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Synthesis Design

Facile Installation of 2-Reverse Prenyl Functionality into Indoles by a Tandem N-Alkylation–Aza-Cope Rearrangement Reaction and Its Application in Synthesis

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Abstract: An unprecedented tandem N-alkylation–ionic aza-Cope (or Claisen) rearrangement–hydrolysis reaction of readily available indolyl bromides with enamines is described. Due to the complicated nature of the two processes, an operationally simple N-alkylation and subsequent microwave-irradiated ionic aza-Cope rearrangement–hydrolysis process has been uncovered. The tandem reaction serves as a powerful approach to the preparation of synthetically and biologically important, but challenging, 2-reverse quaternary-centered prenylated indoles with high efficiency. Notably, unusual nonaromatic 3-methylene-2,3-dihydro-1*H*-indole architectures, instead of aromatic indoles, are produced. Furthermore, the aza-Cope rearrangement reaction proceeds highly regioselectively to give the quaternary-centered reverse prenyl functionality, which often produces a mixture of two regioisomers by reported methods. The synthetic value of the resulting nonaromatic 3-methylene-2,3-dihydro-1*H*-indole architectures has been demonstrated as versatile building blocks in the efficient synthesis of structurally diverse 2-reverse prenylated indoles, such as indolines, indole-fused sultams and lactams, and the natural product bruceolline D.

Introduction

2-Reverse prenylated indole natural products are widely distributed in a number of terrestrial and marine fungi.[1] These natural products display a broad spectrum of biological and pharmacological activities, including cytotoxicity against a number of cancer cell lines, antimicrobial and antiviral activities, and effects on the central nervous systems, which are distinct from the non-prenylated parent structures (Figure 1).[2] Their intriguing biological properties underscore their potential application as useful probes to elucidate the biological pathways and mechanisms and targets involved. They can also serve as lead compounds for the development of new therapeutic agents. A combination of their activity, questions about their modes of biological action, and challenges of their syntheses make them attractive targets for synthesis and mechanism-of-action studies.[3]

2-Reverse prenylated indole alkaloids are among the most challenging class of natural products currently targeted by the synthesis community. The structures of 2-reverse prenylated indole alkaloids feature the same core unit of the 2-reverse prenylated indole component (Figure 1). Therefore, construction of the challenging quaternary-centered reverse prenyl unit in the indole scaffold is critical to their syntheses. The lack of versatile, efficient synthetic methodologies is one of the major bottlenecks in this field. More than a decade has passed, since the only useful method developed by Danishefsky in 1999 was reported [Scheme 1, Eq. (1)].[4] The strategy involves two steps: in situ 3-chlorination of an indole by treatment with *t*BuOCl is followed by a reaction with prenyl 9-BBN through a nucleophilic substitution rearrangement to give the desired 2-reverse prenylated indoles. The reaction has been successfully used as a key step in the total synthesis of the indole alkaloids gypsetin,[5] (+)-ambiguine H,[5] and asterriquinone B1.[6] An alternative approach is the Cope rearrangement reaction [Scheme 1, Eq. (2)].[7] Although the process looks more appealing because it uses readily accessible starting materials, the poor reaction efficiency limits its synthetic application. Not only was the yield (27%) far from satisfactory, two isomers were also produced in the transformation studied by Sakamoto et al.[7c]

Herein, we report the results of an investigation that has led to an unprecedented tandem N-alkylation–ionic aza-Cope rearrangement–hydrolysis reaction (Scheme 2).[8] The process serves as a useful strategy for the facile installation of the challenging 2-reverse quaternary-centered prenyl functionality into

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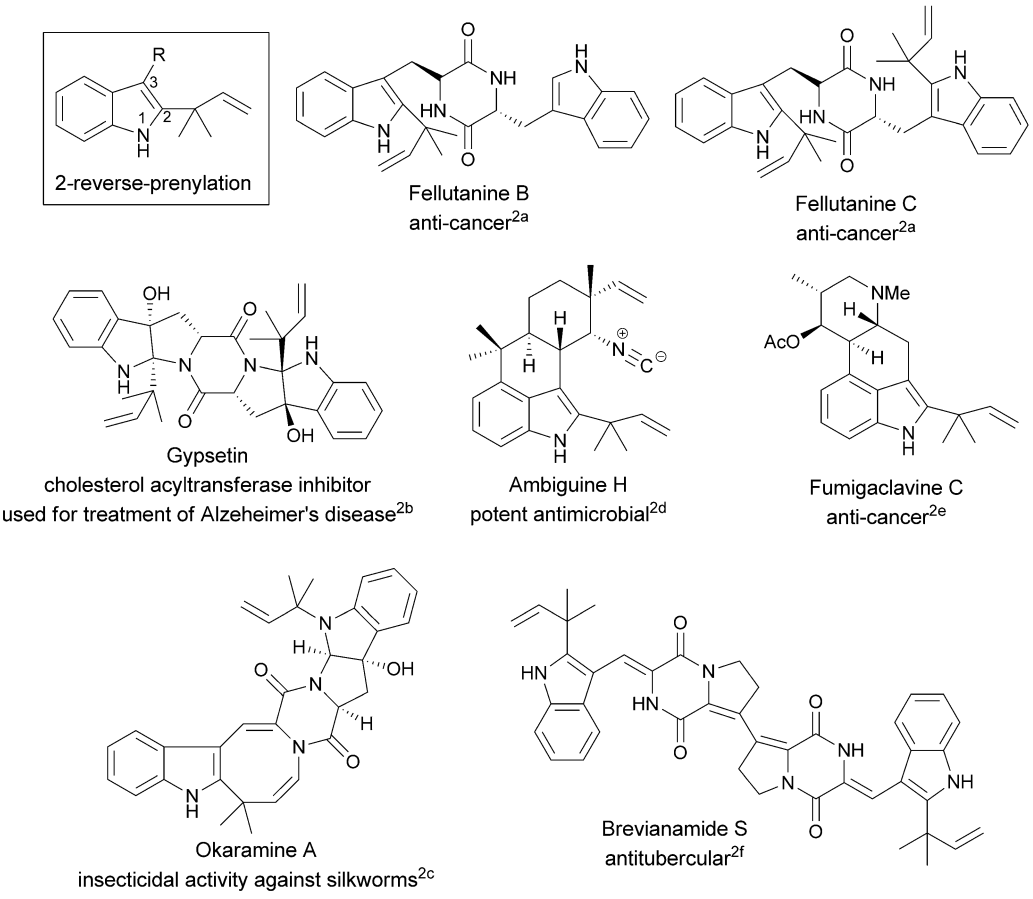
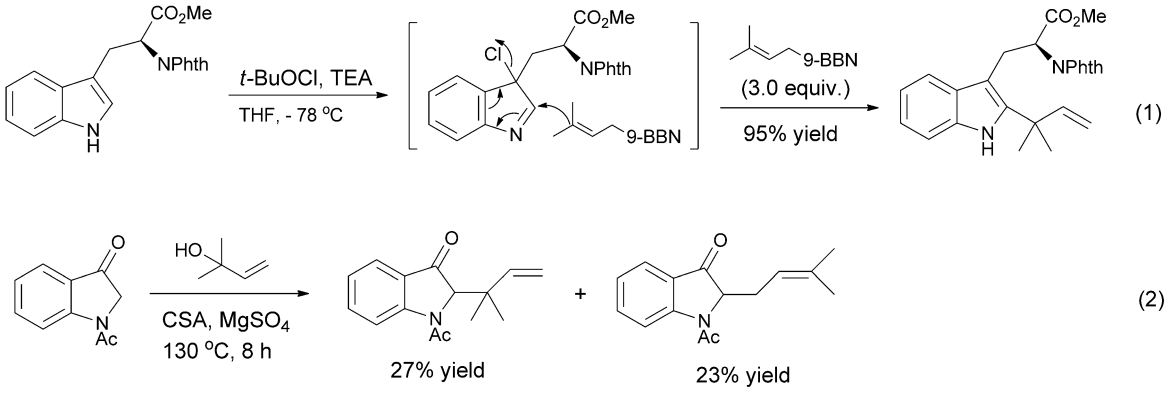
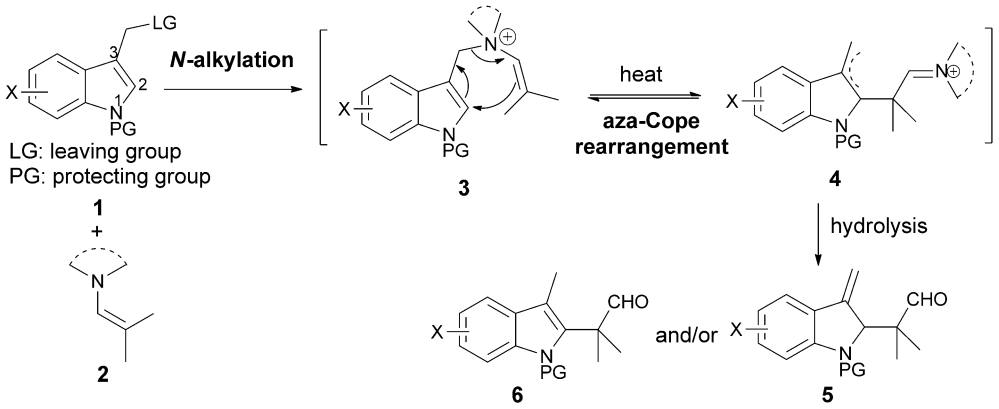


Figure 1. Selected examples of 2-reverse prenylated indole alkaloids.



Scheme 1. Very limited methods available for the synthesis of 2-reverse prenylated indoles. Phth = phthaloyl, TEA = triethylamine, 9-BBN = 9-borabicyclo[3.3.1]-nonane, CSA = camphorsulfonic acid.

indoles with high regioselectivity and in good yields. Through the careful screening of substrates and optimization of the reaction conditions, we have identified readily available indolyl bromides and enamines as effective reactants. Furthermore, the two reactions require different reaction conditions. We have managed to identify an operationally simple, sequential N-alkylation, followed by microwave-irradiated ionic aza-Cope rearrangement–hydrolysis processes. Notably, unusual, nonaromatic, synthetically even more useful 3-methylene-2,3-dihydro-1*H*-indole architectures, instead of aromatic indoles, are produced under the reaction conditions. Moreover, the aza-Cope rearrangement reaction gives a highly regioselective quaternary-centered reverse prenyl functionality, which often produces a mixture of two regioisomers by previously reported methods.[7c] The synthetic utilities of the resulting nonaromatic 3-methylene-2,3-dihydro-1*H*-indole architectures have been demonstrated as versatile building blocks in the efficient synthesis of structurally diverse 2-reverse prenylated indoles, such as in-



Scheme 2. Design of the N-alkylation–aza-Cope rearrangement–hydrolysis cascade process for the synthesis of 2-reverse prenyl indoles.

dolines, indole-fused sultams and lactams, and the natural product bruceolline D.

Results and Discussion

Design of N-alkylation–aza-Cope rearrangement tandem processes

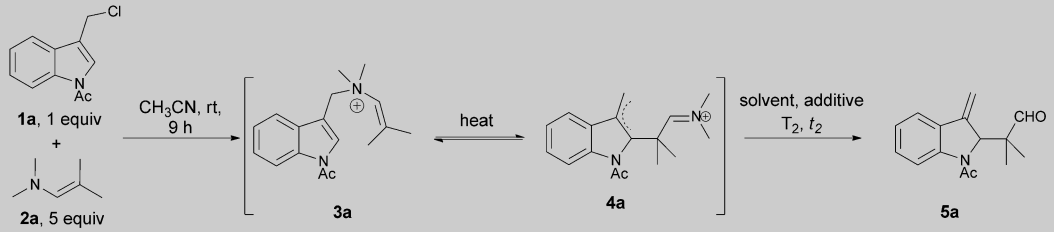
The Claisen and Cope rearrangements are known as viable synthetic tools for the construction of C–C bonds with tertiary and quaternary carbon centers.[9] However, compared with the classic Cope rearrangement reaction, the aza-Cope version requires much harsher reaction conditions because more energy is essential to bring the nitrogen atom into the chair topology of the transition state.[10,11] Recent studies revealed that the quaternized "N" molecules could dramatically reduce the energy and enable the rearrangement to occur under milder conditions.[8,12] As an intriguing extension of these protocols, coupling of 3-substituted indoles **1** with nucleophilic *N*,*N*-dimethylisobutenylamine and its analogues **2** would in situ produce essential quaternized N intermediates, which could undergo a subsequent aza-Cope rearrangement. A class of compounds composed of *N*,*N*-dimethylisobutenylamine and its analogues **2** are specifically designed for this purpose. It is expected that the rearrangement products will contain the 2-reverse prenyl precursor, which is a versatile *gem*-dimethyl aldehyde functionality that can be conveniently transformed into 2-reverse prenyl group and its derivative through a Wittig reaction. It is reasonably proposed that the more stable aromatic indole products **6** may be produced dominantly. Nevertheless, nonaromatic 3-methylene-2,3-dihydro-1*H*-indole holds even more broad synthetic utilities.

Exploration and optimization of the proposed tandem N-alkylation–aza-Cope rearrangement

We commenced our study by exploring the proposed tandem N-alkylation–aza-Cope rearrangement, followed by hydrolysis, by using *N*-acyl indolyl chloride (**1a**) and *N*,*N*-dimethylisobutenylamine **2a** as starting materials (Table 1). As a result of stability concerns for enamine **2a**, an excess amount (5.0 equiv) was used and the N-alkylation reaction was carried out in aprotic CH_3CN. Although, according to the theoretical studies of Jorgensen and Severance,[13] protic solvents offer favorable hydrogen-bonding interaction effects on the rate of pericyclic reactions. Therefore, as a compromise, we carried out the two reactions in two different media. Under these reaction conditions, surprisingly, nonaromatic indoline **5a** was formed exclusively. Furthermore, to our delight, the N-alkylation reaction was completed within 9 h in CH_3CN to give the desired more sterically demanding 2-reverse prenyl regioisomer.

After removal of the solvent, a new protic medium was added for the subsequent aza-Cope rearrangement process. It appeared that the solvents had an important effect on the process (Table 1). An accelerating effect of microwave irradiation was observed with water as the solvent in an initial study (Table 1, entry 3). Under regular heating, a long reaction time was needed and the yield was low (Table 1, entries 1 and 2; 100 °C, 3 and 12 h, 22 and 17% yield, respectively), whereas with microwave irradiation, the reaction time was shortened dramatically and the yield improved as well (Table 1, entry 3; 0.8 h, 26% yield). The addition of ethanol to water (EtOH/H_2O 1:2) delivered a better yield (Table 1; entry 4, 31% yield). It was also observed that the amount of EtOH played a role in governing the yield. A higher ratio of EtOH/H_2O was beneficial, presumably due to improved solubility of the reactants (Table 1, entries 4–6). Nonetheless, interestingly, in pure ethanol, almost no desired product was formed (Table 1, entry 7). This suggests that water is critical for the reaction, which is consistent with the theoretical studies of Jorgensen and Severance.[12] Furthermore, water could also facilitate the hydrolysis of the iminium ion **4a** to give aldehyde **5a**, which rendered the process irreversible (Scheme 1). We then investigated the rearrangement reaction time because the stability of in situ generated iminium species **4a** could also be affected by water (Table 1, entries 6 and 8–10). Indeed, 1.5 h was suitable for achieving a much improved yield of 48%. Accordingly, 1.5 h was chosen for further optimization. Among different solvent systems probed (Table 1, entries 8 and 11–14), a combination of *i*PrOH/water (4:1) showed the best result with 51% yield

Table 1. Exploration and optimization of aza-Cope rearrangement reaction.[a]



Entry	Solvent	Additive (2.0 equiv)	T_2 [°C]	t_2 [h]	Yield [%] (2 steps)[b]
1	H_2O	–	100[c]	3	22
2	H_2O	–	100[c]	12	17
3	H_2O	–	100	0.8	26
4	EtOH/H_2O (1/2)	–	100	0.8	31
5	EtOH/H_2O (2/1)	–	100	0.8	36
6	EtOH/H_2O (4/1)	–	100	0.8	39
7	EtOH	–	100	0.8	<5
8	EtOH/H_2O (4/1)	–	100	1.5	48
9	EtOH/H_2O (4/1)	–	100	2.0	43
10	EtOH/H_2O (4/1)	–	100	2.5	40
11	DMF/H_2O (4/1)	–	100	1.5	41
12	CH_3CN/H_2O (4/1)	–	100	1.5	44
13	*i*PrOH/H_2O (4/1)	–	100	1.5	51
14	*t*BuOH/H_2O (4/1)	–	100	1.5	39
15	*i*PrOH/H_2O (4/1)	$PhCO_2H$	100	1.5	43
16	*i*PrOH/H_2O (4/1)	$[Bu_4N][Br]$	100	1.5	38
17	*i*PrOH/H_2O (4/1)	4 Å MS[d]	100	1.5	40

[a] Unless specified otherwise, the reactions were carried out on a 0.05 mmol scale of **1a** and monitored by the appearance of **5a** by TLC and ^{1}H NMR spectroscopy; see the Experimental Section and Supporting Information. [b] Yields of products isolated. [c] 100 °C was achieved through regular heating, instead of 100 W microwave irradiation. [d] 4 Å MS = 4 Å molecular sieves.

(Table 1, entry 13). Nevertheless, there was no positive effect observed when various additives were applied, including acid (Table 1, entry 15), phase transfer catalyst (PTC) $[Bu_4N][Br]$ (Table 1, entry 16), and 4 Å MS (Table 1, entry 17).

Although the optimization reaction conditions for the tandem N-alkylation–aza-Cope rearrangement process led to significantly improved reaction efficiency, the yield of 51% is far from satisfactory (Table 2, entry 1). Therefore, we turned on our attention to further optimization by probing the structural effects of both reactants **1** and **2** on the cascade process (Table 2).

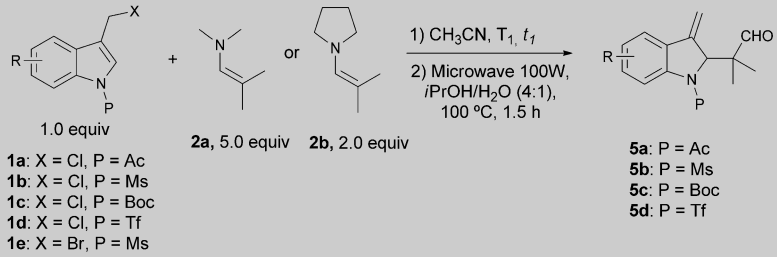
First, we focused on the optimization of the N-alkylation reaction (Table 2). With respect to substrates **1**, it is believed that stronger electron-withdrawing groups (P) on the N atom and a better leaving group X facilitate the process. Therefore, various protecting groups, including Ac, Ms, Boc, and Tf, were examined (Table 2, entries 1–4). Under the same reaction conditions, Ms-protected N-indole **1b** gave an encouraging outcome (Table 2, entry 2, 55% yield). Interestingly, Tf-protected **1d** did not provide the desired product (Table 2, entry 4). However, switching the leaving group from chloride to bromide led to a similar yield of product **5d**, but the reaction proceeded much faster (Table 2, entry 5; 2 h, 45% yield). Shorter reaction times could further improved yields (Table 2, entries 6 and 7; 1 and 0.5 h, 67 and 58% yields, respectively). More stable pyrrolidine-derived enamine **2b** could not only significantly reduce the amount used (2.0 equiv), but also render the process more efficient (Table 2, entries 8–14). When the first step was carried out at room temperature for 12 min with bromide **1e** and enamine **2b**, a yield of 77% for the two-step reaction was obtained (Table 2, entry 10). Longer or shorter reaction times in the first step decreased the total yield (Table 2entries 8, 9, 11, and 12). The reaction temperature in the first step significantly affected the reaction yield (Table 2, entries 10, 13, and 14).

Scope

Having established an optimal procedure for the tandem N-alkylation–aza-Cope hydrolysis process, we probed the generality of the reaction (Table 3). The results show that the protocol serves as a general strategy for the synthesis of structurally diverse indolines **5** containing the 2,2-dimethyl aldehyde moiety. A variety of indole bromides, containing electron-neutral (Table 3, entries 1–3), -donating (Table 3, entries 4 and 5), or -withdrawing substituents (Table 3, entries 6–11), can efficiently participate in the process to give good yields of products **5**.

Although reasonable yields are obtained for the tandem N-alkylation–aza-Cope rearrangement process in most cases, we observed a small amount of compound **7** produced as side product; this is an important factor that contributes to a reduction in the yield. It is believed that the compound is generated from a nucleophilic carbon instead of N attack of indole bromide (Scheme 3).

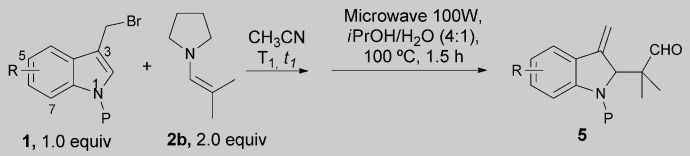
Table 2. Optimization of reaction conditions for the first step of the N-alkylation reaction.[a]



Entry	1	2	T_1 [°C]	t_1	Yield [%] (2 steps)[b]
1	**1a**	**2a**	RT	9 h	51
2	**1b**	**2a**	RT	9 h	55
3	**1c**	**2a**	RT	9 h	35
4	**1d**	**2a**	RT	9 h	no desired product
5	**1e**	**2a**	RT	2 h	45
6	**1e**	**2a**	RT	1 h	67
7	**1e**	**2a**	RT	0.5 h	58[c]
8	**1e**	**2b**	RT	0.5 h	67
9	**1e**	**2b**	RT	15 min	72
10	**1e**	**2b**	RT	12 min	77
11	**1e**	**2b**	RT	10 min	73
12	**1e**	**2b**	RT	5 min	56
13	**1e**	**2b**	50	12 min	58
14	**1e**	**2b**	0	12 min	33

[a] Unless specified otherwise, the reactions were carried out on a 0.05 mmol scale of **1** and monitored by the appearance of **5** by TLC and ^{1}H NMR spectroscopy; see the Experimental Section. Ms = mesyl, Boc = *tert*-butyloxycarbonyl, Tf = trifluoromethanesulfonyl. [b] Yield of product isolated. [c] Some **1e** remained unreacted.

Table 3. Substrate scope of indole bromides.[a]

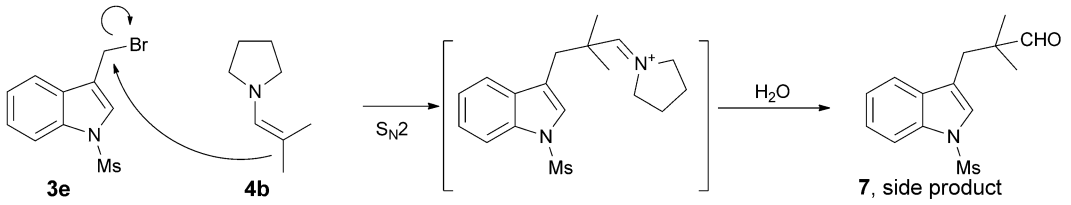


Entry	5	R	P	T_1 [°C]	t_1 [min]	Yield [%] (2 steps)[b]
1	**5b**	–	Ms	RT	12	77
2	**5a**	–	Ac	RT	15	37
3	**5g**	–	Ts	RT	20	48
4	**5h**	5-CH_3	Ms	RT	15	71
5	**5i**	5-OCH_3	Ms	RT	5	73
6	**5j**	5-F	Ms	RT	45	72
7	**5k**	5-Cl	Ms	50	15	66
8	**5l**	5-Br	Ms	50	15	64
9	**5m**	6-Br	Ms	RT	35	66
10	**5n**	5-NO_2	Ms	RT	80	61
11	**5o**	5-CO_2Me	Ms	50	15	85

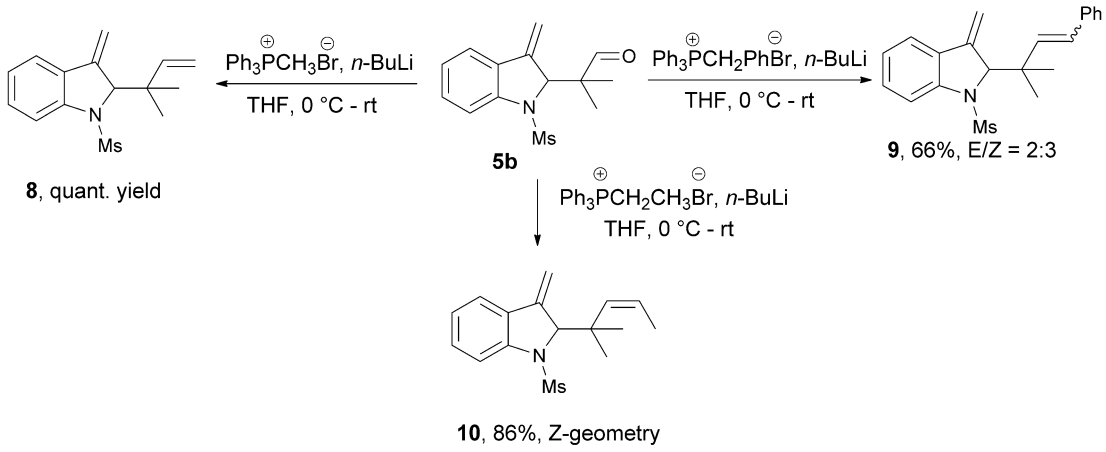
[a] Unless specified otherwise, the reactions were carried out on a 0.05 mmol scale of **1** and monitored by the appearance of **5** by TLC and ^{1}H NMR spectroscopy; see the Experimental Section. Ts = tosyl. [b] Yield of product isolated.

Synthetic applications

The produced indoline compounds **5** are synthetically useful building blocks, which can be conveniently elaborated for the synthesis of valuable targets. In this context, the immediate goal is to build the reverse prenyl group, which is an essential moiety in widely distributed 2-reverse prenylated indole alkaloids. As demonstrated, the 2-reverse prenyl moiety can be readily installed by treatment of **5b** with methyltriphenylphosphonium bromide in the presence of *n*BuLi, through a Wittig reaction, in quantitative yield (Scheme 4). Moreover, reverse prenyl groups containing structurally different olefins, **9** and



Scheme 3. Proposed mechanism for the formation of side product **7**.



Scheme 4. The Wittig reactions of **5b** for the synthesis of 2-reverse prenyl indolines.

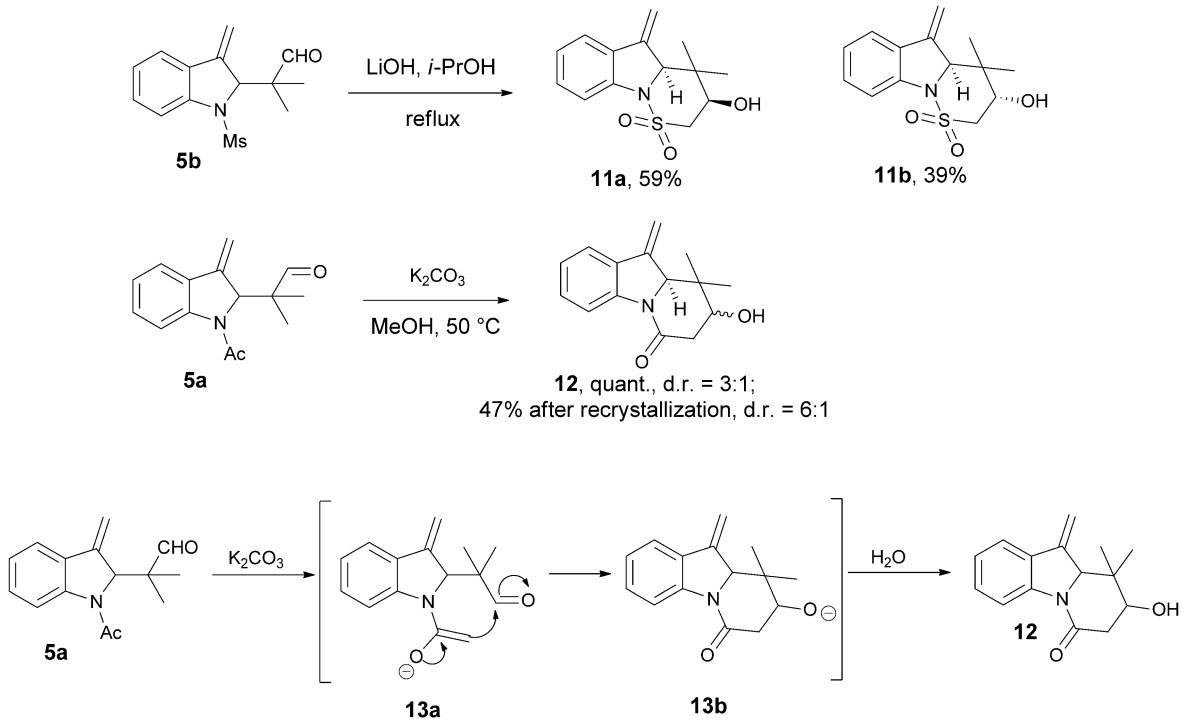
10, can be also introduced successfully with the corresponding Wittig reagents. This may offer an opportunity to generate unnatural 2-reverse prenylated indole alkaloids.

We found that indoline-fused diastereomeric sultams **11a** and **11b** were formed efficiently through an interesting intramolecular aldol reaction when compound **5b** was treated with the base lithium hydroxide (Scheme 5).[14] The sultams (cyclic sulfonamides) have emerged as "privileged" structures in drug discovery.[15] They exhibit broad inhibitory properties against a variety of enzymes, including cyclooxygenase-2 (COX-2),[16] human immunodeficiency virus (HIV) integrase,[17] lipoxygenase,[18] calpain I,[19] and matrix metalloproteinase-2 (MMP-2).[20] In addition, tricyclic lactam **12** was also obtained quantitatively from acetyl-protected indoline **5a** when potassium carbonate was employed as the base in the reaction.[21]

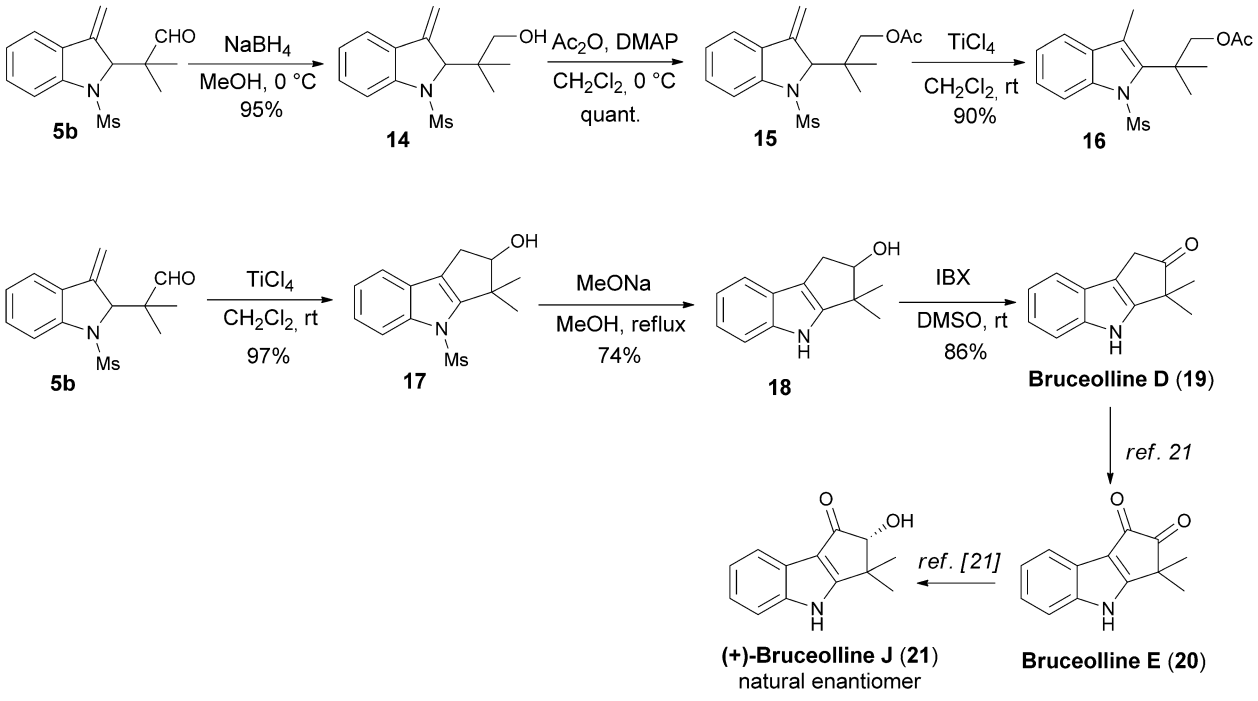
Furthermore, we found that, in the presence of $TiCl_4$, the external olefin moiety in indoline **15**, obtained in two-step reactions, reduction of the aldehyde to an alcohol followed by acylation, could undergo isomerization to give aromatic indole **16** in a high yield (Scheme 6). Finally, an intramolecular carbonyl–ene reaction[22] of **5b** through treatment with $TiCl_4$ gave rise to cyclopent[*b*]indole **17** in excellent yield. Compound **17** is an important precursor for the synthesis of natural product bruceolline D (**19**). Removal of the Ms protecting group by MeONa was followed by an IBX-mediated oxidation, which led to target **19**. Notably, a high overall yield (62%) for the total synthesis of **19** from compound **5b** was impressively achieved. This yield is higher than that reported previously (51% overall yield).[23] In addition, compound **19** could serve as a key intermediate for the syntheses of bruceollines E (**20**) and J (**21**), reported by Lopchuk et al. recently.[23]

Conclusion

Driven by the limited number of methods available for the construction of the synthetically challenging quaternary-centered reverse prenyl indole scaffold, we developed a new, versatile, highly regioselective tandem N-alkylation–aza-Cope rearrangement–hydrolysis process for the facile installation of the functionality into indoles. Notably, careful screening and optimization of the reaction conditions led us to identify an operationally simple protocol for the difficult N-alkylation process, which required mild reaction conditions and nonaqueous medium, whereas the ionic aza-Cope rearrangement took place under relatively harsh conditions in an aqueous medium. Furthermore, the tandem process offered unusual nonaromatic 3-methylene-2,3-dihydro-1*H*-indole products. The versatile aldehyde structures could be conveniently elaborated for the synthesis of structurally diverse 2-reverse prenylated indoles, such as indolines, indole-fused sultams and lactams, and the natural product bruceolline D. Further application of the methodology in complex natural product syntheses is under investigation and the results of these studies will be reported in due course.



Scheme 5. Intramolecular aldol reactions of **5b** and **5a**; d.r. = diastereomeric ratio.



Scheme 6. Syntheses of rearomatized indole **16** and bruceolline D (**19**). DMAP = 4-dimethylaminopyridine, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

Experimental Section

General procedure for the preparation of products 5 through the tandem N-Alkylation–aza-Cope rearrangement reactions (5b as an example; Table 3)

Enamine **2b** (0.1 mmol, 2 equiv) was added to a solution of **1e** (0.05 mmol, 1 equiv) in anhydrous CH_3CN (0.5 mL). The reaction was stirred at room temperature or 50 °C for the time listed in Table 3. *i*PrOH (1.2 mL) and H_2O (0.3 mL) were added to the reaction mixture, and the resulting solution was subjected to microwave irradiation (100 W, 100 °C). After 90 min of microwave irradiation, the reaction mixture was added to brine (10 mL) and extracted with EtOAc (3×). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was submitted to chromatography to afford the corresponding product **5b** (77%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.61$ (s, 1H), 7.53 (d, $J = 8.1$ Hz, 1H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 7.7$ Hz, 1H), 7.19 (t, $J = 7.5$ Hz, 1H), 5.66 (s, 1H), 5.17 (s, 1H), 4.95 (s, 1H), 2.62 (s, 3H), 1.09 (s, 3H), 1.04 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 203.8$ (CH), 144.1 (C), 142.6 (C), 132.1 (C), 130.5 (CH), 126.3 (CH), 120.8 (CH), 118.6 (CH), 108.1 (CH_2), 70.3 (CH), 51.9 (C), 35.2 (CH_3), 18.6 (CH_3), 17.5 ppm (CH_3); HRMS (ESI$^+$): *m/z* calcd for $C_{14}H_{18}NO_3S^+$ $[M+H]^+$: 280.1007; found: 280.1008.

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Keywords: alkaloids · domino reactions · natural products · rearrangement · synthesis design

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