Heterocycle Synthesis

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Dearomative Indole [5+2] Cycloaddition Reactions: Stereoselective Synthesis of Highly Functionalized Cyclohepta[*b*]indoles**

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Abstract: *The first dearomative indole [5+2] cycloaddition reaction with an oxidopyrylium ylide resulted in efficient and diastereoselective construction of some highly functionalized and synthetically challenging oxacyclohepta[b]indoles. The protocol proceeds under very mild reaction conditions, thus enabling high functional-group tolerance and unique endo selectivity.*

Dearomatization of indoles has been a powerful and potentially versatile strategy to construct many unprecedented complex alkaloids from structurally simple substrates.[1] Some dearomative strategies have been developed, including iminium catalysis,[2] allylation,[3] alkylation,[4] arylation,[5] and cycloaddition.[6] Dearomative cycloaddition of the C2=C3 bond of electron-rich aromatic indoles represents an attractive, straightforward, and atom-economic approach to building fused indoline compounds. Moreover, indolines with a fused seven-membered ring at the C2- and C3-positions (cyclohepta[*b*]indoles) are privileged scaffolds which are present in many pharmaceuticals and natural products, such as ajmaline (**1**),[7] kopsifoline D (**2**),[8] ambiguine D isonitrile (**3**)[9] (Figure 1). These compounds have been reported to exhibit a broad range of biological activities. In particular, ajmaline (**1**) is a class Ia antiarrhythmic drug with potent sodium-channel-blocking effects and possesses a very short half-life, thus making it useful for acute intravenous treatments.[10] Consequently, the development of synthetic methods for the preparation of functionalized cyclohepta[*b*]indoles has been of long-standing interest to organic chemists.[11] However, there are few known facile preparations of cyclohepta[*b*]indole skeletons bearing a quaternary stereogenic carbon center at the C*-position (Figure 1).[11c]

Indoles undergo [3+2][12,13] and [4+2][6g–i,14] cycloaddition reactions to generate cyclopenta[b]indoles and hydrocarbazoles, respectively. However, to the best of our knowledge, there has been no report in the literature concerning [5π+2π] cycloaddition reactions[15] where the 2π component is derived from the C2=C3 bond of an indole. Seven-membered cyclohepta[*b*]indoles are difficult to access by direct cyclization reactions because of the combination of entropic factors and the development of nonbonding interactions in the transition state. These difficulties can be overcome if a cycloaddition rather than a cyclization approach is used, whereby two of the bonds in the cyclic framework might be formed simultaneously or almost simultaneously.[16] Herein, we report the unusual intramolecular and intermolecular dearomative indole [5+2] cycloaddition reactions with an oxidopyrylium ylide. These straightforward transformations afford a series of densely functionalized cyclohepta[*b*]indole skeletons containing two adjacent quaternary carbon centers.

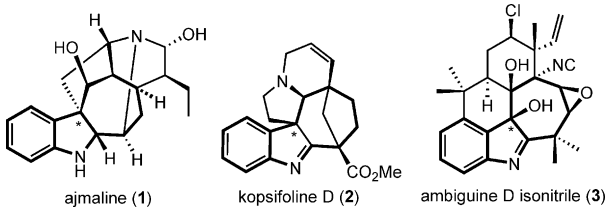

Figure 1. Alkaloids featuring the cyclohepta[*b*]indole core.

Our group has been interested in 1,3-dipolar cycloaddition reactions to access complex natural heterocycles.[17] In particular, we were intrigued by the intramolecular [3+2] dipolar cycloaddition reaction of **4**, as developed by Padwa et al.,[13] for the rapid assembly of the complex oxapolycyclic indoline **5** (Figure 2). Remarkably, the reaction proceeded with simultaneous formation of multiple bonds. Furthermore, this transformation involved the efficient use of the C2=C3 bond of an indole as the 2π component in an intramolecular cycloaddition reaction with a push-pull carbonyl ylide.[13c,d] Based on these studies, it was envisaged that the push-pull nature of oxidopyrylium ylide **6** could enable an intramolecular [5+2] dipolar cycloaddition reaction with the C2=C3 bond of an indole to generate synthetically challenging oxacyclohepta[*b*]indole skeletons, such as **7** (Figure 2). It is noteworthy, however, that the driving force for the facial

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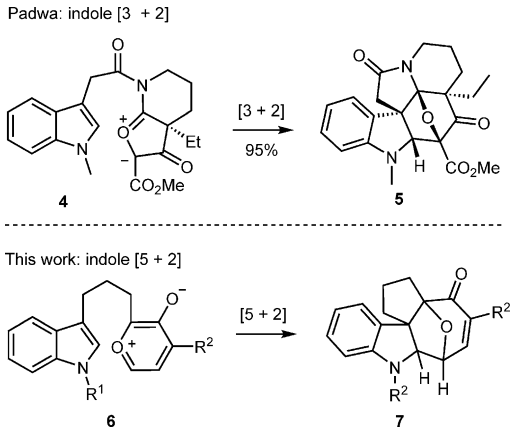


Figure 2. Intramolecular [3+2] and [5+2] dipolar cycloaddition reactions of indoles.

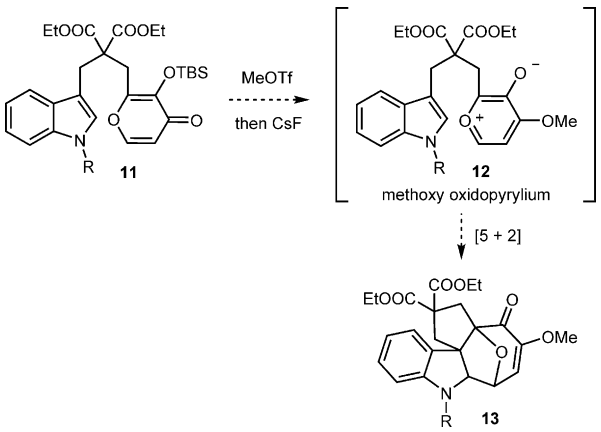
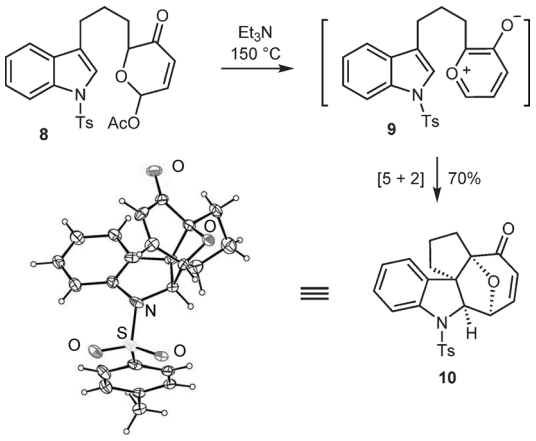


Figure 3. Intramolecular [5+2] cycloaddition of a methoxy oxidopyrylium ylide and an indole. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

selectivity of this dipolar cycloaddition reaction remained unclear.

Our initial attempts focused on the synthesis of acetoxypyranone **8** (Scheme 1; see the Supporting Information for details), which was identified as an important precursor for the oxidopyrylium ylide **9**. Pleasingly, the intramolecular [5+2] dipolar cycloaddition of the oxidopyrylium ylide and indole moieties in **9** occurred when **8** was treated with Et_3N in CH_3CN at 150 °C in a sealed tube, and the compound **10** was formed as the sole product in 70% yield. The pentacyclic structure of **10** was unambiguously confirmed by X-ray crystallographic analysis, which showed the intramolecular [5+2] cycloaddition reaction proceeded with exclusive *endo* selectivity.

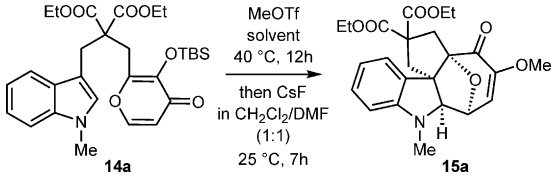


Scheme 1. Synthesis of the pentacyclic core **10** by intramolecular [5+2] cycloaddition.[22] Ts = 4-toluenesulfonyl.

While effective, the high temperature required to form the oxidopyrylium ylide would limit the overall scope and utility of this reaction. With this in mind, we sought inspiration from the group-transfer strategy developed by Wender and Mascareñas.[18] This involves the use of MeOTf as a methylating reagent to form the methoxy pyrylium salt of kojic acid (**11**) at a low temperature, followed by generation of the oxidopyrylium ylide **12** using a fluoride source (Figure 3). It was envisaged that the use of this approach would enable the [5+2] cycloaddition reaction to proceed smoothly under very mild reaction conditions. The key challenge of this strategy, however, would be the development of a method capable of accessing a methoxy pyrylium salt through methylation in the presence of an electron-rich indole system (when R = alkyl group or H).

With the indole kojic acid derivative **14a** in hand (see the Supporting Information for details), we proceeded to investigate the intramolecular [5+2] cycloaddition reaction of the methoxy oxidopyrylium ylide and indole using the group-transfer strategy (Table 1). Treatment of **14a** with MeOTf at

Table 1: Optimization of the reaction conditions.



Entry	MeOTf (equiv)	Solvent	Yield [%]
1	1.0	CH_2Cl_2	16[a]
2	1.5	CH_2Cl_2	60[a]
3	2.0	CH_2Cl_2	80[a]
4	2.0	THF	0
5	2.0	DMF	0
6	2.0	MeCN	41[b]
7	2.0	DCE	26[b]

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy. DCE = 1,2-dichoroethane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

40 °C resulted in methylation to yield the corresponding methoxy pyrylium salt, which was treated with CsF in CH_2Cl_2/DMF[18] at 25 °C to generate the oxidopyrylium ylide. When 1 equivalent of MeOTf was used in CH_2Cl_2, the yield for the adduct **15a** was low (16%), thus suggesting that only small quantities of the oxidopyrylium ylide were generated under

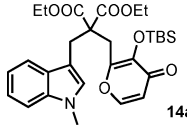
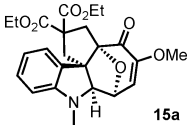
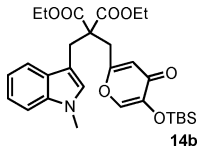
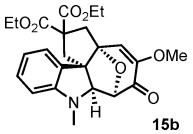
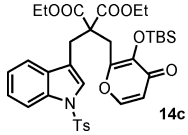
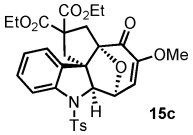
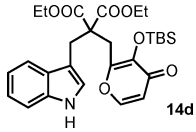
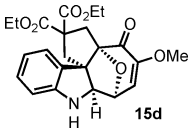
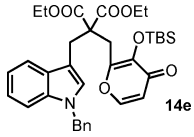
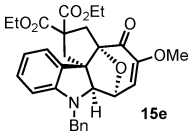
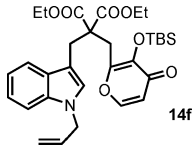
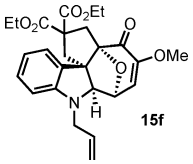
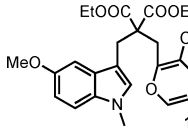
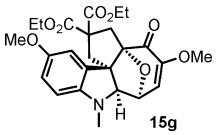
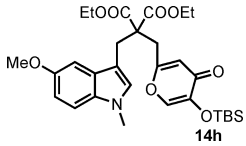
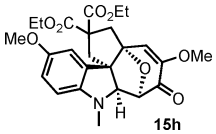
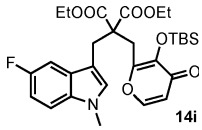
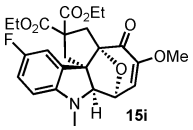
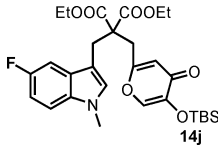
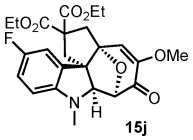
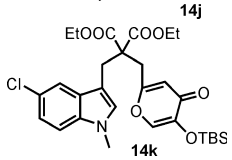
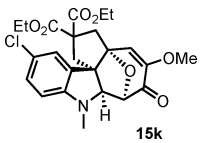
these reaction conditions (entry 1). Gratifyingly, the use of 1.5 equivalents of MeOTf in CH_2Cl_2 led to a significant improvement in the yield of **15a** to 60% (entry 2). Solvent effects were also investigated for the reaction. The results of these screening experiments revealed that the reaction performed poorly when it was conducted in DMF and THF (entries 4 and 5). When MeCN and DCE were used as the reaction solvent, the yield of **15a** was low (entries 6 and 7). Based on these results, CH_2Cl_2 was chosen as the optimal solvent. Under the optimized reaction conditions, **15a** was obtained in 80% yield using 2 equivalents of MeOTf (entry 3).

With the optimized reaction conditions in hand, we proceeded to explore the scope of the intramolecular [5+2] cycloaddition reaction using a variety of different substrates (Table 2). Pleasingly, the reaction performed well with a variety of indole systems bearing electron-donating or electron-withdrawing substituents at C5 and N1 positions. Furthermore, these reaction conditions worked well with the electronically matched and mismatched oxidopyrylium ylides (i.e., the OTBS group was placed at different positions; entries 1 and 2, 7 and 8, 9 and 10). Indoles bearing an electron-donating group provided higher yields, under the optimized reaction conditions (entries 1, 2, 5, 6, 7, and 8), than those bearing an electron-withdrawing group (entries 3, 9, 10, and 11). Pleasingly, the reaction conditions were tolerant of the N-unprotected indoles (entry 4) as well as the indoles bearing a benzyl, allyl, or tosyl group at N1 (entries 5, 6, and 3). The structure of **15c**, which demonstrated exclusive *endo* selectivity, was determined unambiguously by X-ray crystallographic analysis (see the Supporting Information),[19] which showed that the intramolecular dearomative indole [5+2] cycloaddition reactions in Table 2 proceeded with exclusive *endo* selectivity.

DFT (M06-2X/6-31G*) calculations both the [5+2] *endo*- and *exo*-cycloaddition reactions as proceeding through a concerted mechanism,[20] and the *endo* pathway was calculated as having a 15.6 kcal mol^{-1} lower free-energy barrier than the asynchronic *exo* pathway (Figure 4; see the Supporting Information for details). A stepwise pathway[20b] is prohibited by the tether of the substrate. Notably, the *endo*-cycloaddition product is much more stable than the *exo*-cycloaddition product by 22.9 kcal mol^{-1}, and is in agreement with the observed exclusive production of the *endo*-cycloaddition product in our experiments. In addition, our preliminary calculations suggested that the reaction barrier, in the absence of the tether, is slightly increased.

To our delight, under similar reaction conditions,[18b,21] the intermolecular dearomative [5+2] cycloaddition reaction of 1-methyl-indole (**17a**) and maltol (**18**) occurred smoothly to give the tetracyclic core **19a** as the sole product in 61% yield (Scheme 2). Pleasingly, the reaction performed well with a variety of indole systems (**17b**, **17c**, **17d**, **17e**). The structure of **19a** was determined by two-dimensional NMR spectroscopy (see the Supporting Information), which showed that the cycloaddition had proceeded regioselectively with exclusive *endo* selectivity. Our DFT calculations also showed that the free-energy barrier for the intermolecular *endo* cycloaddition is slightly lower than that of the the *exo*-cycloaddition by

Table 2: Scope of the intramolecular [5+2] cycloaddition reaction.

Entry[a]	Substrate	Product	Yield [%][b]
1	 **14a**	 **15a**	80
2	 **14b**	 **15b**	73
3	 **14c**	 **15c**	64
4[c]	 **14d**	 **15d**	63
5	 **14e**	 **15e**	81
6	 **14f**	 **15f**	74
7	 **14g**	 **15g**	90
8	 **14h**	 **15h**	85
9	 **14i**	 **15i**	40
10	 **14j**	 **15j**	45
11	 **14k**	 **15k**	43

[a] Reaction conditions: 1) The substrate and MeOTf (2.0 equiv) in CH_2Cl_2 were reacted at 40 °C for 12 h; 2) CsF (5.0 equiv) in CH_2Cl_2/DMF (1:1) were added at 25 °C for 7 h. [b] Yield of isolated product. [c] MeOTf (1.5 equiv), CsF (5.0 equiv).

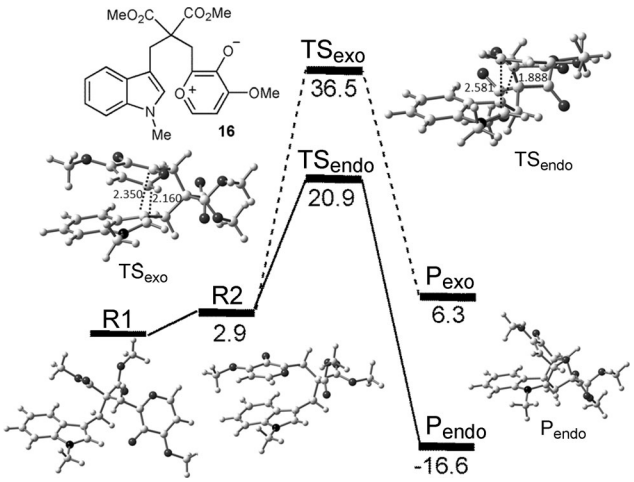
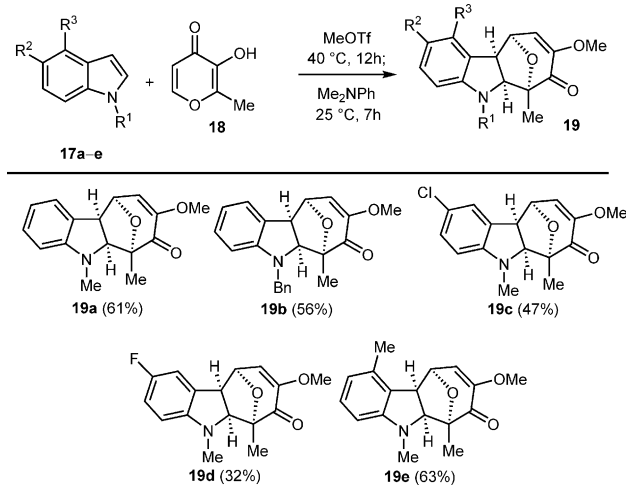


Figure 4. Free-energy profile (kcal mol^{-1}) for the two cycloaddition pathways in the gas phase by M06-2X/6-31G*. P = product, R = reactant, TS = transition state.



Scheme 2. Intermolecular [5+2] cycloaddition of **17** and **18**.

2.6 kcal mol^{-1}. The observed regioselectivity was also computed to have the lowest barrier ($\Delta G^{\pm} = 21.3$ kcal mol^{-1}), which is slightly higher than the intramolecular reaction ($\Delta G^{\pm} = 20.9$ kcal mol^{-1}). Interestingly, the stability of the *endo*- and *exo*-cycloaddition products are similar ($\Delta\Delta G_{endo} = -0.8$ kcal mol^{-1}). Therefore, the kinetic and thermodynamic preference towards the intermolecular *endo* cycloaddition is much smaller than the intramolecular cycloaddition, thus indicating a very high ring strain in the intramolecular *exo*-cycloaddition reaction.

In summary, we have developed a novel dearomative indole [5+2] cycloaddition reaction involving an oxidopyrylium ylide, thus establishing a new protocol for the efficient synthesis of highly functionalized and stereochemically challenging oxa-cyclohepta[*b*]indoles. To the best of our knowledge, this work represents the first example of a [5+2] cycloaddition reaction where the 2π component is derived from the C2=C3 bond of an indole, one of nature's most ubiquitous heterocycles. The intramolecular and intermolecular cycloadditions proceeded under very mild reaction conditions with exclusive *endo* selectivity. Furthermore, DFT calculations have provided some mechanistic insight into the [5+2] reaction. The application of this methodology to the synthesis of selected natural bioactive indole alkaloids and pharmaceutically active agents is currently underway.

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Keywords: cycloaddition · diastereoselectivity · heterocycles · synthetic methods · ylides

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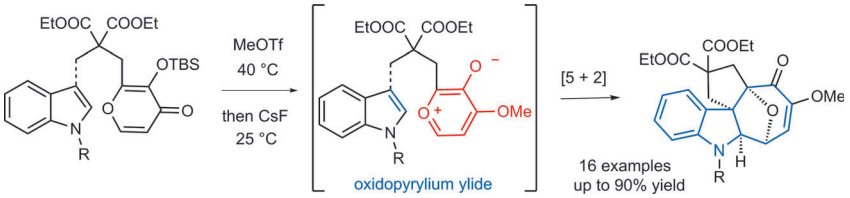
Communications

Heterocycle Synthesis

G. Mei, H. Yuan, Y. Gu, W. Chen, L. W. Chung, C.-C. Li* ——— ■■■■–■■■■

Dearomative Indole [5+2] Cycloaddition Reactions: Stereoselective Synthesis of Highly Functionalized Cyclohepta[*b*]indoles



Bridge construction: The title reaction with an oxidopyrylium ylide resulted in efficient and diastereoselective construction of highly functionalized oxacyclohepta[*b*]indoles. The protocol proceeded under very mild reaction conditions, thus enabling high functional-group tolerance and *endo* selectivity. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.