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Stable Bromiranium Ion Salts as Reagents for Biomimetic Indole Terpenoid Cyclizations

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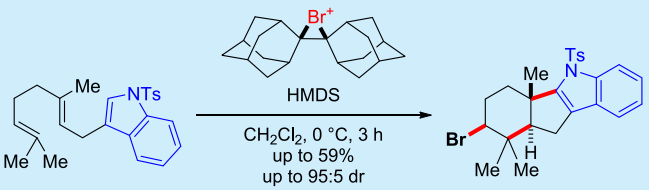
Supporting Information

ABSTRACT: Indole terpene alkaloids are a diverse group of natural products and show significant biological activities. To enable their biomimetic synthesis, electrophilic bromocyclization of polyenyl indole derivatives could be achieved using sterically demanding bromiranium ion salts with the weakly coordinating counterion $BArF^-$ as reagent. Starting from polyenyl indole derivatives, the corresponding bromocyclization products have been obtained with very high diastereoselectivity and in good yields.



Indole terpene alkaloids are a diverse group of natural products mostly isolated from plants or fungi.[1] Quite a few of these alkaloids have been identified in plants used in traditional medicine including the bruceollines[2] (from *Brucea mollis*), polyveoline,[3] or polyavolensinol[4] (both from *Polyalthia suaveolens*). Bruceollines such as bruceolline J (Figure 1)

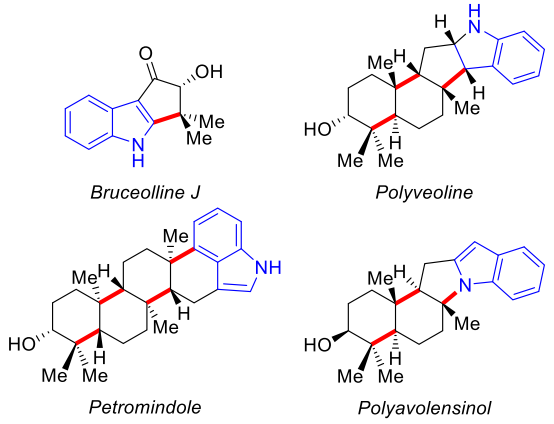


Figure 1. Selected indole terpene alkaloids containing prenyl-, farnesyl-, or geranylgeranyl-based carbon skeletons.

contain a prenylated and cyclized indole core and are active against *P. falciparum*, the causative agent of malaria.[5] Polyveoline and polyavolensinol are more complex, containing cyclized farnesyl side chains. These alkaloids show significant biological acitivity against Trypanosoma and other protozoan organisms.[6] In general, the biosynthesis of indole terpene alkaloids proceeds via alkylation of the indole core by a prenyl transferase, followed by epoxidation and terpene-like cyclization of the side chain, generating highly complex natural products out of simple precursor molecules.[7,8] Due to their complex structure and interesting biological activities, several indole terpene alkaloids have been the target of total syntheses.[9] While most syntheses employed traditional retrosynthetic approaches, several groups followed biomimetic strategies. This includes several attempts to build up the carbon skeleton of a selected indole terpene via biomimetic polyene-type cyclizations.[8,10] For example, Clark and coworkers prepared a linear cyclization precursor for the synthesis of emindole SB.[8e] One disadvantage of these epoxide-induced polyene cyclizations is the requirement for prefunctionalization (selective epoxidation of the terminal alkene) of the isoprenoid chain. This is not necessary for halenium-induced polyene cyclizations, which can be applied directly on the linear polyenes. Furthermore, several recently developed halogenation methods provide highly reactive halenium equivalents, which promise higher reaction yields than the epoxid cyclizations.[11,12] Herein, we investigate biomimetic polyene-type cyclizations of indole-based starting materials employing a stable bromiranium ion salt as highly reactive brominating agent.[13] The results show that by using this reagent, effective and highly diastereoseletive polyene cyclizations to indole terpenoid mimics are possible.

Initially, the monocyclization of prenylated, tosyl-protected indole **1a** was investigated. When **1a** was treated with common electrophilic brominating agents such as NBS, TBCO, or DBDMH in dichloromethane, only traces of the 5-*endo* cyclization product **2a** were observed as determined by gas chromatography (Table 1, entries 1−3). Conducting the reaction with NBS and morpholine in HFIP, as reported by Gulder[11d] for related polyene-type cyclizations, produced the product **2a** in 8% yield (entry 4). The use of Snyder's BDSB reagent[11b] in nitromethane provided a similar yield (5%, entry

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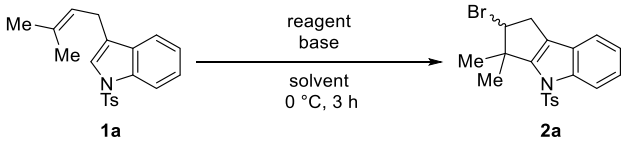
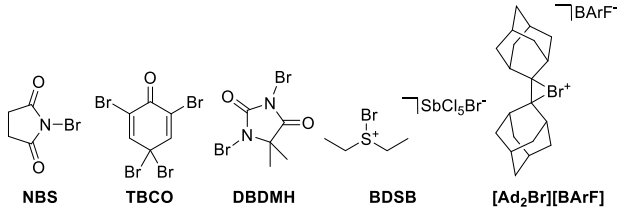
Table 1. Optimization of Conditions for Electrophilic Bromo Cyclization Reaction Using Precursor 1a*



1a **2a**

entry	reagent	eq.	base	solvent	yield[a]
1	NBS	1.2	-	CH_2Cl_2	0
2	TBCO	1.2	-	CH_2Cl_2	0
3	DBDMH	1.2	-	CH_2Cl_2	2
4[b]	NBS	1.2	morpholine[b]	HFIP	8
5[c]	BDSB	1.1	-	$MeNO_2$	5
6	[Ad_2Br][BArF]	1.0	HMDS	CH_2Cl_2	56
7	**[Ad_2Br][BArF]**	**1.2**	**HMDS**	**CH_2Cl_2**	**59**
8[c]	[Ad_2Br][BArF]	1.2	HMDS	CH_2Cl_2	57
9	[Ad_2Br][BArF]	1.5	HMDS	CH_2Cl_2	45
10	[Ad_2Br][BArF]	2.0	HMDS	CH_2Cl_2	31
11	[Ad_2Br][BArF]	1.2	collidine	CH_2Cl_2	17
12	[Ad_2Br][BArF]	1.2	pyridine	CH_2Cl_2	2
13	[Ad_2Br][BArF]	1.2	DTBMP	CH_2Cl_2	49



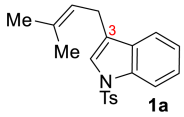
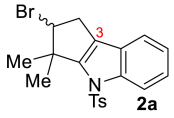
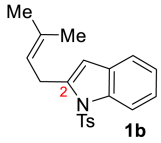
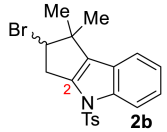
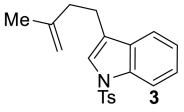
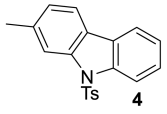
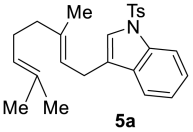
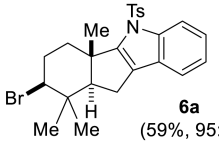
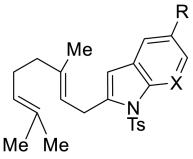
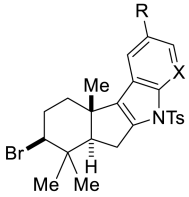
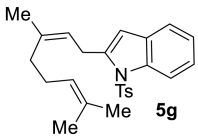
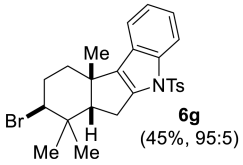
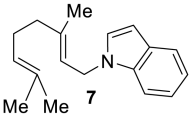
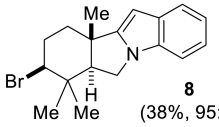
*Conditions: **1a** (0.1 mmol, 1.0 equiv), base (1.2 equiv), CH_2Cl_2 (0.05 M). [a]Yield determined by gas chromatography using *n*-hexadecane as internal standard. [b]Morpholine·2HFIP (1.4 equiv). [c]Reagent added as solution.

5). In general, gas chromatography showed that in many cases either conversions were low or products were accompanied by a large amount of various side products.

When **1a** was treated with 1.0 equiv of [Ad_2Br][BArF][13] and HMDS, the 5-*endo* cyclization product **2a** was obtained in significantly improved yield (56% by GC, entry 6). Using 1.2 equiv of [Ad_2Br][BarF] the yield improved slightly to 59% (entry 7). Adding the reagent as a solution did not lead to an improved yield (entry 8). Surprisingly, higher amounts of the reagent such as 1.5 or 2.0 equiv of [Ad_2Br][BArF] did not result in increased yields, mostly due to the increased formation of unidentifiable side products (entries 9 and 10). When the base HMDS was replaced by less sterically hindered collidine or even pyridine the yield of cyclization product **2a** dropped strongly (entries 11 and 12). However, HMDS could be replaced by the sterically highly demanding 2,6-di(*tert*-butyl)methylpyridine (DTBMP) without a significant drop in yield (entry 13). NMR experiments confirmed that this behavior is caused by the coordination of the smaller pyridines to the [Ad_2Br][BArF] reagent, while HMDS or DTBMP do not coordinate. Attempts to improve the yield by the use of an alternative *N*-protecting group were not successful (see the Supporting Information for details).

With the optimized reaction conditions in hand, the cyclization of various prenylated and geranylated indoles was investigated (Table 2).

Table 2. Bromonium-Induced Polyene-Type Cyclization of Substituted Indoles*

starting material	product (yield[a], dr[b])
 **1a**	 **2a** (48%)
 **1b**	 **2b** (25%)
 **3**	 **4** (20%)
 **5a**	 **6a** (59%, 95:5)
 **5b** (X = CH, R = H) **5c** (X = CH, R = OMe) **5d** (X = CH, R = F) **5e** (X = CH, R = CN) **5f** (X = N, R = H)	 **6b** (X = CH, R = H: 53%, 93:7) **6c** (X = CH, R = OMe: 21%, 93:7) **6d** (X = CH, R = F: 31%, 93:7) **6e** (X = CH, R = CN: 16%, 93:7) **6f** (X = N, R = H: 18%, 93:7)
 **5g**	 **6g** (45%, 95:5)
 **7**	 **8** (38%, 95:5)

*Conditions: substrate (0.4 mmol, 1.0 equiv), HMDS (0.48 mmol, 1.2 equiv), [Ad_2Br][BArF] (0.48 mmol, 1.2 equiv) in CH_2Cl_2 (0.05 M). [a]Isolated yields. [b]Determined by ^1H NMR spectroscopy from the crude reaction mixture.

On a 0.4 mmol scale, the 3-prenylated indole **1a** underwent 5-*endo* cyclization to the product **2a** in 48% isolated yield (56% GC yield), which compares well with the reaction on a lower scale (Table 1). For the 2-prenylated derivative **1b**, the cyclization yield was significantly lower (25%). Indole **3**, the double bond isomer of **1a**, provided upon treatment with [Ad_2Br][BArF] a complex reaction mixture from which only

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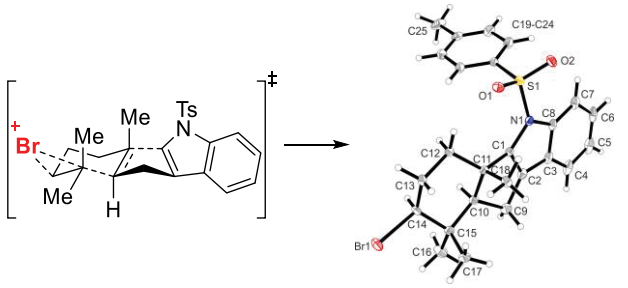
carbazole **4** could be isolated in 20% yield. Compound **4** could be formed by a 6-*endo* cyclization followed by elimination and oxidation to the carbazole. When the 3-geranyl-substituted indole **5a** was utilized, the reaction proceeded smoothly to the corresponding bromocyclization product **6a** with excellent diastereoselectivity (95:5 dr) and very good yield (59%). 2-Geranyl derivative **5b** reacted in a very similar manner and provided cyclization product **6b** with very similar diastereoselectivity (93:7 dr) and good yield (53%). This reaction was repeated on a 1.0 mmol scale, in which case the product was obtained with almost identical yield (51%) and diastereoselectivity (93:7 dr). The indole core had a significant impact on the yield of this cyclization, and starting materials with electron-rich (**5c**) as well as more electron-poor indoles (**5e**, **5f**) led to low yielding cyclizations (16−21%). Fluoroindole **5d** gave the cyclization product in moderate yield (31%). At the moment, it is not fully clear why electron-donating as well as electron-withdrawing substituents have a deleterious effect on the cyclization. However, at least for the electron-rich indole derivative **5c**, bromination of the indole core can be suspected as a problem.

The relative configuration of the major diastereomers of the cyclization of geranyl indoles **6a** and **6b** could be established by X-ray crystallography (**6a**: Scheme 1). The obtained

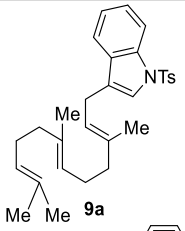
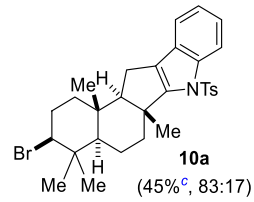
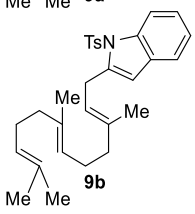
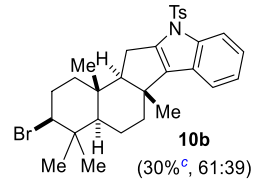
Scheme 1. Transition- and Solid-State Structures of 6a



configuration is in line with the expected configuration for a concerted cyclization reaction via a chair conformation with *trans*-additions across the alkene following the Eschenmoser−Stork postulate (Scheme 1).[14] This also suggested that a diastereomeric product of **6a** should be available by cyclization of a neryl indole. This was confirmed by treatment of 2-neryl indole **5g** with [Ad_2Br][BArF] leading to product **6g** with excellent diastereoselectivity (95:5 dr) and in good yield (45%). The relative configuration of **6g** was established by NOE investigations to be diastereomeric to **6b** as predicted. Finally, the cyclization of *N*-geranyl indole **7** was investigated. This cyclization provided the product **8** again with excellent diastereoselectivity and a yield of 38%. Although the yield is slightly lower than for 2- or 3-geranyl indoles, it shows that the cyclization does not require a strongly electron-withdrawing protecting group at the indole nitrogen.

One of the surprising results of the investigations was the often improved cyclization yield for geranyl substituents, involving two C−C bond-forming steps, compared to prenyl substituents, involving only one C−C bond formation. While this could be caused by the lower stability of **2a**/**2b**, which contain the bromo substituent at a five-membered ring, it cannot be excluded that the cascade cyclization to geranyl products **6** is proceeding via a mechanistically distinct pathway. The good yields obtained for the cyclization of the geranyl-substituted indoles suggested that the cyclization of farnesyl derivatives should also be possible (Table 3). The 3- and 2-

Table 3. Bromo Cyclization of Farnesyl Indoles 9*

starting materials	products (yield[a], d.r.[b])
	
	

*Conditions: substrate (0.4 mmol, 1.0 equiv), HMDS (0.48 mmol, 1.2 equiv), [Ad_2Br][BArF] (0.48 mmol, 1.2 equiv) in CH_2Cl_2 (0.05 M). [a]Isolated yields, [b]Determined by ^1H NMR spectroscopy of the crude reaction mixture, [c]Isolated as inseparable mixture of diastereomers.

farnesyl *N*-tosyl indoles **9a** and **9b** were prepared and subjected to the standard reaction conditions. 3-Farnesyl indole **9a** underwent the bromenium-induced polyene-type cyclization involving three C−C bond formations with a good yield (45%) and acceptable diastereoselectivity (83:17 dr). 2-Farnesyl indole derivative **9b** also underwent the cyclization in moderate yield, but with only low diastereoselectivity (61:39 dr). Based on the observation made for geranyl cyclization, it is assumed that the major diastereomer results from cyclization via a chair−chair conformation; however, no crystals for X-ray crystallography could be obtained. The lower diastereoselectivity for the farnesyl cyclizations might be due to the two pseudo-1,3-diaxial interactions in a possible chair−chair transition state leading also to cyclization via alternative, energetically comparable transition states.

In conclusion, it was shown that [Ad_2Br][BArF] can be applied as an electrophilic brominating agent in bromenium-induced polyene-type cyclization reactions of prenyl, geranyl, and farnesyl indole derivatives. In most cases, the cyclizations were highly diastereoselective and provided a range of terpenoid indole type building blocks, which will be useful for the synthesis of indole terpene alkaloids. This is especially apparent for the polyveoline alkaloids, whose carbon skeleton was assembled in a single bromination/cyclization step from unfunctionalized 2-farnesyl indole.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00259.

General experimental procedures, characterization data, and details on X-ray structure determination (PDF)

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Accession Codes

CCDC 1863343−1863346 contain 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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Notes

The authors declare no competing financial interest.

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