Alkaloids

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Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine**

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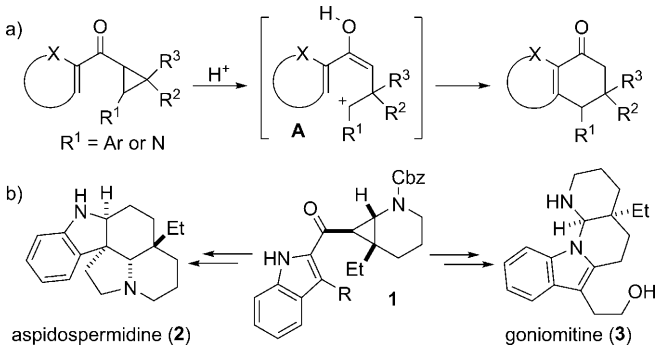
Polyheterocyclic structures are present in most natural and synthetic molecules with important biological activity.[1] Therefore, the discovery of new efficient cyclization reactions is important to access natural products and to explore a broad range of complex scaffolds with potentially enhanced bioactivity.[2] We have recently reported the first catalytic formal homo-Nazarov cyclization of vinyl cyclopropyl ketones for the synthesis of cyclohexenones (Scheme 1 a).[3] In contrast to the well-established Nazarov cyclization of divinyl ketones to give cyclopentenones,[4] examples of homo-Nazarov cyclizations are rare and require stoichiometric amounts of strong Lewis acids or high temperatures.[5] The mild catalytic conditions developed in our work allowed us to apply our method to several unprecedented heterocyclic structures, but the scope of the reaction was limited by the required presence of an electron-rich aromatic group to stabilize the formed carbocationic intermediate **A**.



Scheme 1. Formal homo-Nazarov reaction and applications in the synthesis of polyheterocyclic natural products. Cbz = benzyloxycarbonyl.

A heteroatom should also be able to stabilize the formed carbocation, as demonstrated by the rich chemistry of donor–acceptor cyclopropanes.[6] Aminocyclopropanes in particular may lead to the fused aminocyclohexane core of numerous biologically relevant alkaloids ($R^1 = N$ in Scheme 1). Cyclization of an acyl indole substituted aminocyclopropane **1** would constitute a general entry into the *Aspidosperma* alkaloids, such as aspidospermidine (**2**; Scheme 1 b). The tetracyclic core obtained in the cyclization is present not only in the *Aspidosperma* family, but also in more complex natural products such as vinblastine and vincristine, which are frontline drugs in cancer therapy.[7] Although the combination of synthetically challenging structures and potential medical applications has resulted in a large number of successful total syntheses of aspidospermidine in the past,[8] the development of more general and flexible synthetic approaches is still required to access new analogues. Herein, we report the first example of the formal homo-Nazarov cyclization of aminocyclopropanes and its application in the formal total synthesis of aspidospermidine (**2**). Additionally, we demonstrate how a simple modification in reaction conditions leads to the scaffold of goniomitine (**3**), an indole alkaloid isolated from the tree *Gonioma malagasy*,[9] starting from aminocyclopropane **1**. In contrast to the *Aspidosperma* scaffold, the goniomitine ring system is unique in natural products, and only two total syntheses have been reported so far.[9b,c] Based on our cyclization strategy, an efficient total synthesis of goniomitine (**3**) was accomplished and we present herein the first study of its bioactivity, revealing significant cytotoxicity against several cancer cell lines, including vinblastine and taxol-resistant P-glycoprotein (Pgp, MDR-1) overexpressing cells.

We began our research by examining the cyclization of the simple model system **4** containing the aminocyclopropane derived from the unsubstituted tetrahydropyridine ring and a *N*-methylindole (Scheme 2).[10] Our standard conditions developed for the catalytic homo-Nazarov cyclization were highly successful and the reaction occurred in 90 % yield with high diastereoselectivity for the *cis*-fused product **5**.[11] This result demonstrated that carbamates were also excellent activating groups for the cyclization reaction.

Encouraged by this promising result, we then synthesized the ethyl-substituted cyclopropane **12** required for the core of the *Aspidosperma* alkaloids (Scheme 3). The synthesis of carboxylic acid **10** was accomplished using a slightly modified

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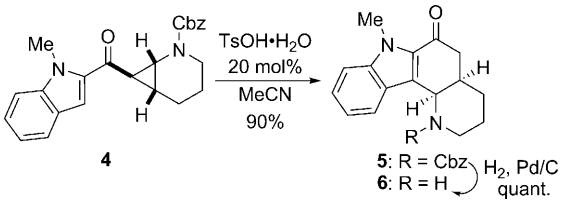
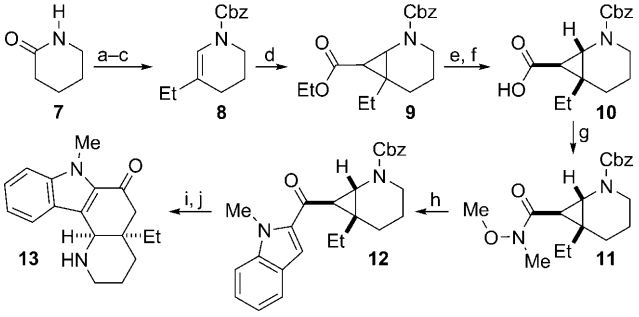


Scheme 2. Model study for the cyclization of aminocyclopropane **4**. Ts = 4-toluenesulfonyl.



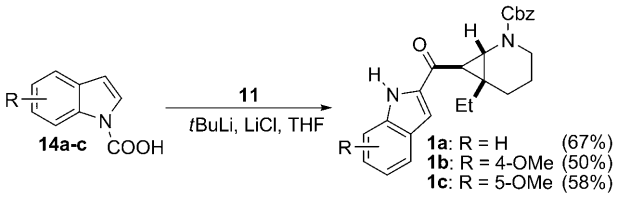
Scheme 3. Synthesis and cyclization of aminocyclopropane **12**. Reagents and conditions: a) *n*BuLi, CbzCl, EtI, THF, −78 °C, 67%; b) $NaBH_4$, MeOH; c) H_2SO_4, THF, 93% overall; d) $(CuOTf)_2{\cdot}C_7H_8$, N_2CHCO_2Et, CH_2Cl_2, 76% (d.r. 1:1); e) $BF_3{\cdot}Et_2O$, CH_2Cl_2; f) NaOH H_2O/THF/EtOH (1:1:3), 91% overall; e) DMTMM, NMM, THF, MeNHOMe·HCl, 93%; h) *N*-methylindole, *n*BuLi, *t*BuOK, THF, 48%; i) TsOH, MeCN, quant; j) H_2, Pd/C, quant. DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)methylmorpholinium chloride, NMM = *N*-methylmorpholine, THF = tetrahydrofuran.

procedure of Grieco and Kaufman.[12] δ-Valerolactam (**7**) was Cbz protected and alkylated in one pot. Reduction and dehydratation led to dehydropiperidine **8**. Enamide **8** was converted into aminocyclopropane **9** by cyclopropanation using CuOTf as the catalyst.[13] The low diastereoselectivity observed in the cyclopropanation reaction is inconsequential, as the diastereomeric mixture of esters equilibrated to the *exo* isomer in the presence of BF_3.[12] The *exo* ester obtained was hydrolyzed to obtain **10** as a pure diastereoisomer.

The choice of DMTMM[14] to convert the sensitive cyclopropane **10** into the Weinreb amide **11** in good yield was crucial. The coupling reaction between amide **11** and 2-lithiated *N*-methylindole afforded the precursor **12** of the homo-Nazarov reaction. To our delight, our catalytic conditions for the cyclization gave the tetracyclic core of *Aspidosperma* alkaloids as a single diastereoisomer **13** after removal of the Cbz protecting group.

The high diastereoselectivity observed is an important advantage of the formal homo-Nazarov cyclization. Other approaches based on aminocyclopropanes in intermolecular Friedel–Crafts reactions used for the synthesis of *Aspidosperma* alkaloids proceeded with low selectivity.[8d] If an enantioselective cyclopropanation method can be developed, an asymmetric synthesis will become possible.[15]

For the synthesis of aspidospermidine (**2**) an indole having an unprotected NH moiety was required. Therefore, we investigated the use of bis-lithiated *N*-carboxy indoles for the addition reaction to the Weinreb amide **11** (Scheme 4).[16] The

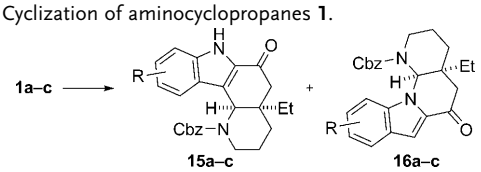


Scheme 4. Coupling of N-carboxylated indoles.

interest in using carbon dioxide as protecting/directing group lies in its easy removal, which occurs upon aqueous workup. However, its use has been limited to simple substrates.[16] We were therefore pleased to observe that the coupling procedure proceeded in moderate to good yields, leading directly to indoles **1a–c**. This approach was highly convergent and allowed the easy variation of coupling partners for the synthesis of analogues.

The obtained product **1a** was submitted to the standard conditions for the homo-Nazarov cyclization. We were surprised to observe the formation of two different products. The two compounds were identified as the desired product **15a** resulting from cyclization at the C3 position of indole, and the compound **16a** obtained from attack upon the N1 position. The cyclic products were isolated in 74% yield and the ratio of **15a** to **16a** was 1.6:1 (Table 1, entry 1). To increase the selectivity for C–C cyclization, we examined several Brønsted and Lewis acids as catalysts (entries 1–4). The use of soft Lewis acids instead of Brønsted acids allowed the desired formation of **15a** as a pure diastereoisomer (entries 2 and 3). Softer, milder Lewis acids could potentially exert an influence on the formation of the acyl iminium intermediate and favor

Table 1: Cyclization of aminocyclopropanes **1**.



Entry	R (**1**)	Catalyst	Solvent	**15/16**	Yield [%]
1	H (**1a**)	TsOH	MeCN	1.6:1[a]	74
2	H (**1a**)	$Cu(OTf)_2$	MeCN	8:1[b]	n.d.[c]
3	H	$Pd(CH_3CN)_4(BF_4)_2$	MeCN	11:1[b]	n.d.
4	H	$Cu(OTf)_2$	MeCN	7:1[a]	91
5	H	TsOH	$MeNO_2$	1.3:1[b]	n.d.
6	H	TsOH	THF	polymers[b]	n.d.
7	H	TsOH	CH_2Cl_2	1:18[b]	n.d.
8	H	TsOH	toluene	1:16[b]	n.d.
9	H	TsOH	CH_2Cl_2	1:21[a]	89
10	4-OMe (**1b**)	TsOH	CH_2Cl_2	1:22[a]	92
11	4-OMe	$Cu(OTf)_2$	MeCN	8:1[a]	88
12	5-OMe (**1c**)	TsOH	CH_2Cl_2	1:20[a]	86
13	5-OMe	$Cu(OTf)_2$	MeCN	8:1[a]	95

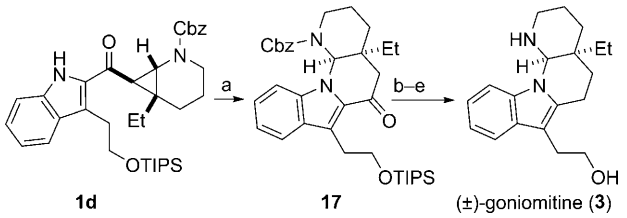
[a] Yields and ratios determined from products isolated after purification. Reaction run with **1a–c** (40–100 mg, 90–250 μmol) and 15–25 mol% catalyst, and at a concentration of 0.025 M. [b] Ratios calculated by integration of peaks in the ^1H NMR spectra of the crude reaction mixture. Reaction carried out on a 10 mg (25 μmol) scale at a concentration of 0.025 M. [c] n.d. = not determined.

the reaction at the softer C3 position of the indole ring. Deprotection of **15a** gave the free amine, concluding the successful formal total synthesis of aspidospermidine (**2**), as this intermediate had already been reported by Wenkert and Hudlicky.[8d,17]

The N-cyclization product **16a** was also highly interesting, as it corresponded to the tetracyclic skeleton of goniomitine (**3**). When considering the rarity of this scaffold, the limited number of synthetic approaches,[9b,c] and the absence of any study on its bioactivity, we found it worthwhile to optimize the formation of the N1-cyclization product **16a**. We hypothesized that the use of a less polar solvent for the cyclization reaction could enhance the reactivity of the iminium intermediate and favor a fast attack on the harder N1 position. Indeed, a strong influence of solvents upon the cyclization was observed in the presence of Brønsted acids (Table 1, entries 5–8). We were delighted to isolate the goniomitine scaffold **16a** in high yield and excellent selectivity using dichloromethane and toluene sulfonic acid as catalyst (entry 9).

Cyclizations involving (acyl)iminium ions are important tools in the synthesis of alkaloids.[18] Examples involving a possible competition between N1 and C3 cyclization are rare, and it is difficult to control the regioselectivity and stereoselectivity of these reactions.[19] The ring-opening of aminocyclopropanes constitutes a new method for the generation of acyl iminium ions and the high level of control on the regio- and stereoselectivity observed is unprecedented. To gain a first impression for the generality of the method, two methoxy indole analogues, **1b** and **1c**, were examined, as similar electron-rich indoles are frequently encountered in natural products. Again, high yields and control of regioselectivity were achieved in these cases (Table 1, entries 10–13).

To finish the total synthesis of goniomitine (**3**) starting from **16a**, it would be necessary to introduce the lateral chain at C3 in the presence of the sensitive aminal functionality. To avoid this difficult task, we envisaged a more convergent approach starting from the cyclization precursor **1d** (Scheme 5). Indole **1d** was obtained from tryptophol by TIPS protection, carboxylation, lithiation, and then addition to the Weinreb amide **11**.[20] The cyclopropane **1d** was cyclized in the presence of a catalytic amount of TsOH, affording the tetracyclic core **17** of goniomitine (**3**) in 93% yield. The carbonyl group was reduced to the alcohol and acetylated. The acetate and the benzyl carbamate were cleaved in one step through hydrogenolysis. Deprotection of the primary alcohol gave goniomitine (**3**) in 77% overall yield from **17**.[21] The total synthesis of (±)-goniomitine (**3**) was accomplished in a longer linear sequence of 13 steps (5 purifications by column chromatography) with an overall yield of 11%.



Scheme 5. Total synthesis of goniomitine (**3**). Reagents and conditions: a) TsOH, CH_2Cl_2, 93%; b) $NaBH_4$, MeOH; c) Ac_2O, pyridine; d) Pd/C, H_2, EtOH; e) TBAF, THF, 77% overall. TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

Somewhat surprisingly, we were unable to find any studies about the bioactivity of goniomitine (**3**). In a first biological assessment we therefore investigated the cytotoxicity of this natural product. Preliminary results are highly promising as goniomitine displays nanomolar antiproliferative effects in several tumor cell lines (Table 2). Interestingly, unlike taxol and vinblastine, which are approximately 100-fold less effective in cells overexpressing P-gp (not shown), goniomitine did not lose its effect in the resistant MDR-1-MDCK cell line.

Table 2: Antiproliferative activity of goniomitine.

Cell lines	IC_{50} [nM][a]
A549	205 ± 27
MCF-7	239 ± 13
HCT116	281 ± 29
PC-3M	159 ± 24
MDCK	247 ± 10
MDR-1-MDCK	381 ± 17

[a] IC_{50} values for inhibition of human tumor cell growth; A549 (lung), MCF-7 (breast), HCT-116 (colon), PC-3M (prostate), MDCK (canine kidney). MDR-1-MDCK is a human P-glycoprotein 170 (P-gp170)-overexpressing multidrug-resistant cell line.[22]

In conclusion, we have demonstrated the versatility of aminocyclopropanes as (acyl)iminium precursors for intramolecular cyclizations. The reaction proceeded under mild conditions and control of the regioselectivity was possible by the right choice of catalyst and solvent. The power of the methodology has been demonstrated in the efficient formal total synthesis of aspidospermidine (**2**) and the total synthesis of goniomitine (**3**). First studies on the bioactivity of goniomitine revealed its relatively potent cytotoxicity (antiproliferative effect; IC_{50} = 150–400 nM) against several tumor cell lines. Preliminary data show that this natural product disrupts the microtubule network (not shown). Therefore, goniomitine is a potential new anticancer lead structure. In the future, the high convergence of our synthetic approach will allow access a large number of analogs of goniomitine (**3**) for structure–activity relationship studies. Applications of aminocyclopropanes as iminium precursors for other types of cyclization or addition reactions as well as the development of asymmetric cyclopropanation methods for enamides are currently under investigation in our laboratory and the results of this work will be reported in due course.

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[20] See the Supporting Information.

[21] The data contained in the 400 MHz ^{1}H NMR spectra of goniomitine (**3**) were identical to those of natural[9a] and synthetic[9b,c] goniomitine. The obtained values for ^{13}C NMR spectra fitted perfectly with the reported values for synthetic goniomitine, but small differences were apparent when compared with natural goniomitine. A comparison of the spectra is provided in the Supporting Information.

[22] See the Supporting Information for more details. See also: J. Gertsch, F. Feyen, A. Bützberger, B. Gerber, B. Pfeiffer, K. H. Altmann, *ChemBioChem* **2009**, *10*, 2513.

