the chiral centre formed.[14]

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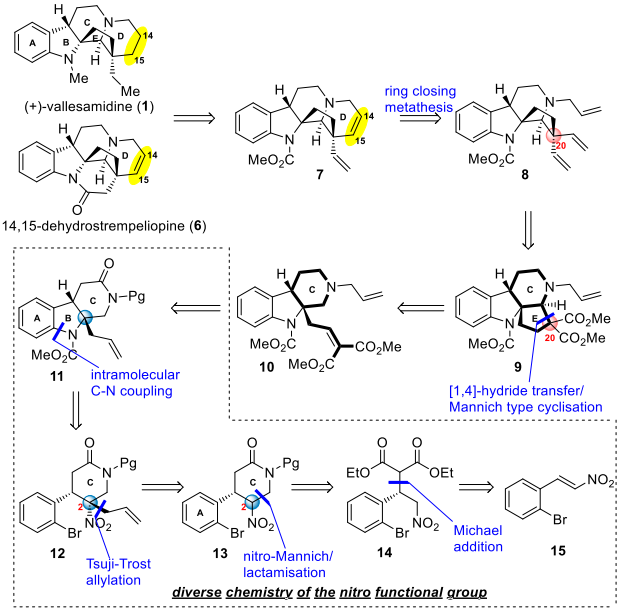
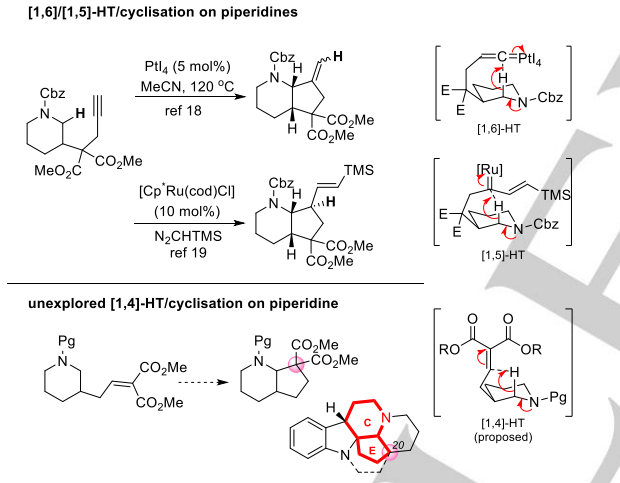


Scheme 1. Retrosynthesis of (+)-vallesamidine (**1**)

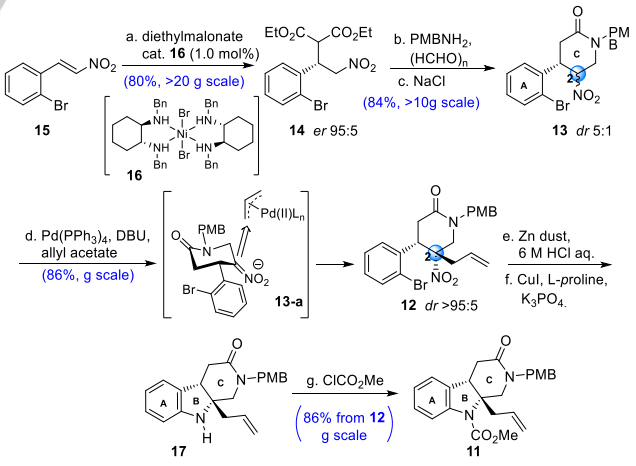


Scheme 2. [1,n]-HT/cyclisation strategy of piperidines

The [1,n]-hydride transfer (HT)/cyclisation, also regarded as an internal redox neutral C-H functionalisation, is an unusual method for ring formation that has been recently developed for more complex systems[15] since the first examples that were classified under the term the 'tert-amino effect'[16] (Scheme 2). In this transformation, the conformational requirement for hydride donor and acceptor in a spatially closed relationship is crucial and thus substrate scopes are still limited. Based on our retrosynthesis a [1,4]-HT/cyclisation on a 3-substituted piperidine was proposed to construct the C/E bicyclic skeleton and install the C-20 quaternary centre. Currently there have been very few reports of [1,4]-HT/cyclisation reactions and all of these involved benzylic C-H bonds.[17] The work by Sames[18] and Saá[19] disclosed the [1,6] and [1,5]-HT/cyclisation on 3-substituted piperidines with alkynes as hydride acceptors and these impressive results indicated the stereochemical requirements and possibilities for applying the [1,4]-HT/cyclisation on piperidines.

Results and Discussion

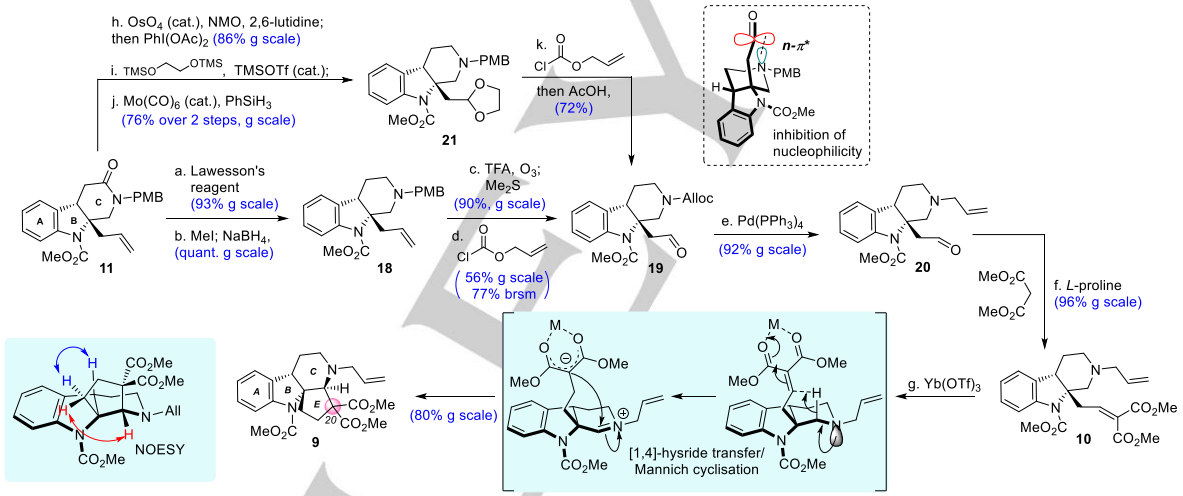
The total synthesis of (+)-vallesamidine (**1**) and (+)-14,15-dehydrostrempeliopine (**6**) commenced with the asymmetric Michael addition of diethyl malonate to 2-bromonitrostyrene **15** using chiral nickel (II) complex **16**, developed by Evans *et al*, as the catalyst.[20] The ease of catalyst preparation and mild conditions made the reaction scalable and the enantioselectivity of adduct **14** could be maintained at 95:5 *er* at 20 grams scale. The nitro-Mannich/lactamisation cascade was followed by Krapcho decarboxylation of the crude reaction mixture to give the nitro lactam **13** in 84% overall yield in ~5:1 *dr* at C-2. The diastereoselectivity was immaterial as subjection of the mixture to a palladium catalysed Tsuji-Trost allylation to introduce the C-2 quaternary centre stereoselectively (**13-a**) and the allylated product **12** was obtained in 86% yield with 95:5 *dr*. Reduction of the nitro group with Zn/HCl provided the free amine quantitatively and the crude product was directly used in the intramolecular C-N coupling reaction. The palladium catalysed C-N coupling reaction ($Pd(PPh_3)_4$/*t*-BuONa/PhMe)[12] was attempted first and the desired indoline **17** was obtained in 65% yield. Ligand free Ullmann type coupling using cheaper CuI catalyst only gave 56% conversion and 40% yield and increasing the catalyst loading from 5 mol% to 10 mol% improved the yield to only 55%. The moderate yield of this clean reaction led us to consider adding ligands to accelerate the progress.[21] We first tested Ma's conditions[22] using commercial proline as ligand and it significantly shortened the reaction time to 1 h and improved the yield of crude indoline to 94% without further purification (see SI for spectral comparison). Protection of the free indoline in neat methyl chloroformate gave **11** in 86% yield over three steps from **12**.[23]



Scheme 3. Synthesis of ABC ring intermediate **11**. Conditions: a) diethylmalonate, cat. **16** (1.0 mol%), PhMe, rt, 72 h, 80%; b) $PMBNH_2$, $(HCHO)_n$, EtOH, 80 °C, 2 h; c) NaCl, DMSO, 160 °C, 16 h, 84% from **14**; d) $Pd(PPh_3)_4$ (1.0 mol%), allyl acetate, DBU, CH_2Cl_2, 0 °C, 30 min, 86%; e) Zn dust, 6 M HCl aq., EtOH/EtOAc, 0 °C, 1 h, quant.; f) CuI (10 mol%), *L*-proline (20 mol%), K_3PO_4 (2.0 eq.), DMSO, 80 °C, 1 h; g) $ClCO_2Me$ (neat), 65 °C, 16 h, 86% from **12**.

$PMBNH_2$ = *p*-methoxybenzylamine; DMSO = dimethylsulfoxide; DBU = 1,8-diazabicyclo [5.4.0]undec-7-ene.

Ring E was formed using a [1,4]-HT/Mannich cyclisation (Scheme 4). The expected challenges for the desired hydride transfer/cyclisation were the accessibility of the necessary reactive conformation for hydride transfer and good affinity between the Lewis acid and malonate motif over the basic piperidine nitrogen atom. Normally a basic amine would sequester the Lewis acid and prohibit the hydride transfer/cyclisation to occur, presumably why most hydride transfer/cyclisation substrates are aniline type structures. From an inspection of the likely conformation of our desired precursor **10** we speculated that the correct stereoelectronic geometry could be easily obtained and that the steric complexity around the piperidine nitrogen could inhibit coordination of a Lewis acid. To this end piperidine **18** was obtained in high yield by chemoselective reduction *via* an *in situ* thionium ion formed by sequential treatment of lactam **11** with Lawesson's reagent, MeI and $NaBH_4$. The oxidative cleavage of the allyl group in **18** was initially problematic either with ozonolysis or $OsO_4/NaIO_4$ conditions, probably due to the oxidation sensitive piperidine nitrogen. Protonation of the basic piperidine nitrogen with trifluoroacetic acid acted as *in situ* protection, which upon ozonolysis, smoothly gave the aldehyde in 90% yield.[24] In preparation for the late stage ring closing metathesis to form ring D, the PMB group had to be removed and changed to the allyl group. Therefore, treatment of the aldehyde with allyl chloroformate yielded the allyl carbamate **19** in an acceptable yield of 56% (77% brsm). Increasing the reaction time slightly improved the yield but the starting material could not be fully converted. Based on the conformation of the aldehyde, we suggest that hyperconjugation between the nitrogen lone pair orbital and π^* orbital of the aldehyde[25] inhibits the nucleophilicity of the piperidine amine and accounts for the slow, incomplete functional group interconversion. To explore this hypothesis and increase the efficiency of the PMB/allyl group exchange, dioxolane compound **21** was prepared through oxidative cleavage of alkene **11**,[26] followed by aldehyde protection and catalytic amide reduction.[27] The reaction of **21** with allylchloroformate was significantly improved with complete conversion, a shorter reaction time (1 h) and reduced reagent usage (10.0 eq. to 5.0 eq. of allylchloroformate). The crude product, after removal of any volatile species, was subjected to acidic hydrolysis directly and aldehyde **19** was obtained in 72% yield from **21**.



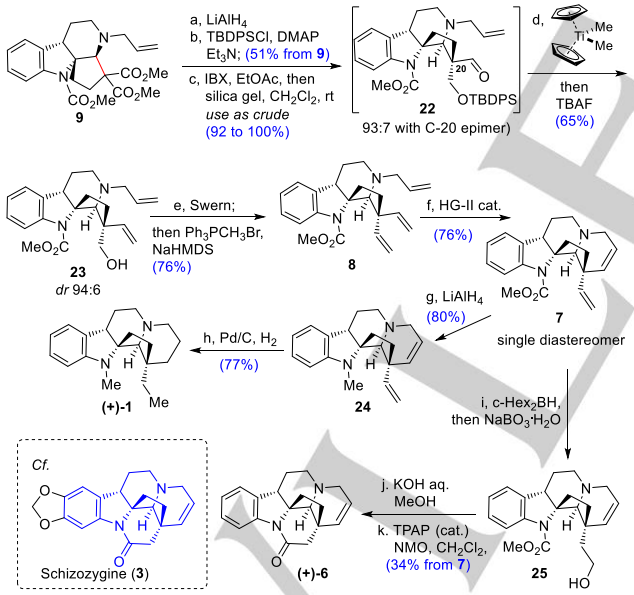
Scheme 4. Synthesis of ABCE ring intermediate **9** through [1,4]-hydride transfer/Mannich cyclisation. Conditions: a) Lawesson's reagent, PhMe, 80 °C, 1 h, 93%; b) MeI, reflux, 2 h, then $NaBH_4$, MeOH, 0 °C, 1 h, quant.; c) TFA, 0 °C, CH_2Cl_2, 10 min, then O_3, CH_2Cl_2, -78 °C, then Me_2S, -78 °C to rt, 90%; d) allyl chloroformate, DCE, 75 °C, 48 h, 56%; e) $Pd(PPh_3)_4$ (2.5 mol%), CH_2Cl_2, rt, 1 h, 92%; f) dimethyl malonate, *L*-proline, DMSO, rt, 24 h, 96%; g) $Yb(OTf)_3$ (10 mol%), PhMe, reflux, 80%; h) OsO_4 (2 mol%), NMO, 2,6-lutidine, acetone-H_2O, 24 h, then $PhI(OAc)_2$ 0.5 h, 78%; i) $(CH_2OTMS)_2$, TMSOTf (10 mol%), CH_2Cl_2, -78 °C to rt, quant; j) $Mo(CO)_6$ (10 mol%), $PhSiH_3$, THF, 65 °C, 8 h, 76% over 2 steps; k) allylchloroformate, $NaHCO_3$, DCE, 80 °C, 1 h, then AcOH, THF-H_2O, 90 °C, 24 h, 72% from **21**. Lawesson's regent = 2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane; TFA = trifluoroacetic acid; DCE = 1,2-dichloroethane.

Subsequent treatment of allyl carbamate **19** with catalytic $Pd(PPh_3)_4$ triggered the decarboxylative allylation to give **20** and Knoevenagel condensation with dimethyl malonate afforded the α,β-unsaturated malonate **10**, the precursor for the [1,4]-HT/Mannich cyclisation again in high yields. To our satisfaction, treatment of **10** with catalytic $Yb(OTf)_3$ in reflux toluene promoted the desired [1,4]-hydride transfer/Mannich cyclisation cleanly to give the ABCE ring intermediate **9** in 80% yield for the efficient formation of the second quaternary centre. The relative stereochemistry was confirmed by a NOESY experiment. This unique transformation provided a good example of ring construction in alkaloids synthesis and may find potential application in the synthesis of other complex molecules.

Manipulations to form the metathesis precursor **8** for the formation of the ring D began with the chemoselective reduction of malonate **9** to the corresponding diol under optimised conditions ($LiAlH_4$, room temperature, 15 min) (Scheme 5). A concise route to **8**, based on Feldman's work,[10a,c] was to oxidise the diol to dialdehyde, followed by Wittig reaction to give dialkene **8**. However, degradation was observed during the oxidation and no appropriate conditions could be found. Therefore a sequential olefination sequence was necessary and began with the selective

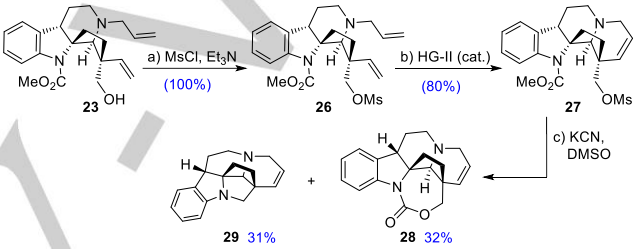
mono-protection of the diol on the sterically less hindered hydroxyl group in 51% yield from **9**. Oxidation of the remaining alcohol using IBX in EtOAc[28] gave the aldehyde **22** quantitatively but with epimerisation at C-20 (~1:1), either from silyl exchange before oxidation or Mannich type retro ring opening/re-cyclisation. Fortunately, simple treatment of the epimers with silica gel in dichloromethane led to the nearly diastereomerically pure desired, thermodynamically more stable isomer **22** (93:7). The Petasis olefination was applied on hindered aldehyde **22** and the crude alkene was treated with TBAF to give **23** in 65% yield. Ultimately, the trialkene intermediate **8** was obtained in good yield after a Swern oxidation and Wittig olefination sequence. A diastereoselective ring closing metathesis was then performed and the ring D cyclised product **7** was isolated as a single diastereomer in 76% yield.

The ABCDE ring intermediate **7** represents a divergent intermediate from which vallesamidine, strepeliopine and schizozygine type alkaloids can be prepared. For example **7** was subjected to $LiAlH_4$ reduction to give dehydrovallseamidine **24** and catalytic hydrogenation proceeded uneventfully to give (+)-vallesamidine (**1**), the spectral data of which were consistent with literature data.[6] For the preparation of 14,15-dehydro-strempeliopine (**6**), that possesses the same skeletal features as schizozygine (**3**), regioselective hydroboration/oxidation[30] of **7** was performed first to provide primary alcohol **25**. Hydrolysis of the carbamate followed by oxidative cyclisation gave **6** and the spectral data of the core skeleton was in agreement with that of schizozygine (**1**).[31]



Scheme 5. Synthesis of divergent intermediate **7** and total synthesis of (+)-vallesamidine (**1**) and (+)-14,15-dehydrostrempeliopine (**6**). Conditions: a) $LiAlH_4$, THF, 0 to 22 °C, 15 min; b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 51% from **9**; c) IBX, EtOAc, reflux, 2 h, then silica gel, CH_2Cl_2, 2 h; d) Cp_2TiMe_2, PhMe, 80 °C, simple work-up, then TBAF, THF, 70 °C, 3 h, 65% from IBX oxidation; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, simple work-up, then Ph_3PCH_3Br, NaHMDS, THF, -78 °C to rt, 76%; f) Hoveyda-Grubbs 2nd catalyst (10 mol%),[29] PhMe, 80 °C, 1.5 h, 76%; g) $LiAlH_4$, THF, 0 to 65 °C , 30 min, 80%; h) Pd/C, H_2, MeOH, rt, 3 h, 77%; i) c-Hex_2BH, then $NaBO_3{\cdot}H_2O$, THF; j) 6M KOH aq., MeOH, 100 °C, 16 h; k) TPAP (10 mol%), NMO, CH_2Cl_2, 30 min, 34% from **7**. THF = tetrahydrofuran; Im = imidazole; IBX = 2-Iodoxybenzoic acid; Cp = cycopentadienyl; Hoveyda-Grubbs 2nd catalyst = (1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxy-phenyl-methylene) ruthenium; TBAF = tetra-n-butylammonium fluoride.

As an example of the opportunities this divergent route opens for the synthesis of unnatural analogues of the schizozygine alkaloid family, we isolated two new structures during our studies towards the synthesis of 14,15-dehydro-strempeliopine (**6**) (Scheme 6). Treatment of **23** with methanesulfonyl chloride gave the mesylate **26** in quantitative yield. After ring closing metathesis to **27**, attempted displacement of the mesyl group with KCN in DMSO at 100 °C gave two new products **28** (32%)and **29** (31%).These represent key molecules for SAR studies around the importance of the lactam function of the schizozygine alkaloids for biological activity.



Scheme 6. Manipulation of alcohol **23** and preparation of unnatural analogues **28** and **29**. Conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt**,** 1.5 h, quant.; b) Hoveyda-Grubbs cat. (10 mol%), PhMe, 80 °C, 4 h, 80%; c) KCN, DMSO, 100 °C, 16 h, **28** 32% and **29** 31%. Ms = methanesulfonyl.

Conclusion

In conclusion, an efficient, high yielding and selective asymmetric synthetic route to a late stage C-14,15 alkene divergent intermediate **7** that could be simply transformed into (+)-vallesamidine (**1**) and (+)-14,15-dehydrostrempeliopine (**6**) has been realised. Although the step count of this synthetic approach (23 steps to vallesamidine) is slightly higher than other asymmetric routes to inidividual alkaloids of this family, such as vallesamidine, our route only required 14 chromatographic purifications and we have shown its valuable and unique synthetic diversity to other natural and unnatural structurally related strempeliopine and schizozygine alkaloid skeletons. The route is flexible in terms of absolute stereochemistry, the opportunity for more functionalised aromatic cores in the Michael reaction of the starting nitro alkene **15** and other late stage synthetic manipulations. The synthesis makes good use of simple nitroalkane/alkene chemistry, including Michael addition, nitro-Mannich/ lactamisation, Tsuji-Trost allylation and nitro-reduction/C-N coupling reaction, to quickly generate complexity in the A/B/C ring skeleton in high yield and gram scale. A novel and high yielding Lewis acid catalysed [1,4]-hydride transfer/Mannich type cascade cyclisation was used to construct ring E in gram scale. This C-H functionalisation reaction should be highly useful for the synthesis of other complex molecules. The successful installation of the key C-14,15 double bond in ring D was achieved

through a diastereoselective ring closing metathesis. We are using this divergent route for the synthesis of similar alkaloid targets for the investigation of their biological activity.

Experimental Section

Experimental details, compounds characterisation data and spectra are attached in supporting information.

Acknowledgements

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Keywords: Total synthesis, Asymmetric synthesis, Alkaloids, Nitro-Mannich, Hydride transfer/cyclisation

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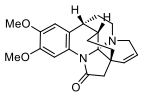

Isoschizogamine

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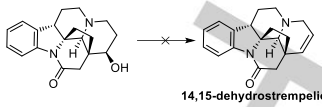

14,15-dehydrostrempeliopine

[9] We could not exemplify the synthesis of schizozygine (**3**) directly as the corresponding starting material, the aldehyde piperonal, is a restricted substance as it is a precursor to illicit drug manufacture.

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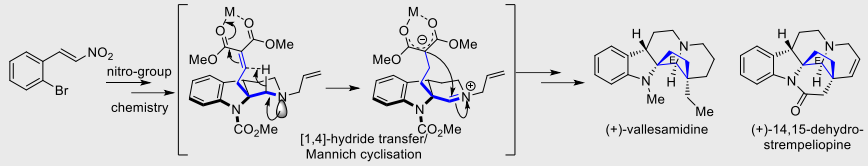
RESEARCH ARTICLE



Necessity is the mother of invention and never more so than in target synthesis. The total synthesis of (+)-vallesamidine and (+)-14,15-dehydrostrempeliopine were achieved from a common intermediate that is related to other alkaloids and necessitated the development of a novel [1,4]-hydride transfer/Mannich cyclisation to build ring E.

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