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Cascade Annulation Reactions To Access the Structural Cores of Stereochemically Unusual Strychnos Alkaloids

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Keywords: Malagashanine / Strychnos / Alkaloids / Iminium / Cascade / Annulation / Reaction mechanisms / Polycycles / Natural products

A new cascade annulation reaction has been developed to access the core structures of a novel family of strychnos alkaloids with a unique stereochemical arrangement. The new annulation cascade is facilitated by the development of a robust reaction sequence to access extremely sensitive *N*-acyliminium ions.

Introduction

In 1946, following decades of careful research, Sir Robert Robinson reported the structure of strychnine (**1**).[1] In the 60 years that have followed, numerous strychnos and aspidosperma alkaloids have been isolated, all sharing a common complex architecture and yet offering diverse biological activities. The dense functionalization and complexity of these molecules has captured the imagination of generations of chemists and inspired the development of a dazzling array of synthetic methodologies.[2]

In considering these venerable families of natural products, we noted that the vast majority of the molecules shared a common stereochemical pattern around the D ring. In particular, the stereochemistry at C-2, C-3, C-7, C-15 and C-16 is highly conserved,[3] and this sterochemical pattern has been the focus of *all* the synthetic attention to date (Figure 1). In 1995, Caira and Rasoanaivo reported the structure of malagashanine (**2**), a unique strychnos alkaloid with inverted C-3 stereochemistry, isolated from the Madagascan shrub *Strychnos myrtoides*.[4] Malagashanine was isolated as part of a study to identify the bioactive components of traditional herbal remedies for malaria treatment in areas with high incidence of chloroquine (CQ) resistant *Plasmodium falciparum*. Despite sharing many structural features with strychnine, malagashanine does not exhibit significant toxicity. Furthermore, it has been shown to restore the activity of CQ against drug-resistant populations of *P. falciparum*.[5] It is postulated that malagashanine acts by inhibiting a P-glycoprotein efflux pump, similar to those found in multi-drug-resistant cancer cells.[5d]

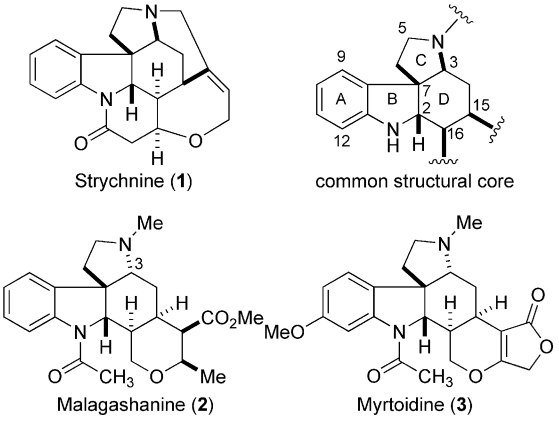

Figure 1. Malagashanine – a stereochemically unusual strychnos alkaloid.

Since the discovery of malagashanine, Galeffi and coworkers have identified several other strychnos alkaloids bearing the unusual inverted C-3 stereochemistry [e.g. myrtoidine (**3**)].[6] The intriguing biological activity exhibited by malagashanine combined with its unprecedented stereochemical motif has prompted us to develop a methodology for the direct entry into this new class of strychnos alkaloids. Specifically, we felt it was important to develop a single methodology that would allow access to the novel malagashanine core, but that would be flexible enough to facilitate the synthesis of all members of this new family, as well as a diverse range of analogues to further explore the biological activity in the context of both CQ potentiation and *p*-glycoprotein inhibition.

Cognizant of recent advances in Brønsted acid and hydrogen-bonding catalysis for the asymmetric addition of nucleophiles to imines,[7] we envisioned a process, in which imine **4** could be activated by either a chiral phosphoric acid or by acylation in the presence of a chiral thiourea

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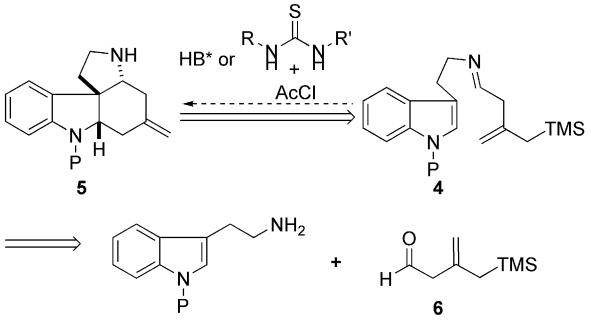
catalyst, leading to cascade cyclization and formation of the desired heterocyclic core of the *S. myrtoides* alkaloids (**5**) (Scheme 1). Conceptually, this process fulfilled many of the requirements we had outlined. However, in practice, the existing protic acid imine activation protocols were not compatible with this sensitive β,γ-unsaturated imine, and the β,γ-unsaturated aldehyde **6** was extraordinarily sensitive to isomerization under both acidic and basic conditions, rendering imine **4** virtually impossible to access.[8]



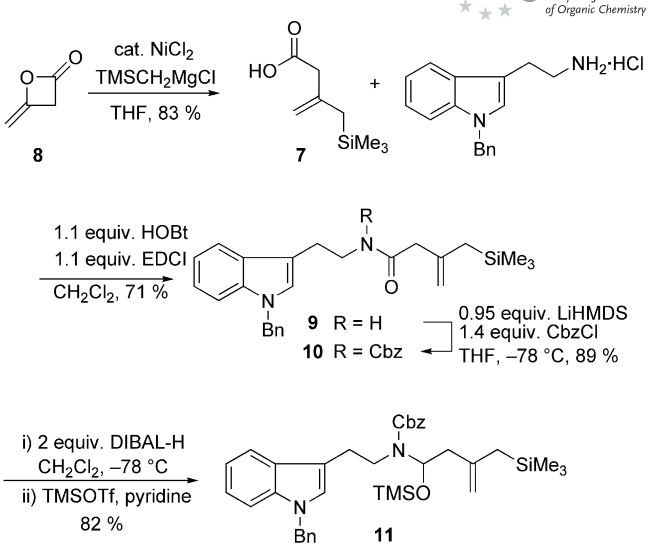
Scheme 1. Retrosynthetic analysis of the malagashanine core. P = protecting group.

Herein, we describe the evolution of a general strategy for the construction of polycyclic indole alkaloids via β,γ-unsaturated iminium ion intermediates that circumvents the isomerization issues associated with the generation of these species.

Results and Discussion

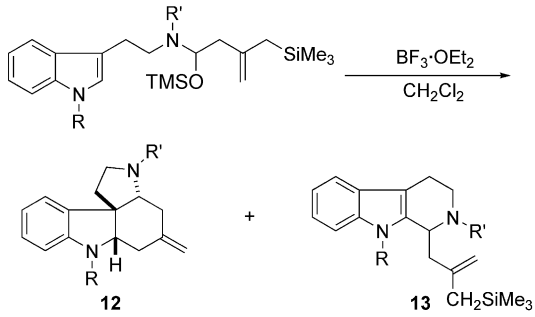
Having ruled out the condensation of aldehyde **6** with an amine as a viable entry to the malagashanine alkaloids, we adopted a strategy, in which an activated *N*-acyliminium ion could be accessed from a stable amide precursor (Scheme 2).[9] Thus, carboxylic acid **7** was synthesized by nickel-catalyzed Kumada coupling of [(trimethylsilyl)-methyl]magnesium chloride with diketene **8**.[10] The requisite amide **9** was constructed by using standard conditions and could be acylated in excellent yield with 0.95 equiv. of LiHMDS and 1.4 equiv. of CbzCl. Under these conditions, no olefin isomerization was observed. Reduction of amide **10** with DIBAL-H and in-situ trapping of the resulting aluminate complex with TMSOTf gave *N*-acyl-*O*-TMS-aminol **11** in good yield (82%). These *N*-acyl-*O*-TMS-aminol species are generally stable to chromatography on silica gel and can be stored for extended periods, making them convenient precursors to reactive acyclic *N*-acyliminium ions.

With *N*-acyl-*O*-TMS-aminol **11** in hand, our attention turned to the crucial cascade cyclization reaction. When aminol **11** was treated with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at –78 °C, the desired tetracyclic product **12** was obtained in only modest yield (36%), with the majority of the iminium ion intermediate undergoing competitive Pictet–Spengler cyclization to give tetrahydro-β-carboline **13** (Table 1, Entry 1).[11] In order to tune the reaction for the desired cascade process, we studied the effects exerted by the protecting groups on both the indole nitrogen atom and the iminium ion nitrogen atom. Removal of the benzyl protecting group from the indole resulted in almost exclusive formation of the undesired Pictet–Spengler product (Entry 2), and use of electron-withdrawing groups on this nitrogen atom led to substantially longer reaction times, competitive iminium ion hydrolysis and a complex mixture of undesired products (not shown).



Scheme 2. Synthesis of *N*-acyl-*O*-TMS-aminol **11** as an *N*-acyliminium ion precursor.

Table 1. Optimization of the cascade annulation process.

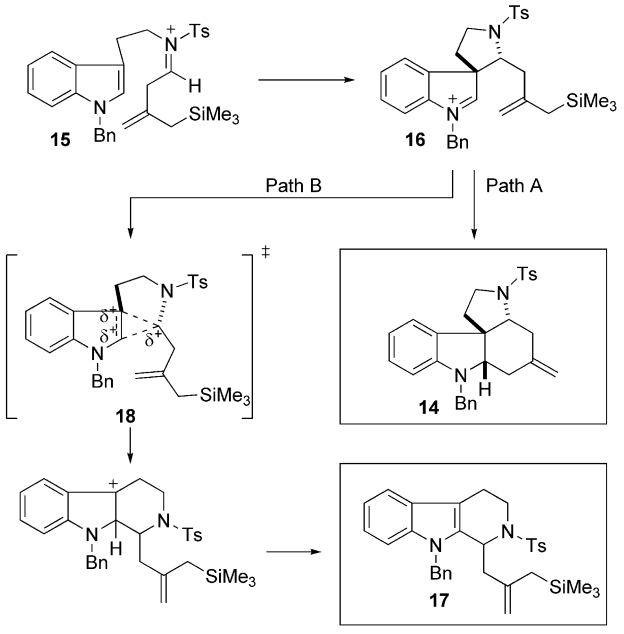


Entry	R	R'	Temp. [°C]	Time [h]	Yield **12** [%]	Yield **13** [%]
1	Bn	Cbz	–78	0.25	36	43
2	H	Cbz	–78	0.25	<5	73
3	Bn	Boc	–78	0.25	33	53
4	Bn	C(O)OMe	–78	0.25	24	69
5	Bn	C(O)*t*Bu	–78	6	34	<5
6	Bn	Ts	–78	1	52	15
7	Bn	Ts	0	1	79	<5

With respect to the iminium ion protecting group, steric factors did not significantly impact the product distribution. Benzyl, *tert*-butyl and methyl carbamates all gave similar results (Entries 1, 3 and 4). However, when the carbamate was replaced with more electron-withdrawing amide or sulfamate auxiliaries, an improvement in the ratio of cascade product/Pictet–Spengler rearrangement was observed

(Entries 5 and 6). Under the optimal conditions, the *N*-tosyl-*O*-TMS-aminol is treated with $BF_3{\cdot}OEt_2$ at 0 °C to give alkaloid **14** corresponding to the A,B,C,D-ring core of the malagashanine alkaloids in good yield (79%) with excellent chemo- and stereoselectivity (Entry 7). The cascade product is obtained as a single diastereomer, and only trace quantities of the product arising from Pictet–Spengler rearrangement are observed.

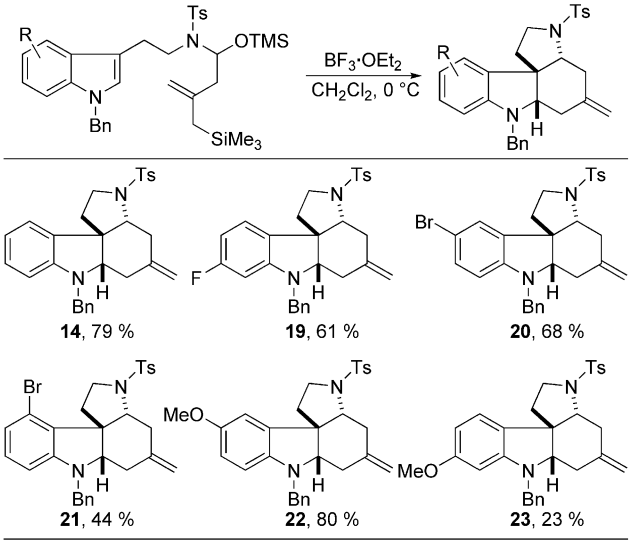
In considering the mechanism of this reaction, we hypothesize that both products arise from an initial C-3 attack of the indole on (*E*)-iminium ion **15**, establishing the relative stereochemistry between the spirocyclic quaternary center and the adjacent amine. The resulting indolium ion **16** can subsequently be trapped by the pendant allylsilane (Path A) leading to the desired cascade product **14**, or a competitive C-3–C-2 migration (Path B) will result in the formation of the undesired Pictet–Spengler product **17**. We believe that strongly electron-withdrawing groups on the iminium ion nitrogen atom destabilize the three-membered transition state **18**, leading to the Pictet–Spengler reaction, and as such promote selective formation of the cascade product **14** (Scheme 3).



Scheme 3. Mechanistic rationale for the observed selectivity.

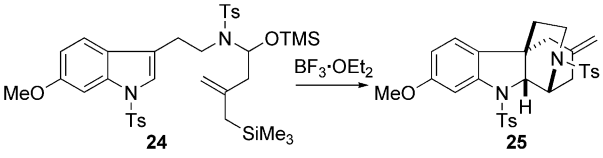
Having established conditions for the cascade cyclization to give parent compound **14**, we investigated the generality of this reaction with respect to substitution of the indole ring. Electron-withdrawing substituents in the 4-, 5- and 6-positions were well tolerated (**19**–**21**, Table 2), as were electron-donating methoxy groups (**22**, **23**). In most cases, the use of a tosyl auxiliary on the iminium ion nitrogen atom and a benzyl group on the indole nitrogen atom provided exquisite selectivity for the desired cascade product. However, for the 6-methoxyindole substrate (particularly pertinent for the synthesis of myrtoidine), this auxiliary pattern resulted in only 23% yield of the desired product, with competitive Pictet–Spengler rearrangement dominating the reaction profile.[12]

Table 2. Cascade cyclizations of substituted indoles.[a]



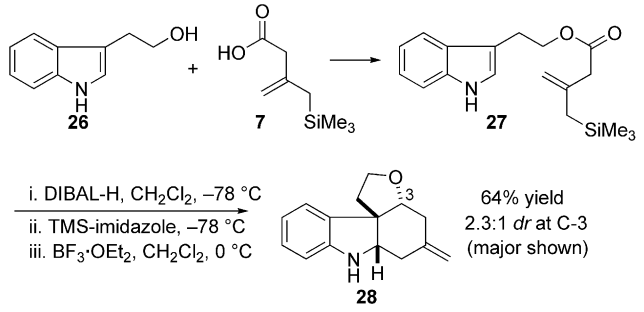
[a] The relative stereochemistry of **22** was established by X-ray crystallography (see Supporting Information for details). Other compounds in this series were assigned by analogy and extensive NOE studies.

This observation can be accounted for in our mechanistic hypothesis, with the electron-donating 6-methoxy group stabilizing the three-membered transition state leading to the undesired rearrangement product. In order to overcome this side reaction, we attempted to tune the electronics of the substrate by placing an electron-withdrawing tosyl group on the indole nitrogen atom [**24**, Equation (1)]. This simple change resulted in a dramatic shift in the reaction profile, with the initial electrophilic aromatic attack now taking place at the 2-position of the indole and subsequent intramolecular allylation of the C-3 cation resulting in the formation of the regioisomeric cascade product **25** in 62% yield [Equation (1)].



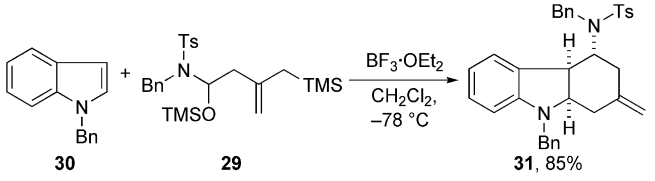
(1)

In an extension of this methodology, we have demonstrated that the cascade annulation process can be adapted for the cyclization of analogous oxocarbenium intermediates.[13–15] Tryptophol (**26**) was condensed with carboxylic acid **7** to give ester **27** (Scheme 4). Conversion to the mixed acetal followed by $BF_3{\cdot}OEt_2$-promoted cyclization provided tetrahydrofuran analogue **28** in good yield (64%).



Scheme 4. Oxonium ion cascade annulation reaction.

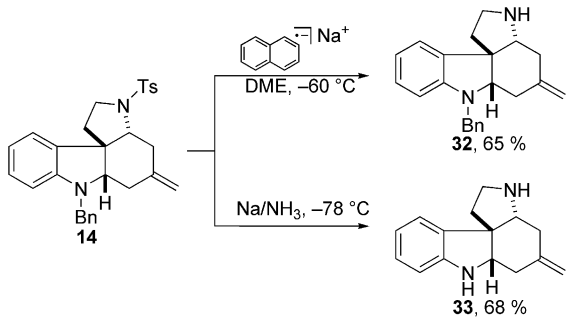
Furthermore, we have shown that intermolecular cascade annulations are possible. *N*-Tosyl-*O*-TMS-aminol **29** was synthesized by using our standard protocol.[12] When this aminol was treated with $BF_3{\cdot}OEt_2$ in the presence of 1.05 equiv. of *N*-benzylindole (**30**), annulation product **31** containing three contiguous stereocenters was obtained in excellent yield (85%) as a single diastereomer (relative stereochemistry determined by X-ray crystallography) [Equation (2)].



(2)

Despite the fact that *N*-acyliminium ions have been shown to be excellent substrates for hydrogen-bond-catalyzed Pictet–Spengler reactions,[16] our preliminary investigations with known chiral thiourea and phosphoric acid catalysts did not furnish the desired cascade annulation product. The development of an appropriate chiral catalyst for this new cascade process remains a research priority in our laboratory.

Finally, we have demonstrated that both the tosyl and benzyl groups used to tune the chemoselectivity of the reaction are readily removed under standard conditions. Treatment of tetracycle **14** with sodium naphthalide in DME at –60 °C leads to clean removal of the tosyl group providing monoamine **32** in 65% yield (Scheme 5). Both the *N*-benzyl group and the tosyl group can be removed by treatment of **14** with sodium in ammonia providing diamine **33** in 68% yield.



Scheme 5. Protecting group removal following cascade annulation.

Conclusions

We have developed an efficient cascade annulation strategy to access the unusual structural core of the malagashanine alkaloids. The annulation strategy has proved effective in both intra- and intermolecular reactions. The use of *N*-acyl- and *N*-tosylamides as iminium ion precursors circumvents problems associated with the condensation of primary amines with sensitive aldehydes and exhibits significant promise as an alternative entry into iminium ion chemistry. The total synthesis of malagashanine and SAR studies to further understand its mode of action are being actively pursued in our laboratory.

Supporting Information (see footnote on the first page of this article): Experimental procedures, NMR spectroscopic data and X-ray structures of key compounds.

Acknowledgments

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