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Synthesis of Aristoquinoline Enantiomers and Their Evaluation at the α3β4 Nicotinic Acetylcholine Receptor

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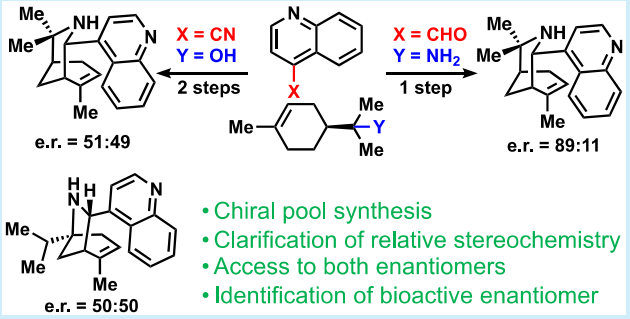
ABSTRACT: The first synthesis of aristoquinoline (**1**), a naturally occurring nicotinic acetylcholine receptor (nAChR) antagonist, was accomplished using two different approaches. Comparison of the synthetic material's spectroscopic data to that of the isolated alkaloid identified a previously misassigned stereogenic center. An evaluation of each enantiomer's activity at the α3β4 nAChR revealed that (+)-**1** is significantly more potent than (−)-**1**. This unexpected finding suggests that naturally occurring **1** possesses the opposite absolute configuration from indole-containing *Aristotelia* alkaloids.



Plants of the *Aristotelia* genus produce a family of alkaloids that feature indoles bonded to a monoterpene.[1] In most monoterpene indole alkaloids, the terpenoid portion is derived from secologanin. In contrast, the *Aristotelia* alkaloids incorporate tryptamine with a nonrearranged geranyl unit.[1,2] The resulting *Aristotelia* indole alkaloids possess a characteristic 3-azabicyclo[3.3.1]nonane architecture, as in hobartine (Figure 1A).[3] Additional family members such as peduncularine and aristoteline arise through cyclization with and rearrangements of the azabicyclic core.[4−6] The related quinoline alkaloid aristoquinoline (**1**) was isolated from the leaves of *Aristotelia chilensis* in 1993.[7,8] The biological activity of **1** went uninvestigated for >25 years, but recently Arias et al. determined that **1** is an antagonist of the nicotinic acetylcholine receptors (nAChRs).[8] Notably, **1** demonstrated an uncommon and desirable preference for the α3β4 subtype of nAChRs, which have been proposed as targets to treat a variety of substance use disorders.

Driven by this rare subtype selectivity and our group's interest in natural products to treat addiction,[9] we sought an efficient synthesis of **1** to characterize its biological activity. However, unlike the indole-containing *Aristotelia* alkaloids, whose absolute configurations have been confirmed by X-ray crystallography and total synthesis,[6,10] neither the absolute configuration nor the specific rotation of **1** has been reported. Moreover, the configuration of the C9 stereogenic center reported by Arias differs from that originally proposed by Cespedes.[7,8] Thus, while the configuration of **1** depicted in Figure 1A may be inferred from other *Aristotelia* alkaloids, we elected to define the relative and absolute configurations of **1** by synthesizing and evaluating the activity of each of its enantiomers.

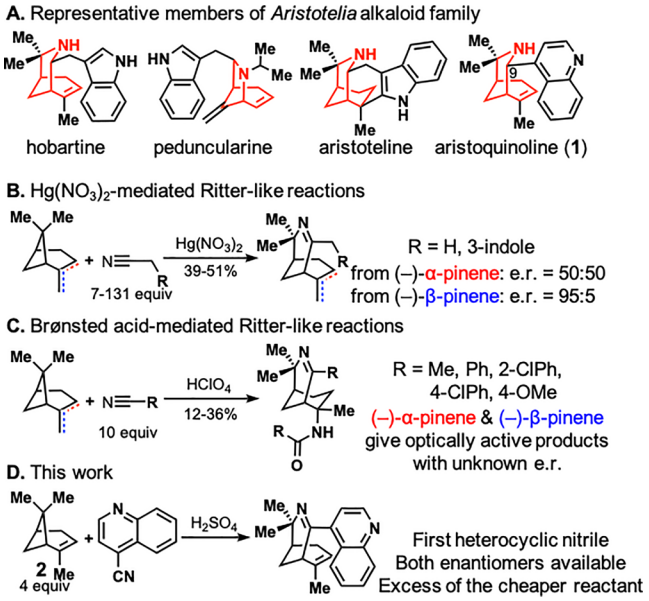


Figure 1. Convergent Ritter-like reactions between monoterpenes and nitriles are employed to synthesize the characteristic *Aristotelia* azabicyclic scaffold.

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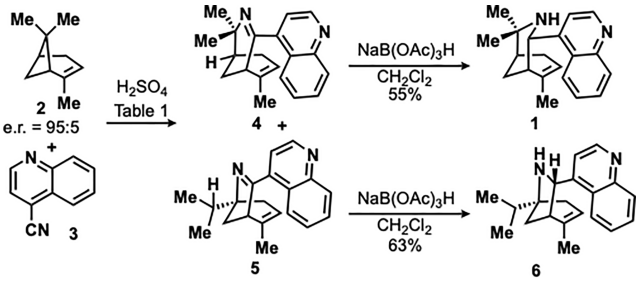
Several *Aristotelia* alkaloids have been synthesized by a variety of methods.[11−14] The earliest of these approaches employed $Hg(NO_3)_2$-mediated Ritter-like reactions between α- or β-pinene and alkyl nitriles to generate the 3-azabicyclo[3.3.1]non-6-ene core (Figure 1B).[11,12] When (−)-β-pinene was employed, these reactions were highly stereospecific, whereas (−)-α-pinene (**2**) yielded racemic products. Applying this strategy to the synthesis of both enantiomers of **1** is problematic, given the limited availability of (+)-β-pinene. Later studies did establish that Brønsted acids induced similar Ritter-like reactions, with both α- and β-pinene producing optically active products.[15−17] However, with Brønsted acids, amides arising from a second Ritter reaction were formed as the major products (Figure 1C). Moreover, the enantiopurity of these products was not reported. In addition to the stereochemical issues, the established Ritter-like reactions have suffered from the need for large excesses of the nitrile and have not been explored to introduce heterocycles like quinolines to the monoterpene core. Thus, we looked to overcome these limitations and leverage the Ritter-like reaction to provide rapid access to both enantiomers of **1** (Figure 1D).

Gratifyingly, the reaction of **2** and 4-cyanoquinoline (**3**) in the presence of H_2SO_4 produced the intended product **4** as the major product alongside an additional isomeric imine **5** (Scheme 1). A comparison of the corresponding ^1H and ^{13}C

Scheme 1. Synthesis of Aristoquinoline and Isoaristoquinoline[a]



[a]e.r. of **2** determined by optical rotation: $[\alpha]^{23}_D$ = −42.52, lit.[18] $[\alpha]^{23}_D$ = −47.25.

NMR spectra revealed a striking similarity between the two products, except for the geminal methyl groups, which appeared as a pair of singlets in **4** and a pair of doublets in **5**. COSY correlations in **5** indicated these methyl groups are contained in an isopropyl group adjacent to a quaternary carbon. Further analysis of the HMBC and COSY spectra revealed the imine nitrogen of the minor product was bound to the cyclohexene ring, consistent with the structure of **5**. Reduction of **4** with $NaB(OAc)_3H$ delivers a hydride to the less hindered face of the imine, producing a single diastereomer whose ^1H and ^{13}C spectra are consistent with naturally occurring **1** and (−)-**1** whose structure was confirmed by X-ray crystallography (*vide infra*). A similarly diastereoselective reduction of **5** yielded isoaristoquinoline (**6**).

Encouraged by these initial results, we looked to develop reaction conditions that would favor the selective formation of **4** (Table 1). The yields of **4** and **5** were minimally impacted when toluene was used in place of benzene, whereas the use of polar solvents such as acetic acid, DMF, and DMSO proved detrimental to the reaction (entries 1−5). Replacing H_2SO_4

Table 1. Optimization of the Ritter-Like Reaction Conditions

entry	2:3	solvent	temp	% yield **4**[a]	% yield **5**[a]
1	1:1	benzene	rt	21	3
2	1:1	toluene	rt	23 (20)	4 (4)
3	1:1	AcOH	rt	0	0
4	1:1	DMF	rt	0	0
5	1:1	DMSO	rt	0	0
6[b]	1:1	toluene	rt	0	0
7	1:1	toluene	−10 °C	19	3
8	1:1	toluene	110 °C	15	3
9	1:4	toluene	rt	23	8
10	4:1	toluene	rt	35	7
11[c]	4:1	toluene	rt	29	5
12[d]	4:1	toluene	rt	41	6

[a]Yields determined by ^1H NMR. Isolated yields in parentheses. [b]$HBF_4{\cdot}OEt_2$, TFA, or polyphosphoric acid used instead of H_2SO_4. [c]**7** used in place of **2**. [d]**8** used in place of **2**.

with other Brønsted acids resulted in no observed product formation (entry 6). Neither cooling nor heating the reactions led to substantial changes in the product yields (entries 7−8). Conducting the reactions with an excess of α-pinene **2** did improve the yields of imine **4**, whereas increasing the relative amounts of nitrile **3** led to a slight increase in the undesired product **5** (entries 9−10).

Finally, both **4** and **5** were produced in similar yields when (−)-limonene (**7**) and (−)-α-terpineol (**8**) were used in place of **2** (entries 11−12). Interestingly, under all the reaction conditions tested, no evidence of products arising from a second Ritter reaction was observed via LC/MS or ^1H NMR analysis of the crude reaction mixtures. With these optimized conditions, the yield of **4** is comparable to that observed with previous studies; however, these conditions avoid the use of large excess of the nitrile and instead rely on an excess of the abundant, inexpensive terpenes.

While these conditions allowed for a convergent synthesis of **1**, the products from these reactions were nearly racemic. Notably, terpenes **2**, **7**, and **8** all resulted in products with similarly low levels of enantiopurity. Given this surprising departure from previous Brønsted-acid-catalyzed Ritter reactions,[15] we looked to investigate the reaction mechanism in hopes of being able to design a more stereoselective reaction. The formation of **4** and **5** is consistent with the mechanism proposed in Scheme 2A. In the presence of acid, **2**, **7**, and **8** generate the same carbocation intermediate **9**. Nucleophilic attack of the carbocation of intermediate **9** by **3** in a Ritter-like reaction forms a nitrilium ion that is subsequently intercepted by the endocyclic olefin, ultimately giving rise to **4**. Conversely, if **9** undergoes a 1,2-hydride shift to form **10** prior to attack by the nitrile, imine **5** is produced. Intermediate **10** may also be formed from the deprotonation of **9** to **11** and subsequent reprotonation of the tetrasubstituted olefin. The low enantiomeric ratio of **4** suggests that the conversion of **9** to the achiral intermediates **10** or **11** is reversible. Alternatively, the stereochemical scrambling of the products may arise from the reversible protonation of the endocyclic olefin to generate an achiral carbocation intermediate.

To investigate these possible mechanisms, two isotopic labeling studies were conducted. First, the reaction between **3** and **8** was conducted in the presence of D_2SO_4 (Scheme 2B). If intermediate **11** is formed during the reaction, products **4**

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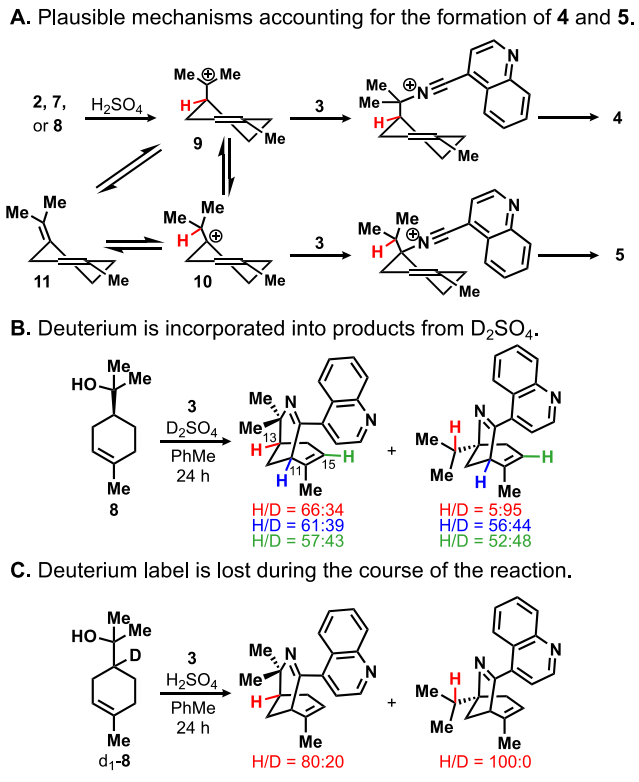
Scheme 2. Mechanistic Studies Examining Racemization and Product Formation

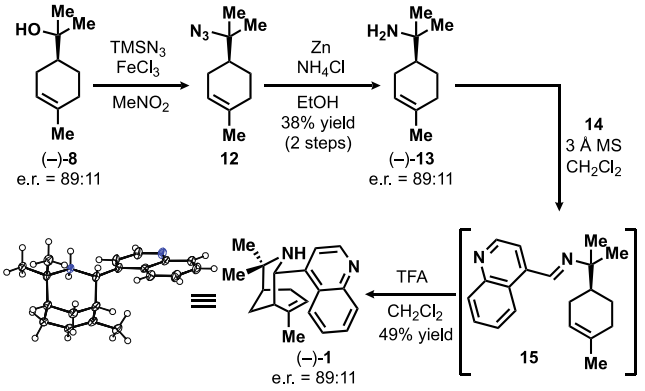


and **5** would be expected to incorporate a deuterium atom at C13. Indeed, under these conditions, compounds **4** and **5** are 34% and 95% deuterated at these positions, clearly showing intermediate **11** is formed in the reaction. To confirm that a concerted 1,2-hydride shift does not occur, deuterium-labeled terpineol (d_1-**8**) was synthesized from the reduction of terpinolene oxide with $LiAlD_4$.[19] Reacting d_1-**8** with **3** in the presence of H_2SO_4 produced **4** and **5** with 80% and 100% loss of deuterium at C13, respectively (Scheme 2C). Taken together, these studies reveal that the interconversion of **9** and **10** occurs through the generation of intermediate **11**.

With these mechanistic understandings, it is likely the modest yields of **4** are due to the poor nucleophilicity of **3**, particularly under the acidic reaction conditions that lead to the protonation of the quinoline nitrogen. Notably, under similar reactions aryl nitriles that lack a basic nitrogen do not produce isomeric products like **5**.[15,16] This finding suggests that the reduced nucleophilicity of **3** also contributes to the formation of **5**, by slowing the production of **4** such that the conversion from **9** to **10** is competitive. The low nucleophilicity of **3** may also explain why products arising from the second Ritter reaction were not observed. Regarding the stereoselectivity of the transformation, the incorporation of deuterium at C11 and C15 of **4** and **5** in the presence of D_2SO_4 (Scheme 2B) indicates that protonation of the endocyclic olefin also contributes to the racemization of the products. This suggests that Brønsted-acid-promoted Ritter reactions are unlikely to yield **4** with high levels of enantiopurity.

In light of these considerations, we reasoned that reversing the roles of the nucleophile and electrophile could improve both the yield and stereoselectivity of the reaction. To test this hypothesis, we adopted an alternative approach employing an aza-Prins reaction as the key cyclization event (Scheme 3).[13] The tertiary alcohol of (−)-**8** was first converted to the

Scheme 3. Stereoselective Synthesis of (−)-Aristoquinoline[a]



[a]X-ray crystallography was performed on the dihydrochloride salt of (−)-**1**. Ellipsoids in the ORTEP drawing indicate 50% probability.

corresponding azide **12**.[20] Subsequent reduction of **12** with zinc provided the primary amine (−)-**13**. Condensation of (−)-**13** and 4-quinolinecarboxaldehyde (**14**) in the presence of 3 Å molecular sieves produced the imine **15**. Although **15** proved difficult to isolate, the addition of a solution of **15** generated *in situ* to TFA led to the rapid and exclusive formation of **1**.

Excitingly, **1** formed through this route possessed considerably improved enantiopurity (e.r. = 89(−):11(+)) compared to the Ritter-like reaction product. A closer inspection of (−)-**8** by optical rotation and (−)-**13** by conversion to its corresponding (*R*)-Mosher amide revealed the intermediates possessed similar levels of enantiopurity, indicating the aza-Prins reaction proceeds with complete stereospecificity. Using this enantioenriched material, the configuration of the C9 stereogenic center and absolute configuration of (−)-**1** was determined through single-crystal X-ray diffraction.[21] In this X-ray crystal structure, the aromatic quinoline ring is positioned directly over the C17 methyl group, accounting for its considerable upfield shift in the ^{1}H NMR spectrum (δ = 0.66 ppm).[7] Notably, the structure proposed by Arias places the quinoline distal to the C17 methyl group and is unlikely to produce the observed anisotropic effect.[8] Finally, adopting an identical procedure, (+)-**8**[22] was successfully converted to (+)-**1** in 13% overall yield and high enantiopurity (e.r. ≤ 1(−):99(+)).

With both enantiomers of **1** in hand, we turned our attention to evaluating their activities at the rat $\alpha3\beta4$ nAChRs by employing a cell-based Ca^{2+} influx assay (Table 2). As expected, neither the enantiomer of **1** nor racemic **6** produced any activation of the nAChRs at concentrations up to 100 μM. However, **1** and **6** effectively inhibited the action of (±)-epibatidine with similar potency to the pan-nAChR channel blocker (±)-mecamylamine. Interestingly, (+)-**1** antagonizes the $\alpha3\beta4$ nAChRs more potently than (−)-**1** and is nearly identical to the IC_{50} reported for **1** isolated from *A. chilensis*,[8] strongly implying that (+)-**1** is the naturally occurring enantiomer.

In conclusion, we have investigated two approaches to **1**, resulting in the first synthesis of the alkaloid. By studying the mechanism behind the Ritter-like reaction, we determined this classical approach is unlikely to lead to enantioenriched **1**. Our

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Table 2. Activity at the Rat $\alpha3\beta4$ nAChRs Determined by Calcium Influx Assay

compound	e.r.[a]	EC_{50} (μM)[b]	E_{max} (%)[c]	IC_{50} (μM)[d]
(±)-**1**	51:49	--	<5	3.5 ± 0.9
(−)-**1**	89:11	--	<5	3.4 ± 1.2
(+)-**1**	1:99	--	<5	0.89 ± 0.36
6	50:50	--	<5	3.4 ± 0.6
MEC[e]	50:50	--	<5	1.1 ± 0.1
EPI[f]	50:50	0.028 ± 0.006	100	0.012 ± 0.001

[a]Ratios of (−)-**1**:(+)-**1** and (−)-**6**:(+)-**6** determined by chiral HPLC. [b]Half maximal effective concentration. EC_{50} values are not reported for compounds eliciting <5% receptor activation. [c]Maximal effective concentration relative to the maximal effect elicited by the agonist (±)-epibatidine. [d]Half maximal inhibitory concentration for inhibition of receptor activation evoked by 100 nM (±)-epibatidine. [e](±)-Mecamylamine. [f](±)-Epibatidine.

second strategy to form the 3-azabicyclo[3.3.1]non-6-ene via an aza-Prins cyclization led to **1** with good enantiopurity, which enabled us to unambiguously establish the absolute and relative configuration via X-ray crystallography. With access to both enantiomers of **1**, we identified that (+)-**1** possesses considerably greater inhibitory activity at the $\alpha3\beta4$ nAChR than its antipode. While the activity observed is similar to that reported for the isolated alkaloid, the configuration of (+)-**1** is opposite that reported for other *Aristotelia* alkaloids including those found in *A. chilensis*. This unexpected result indicates that in addition to being unique as the sole quinoline-containing *Aristotelia* alkaloid **1** also appears to be the only member of its enantiomeric series. In addition to these naturally occurring alkaloids, the novel isoaristoquinoline **6** bearing a 6-azabicyclo[3.2.1]oct-2-ene scaffold reminiscent of peduncularine was also shown to possess inhibitory activity and thus represents the first entry into a previously unknown class of nAChR ligands. The application of this step-economic synthesis to the generation of aristoquinoline analogues to elucidate structure−activity relationships is ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02057.

Experimental details, compound characterization data, results of deuterium labeling experiments, representative assay results, and concentration−response curves (PDF)

Accession Codes

CCDC 2084820 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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