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Acid-promoted Cascade Cyclization to Produce Fused-polycyclic Indole Derivatives

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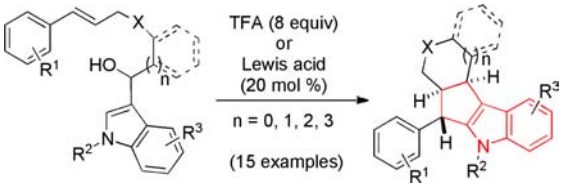
ABSTRACT



An acid-promoted novel cascade cyclization is described. Using 8 equiv of trifluoroacetic acid or a catalytic amount of Lewis acid as the promoter, structurally diverse polycyclic cyclopenta[*b*]indoles were obtained in moderate to excellent yield. This cascade process was extremely effective for the synthesis of 8-membered ring-fused cyclopenta[*b*]indole derivatives.

Fused-polycyclic molecular frameworks with indole units are attractive scaffolds for drug discovery because of their potentially diverse bioactivities.[1] Efficient and divergent production of such polycyclic indoles is an important challenge for synthetic and medicinal organic chemists.[2] The cyclopenta[*b*]indole ring system is found in a large number of biologically active natural products, such as paspaline,[3] yuehchukene,[4] and fischerindoles.[5] In addition, cyclopenta[*b*]indole derivatives **I** (MK-0524) and **II** exhibit prostaglandin D_2 receptor antagonist activity[6] and liver-X-receptor antagonist activity, respectively (Figure 1).[7] These biological and pharmaceutical profiles clearly indicate that the cyclopenta[*b*]indole skeleton is a privileged heterocyclic core for drug design. Therefore, considerable effort has been devoted to the development of an efficient synthetic method for functionalized cyclopenta[*b*]indoles.[8]

We previously reported a novel method for synthesizing tricyclic indole derivatives based on an acid-promoted skeletal rearrangement (Scheme 1a).[9] The developed process is based on a three-step sequence. Intramolecular *ipso*-Friedel–Crafts-type addition of phenol derivatives

(1) For selected reviews, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *24*, 843. (d) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (e) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491.

(2) For recent representative examples, see: (a) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533. (c) Wang, W.; Herdtweck, E.; Dömling, A. *Chem. Commun.* **2010**, *46*, 770. (d) Sun, K.; Liu, S.; Bec, P. M.; Driver, T. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 1702. (e) Gigant, N.; Claveau, E.; Bouyssou, P.; Gillaizeau, I. *Org. Lett.* **2012**, *14*, 844. (f) Vallakati, R.; May, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 6936. (g) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680. (h) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci* **2013**, *4*, 97. (i) Unsworth, W. P.; Kitsiou, C.; Taylor, R. J. K. *Org. Lett.* **2013**, *15*, 258.

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(5) (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935. For examples of the synthesis of Fischerindoles, see: (c) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T. S.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938. (d) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (e) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.

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(7) Ratni, H.; Blum-Kaelin, D.; Dehmlow, H.; Hartman, P.; Jablonski, P.; Masciadri, R.; Maugeais, C.; Patiny-Adam, A.; Panday, N.; Wright, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1654.

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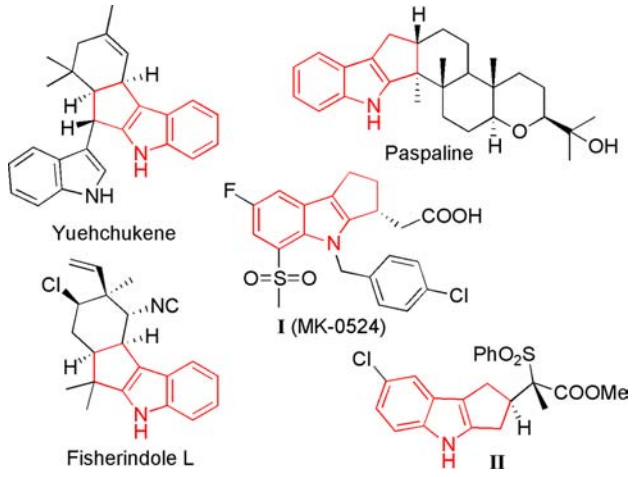


Figure 1. Examples of bioactive molecules with a cyclopenta-[*b*]indole skeleton.

to 3-alkylidene indolenium cations first occurs to form spirocyclohexadienone intermediates (step A). A subsequent C−C bond cleavage through rearomatization of spirocyclohexadienone units gives iminium cations (step B), which are then transformed into tricyclic indole derivatives via an intramolecular Pictet-Spengler reaction (step C). This mechanistic finding led us to hypothesize that minor structural modifications of the substrates for this reaction would drastically change the product structure. That is, if substrates with a cinnamyl derivative unit are treated under acidic conditions, the 3-alkylidene indolenium cations would react with the double bond through an intramolecular ene-type addition to generate cationic intermediates stabilized by the aromatic ring, which would be transformed into fused-polycyclic cyclopenta[*b*]indoles (Scheme 1b) .[10]

To explore this hypothesis, model substrate **1a** was treated with various acid promoters in CH_2Cl_2 (Table 1). We first examined the reaction using trifluoroacetic acid (TFA) as a promoter. Increasing the amount of TFA gradually improved the reactivity (entries 1−3). When the reaction was performed using 8 equiv of TFA, tetracyclic indole derivative **2a** was obtained in 56% yield as a

(8) For selected examples of the synthesis of cyclopenta[*b*]indole frameworks, see: (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (b) Venkatesh, C.; Singh, P. P.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2006**, 5378. (c) Yadav, A. K.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1388. (d) Balskus, E. P.; Walsh, C. T. *J. Am. Chem. Soc.* **2009**, *131*, 14648. (e) Tseng, N.-W.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1809. (f) Churruca, F.; Fousteris, M.; Ishikawa, Y.; von Wantoch Rekowski, M.; Hounsou, C.; Surrey, T.; Giannis, A. *Org. Lett.* **2010**, *12*, 2096. (g) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 689. (h) Xu, B.; Guo, Z.-L.; Jin, W.-Y.; Wang, Z.-P.; Peng, Y.-G.; Guo, Q.-X. *Angew. Chem., Int. Ed.* **2012**, *51*, 1059. (i) Chen, B.; Fan, W.; Chai, G.; Ma, S. *Org. Lett.* **2012**, *14*, 3616.

(9) Yokosaka, T.; Nemoto, T.; Hamada, Y. *Chem. Commun.* **2012**, *48*, 5431.

(10) For a precedent example of this type of transformation based on an intermolecular ene-type addition using a stoichiometric amount of $SnCl_4$ as a promoter, see: Harisson, C.-A.; Leineweber, R.; Moody, C. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 8527.

Scheme 1. Background and Plan of This Work

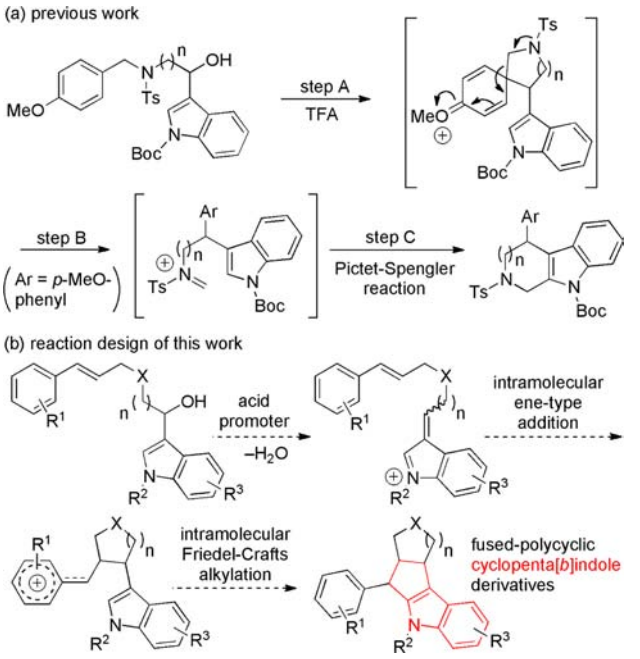
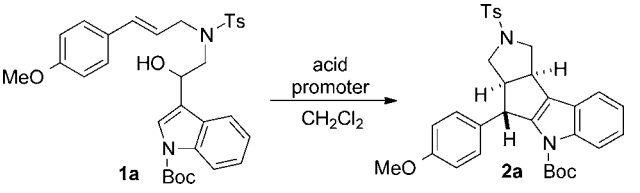


Table 1. Optimization of the Reaction Conditions

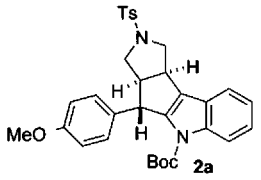
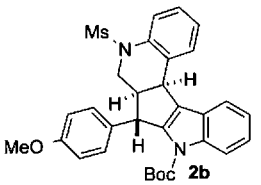
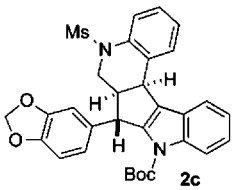
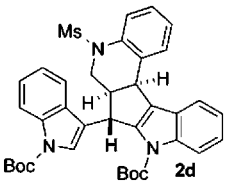
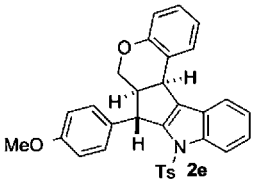
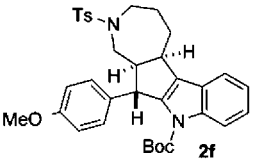
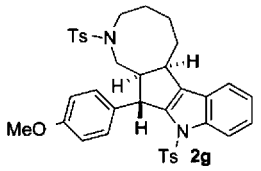
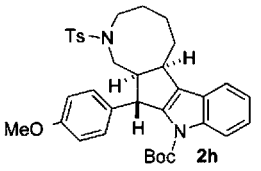
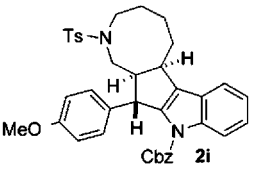
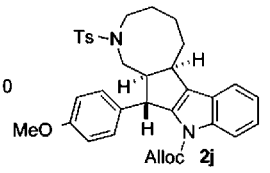
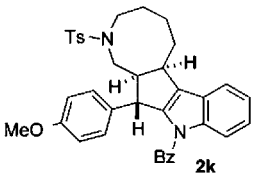
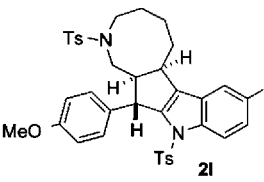
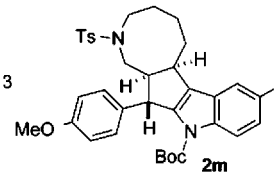
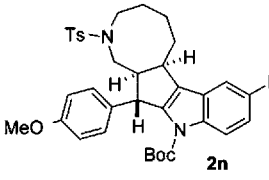
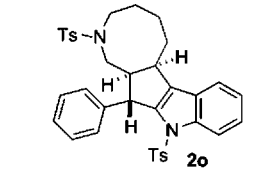


entry	acid (equiv)	conc. (M)	temp (°C)[a]	time (h)	yield (%)[b]
1	TFA (1)	0.1	0	24	7
2	TFA (4)	0.1	0	9	53
3	TFA (8)	0.1	0	2	56
4	TFA (15)	0.1	0	2	46
5	TFA (8)	0.05	0	2	60
6	TFA (8)	0.02	0	2	62
7	$TsOH\cdot H_2O$ (1)	0.1	rt	2	49
8	$TsOH\cdot H_2O$ (8)	0.1	rt	1.5	53
9	TfOH (1)	0.1	0	0.2	trace
10	Tf_2NH (1)	0.1	0	0.2	trace
11	$BF_3\cdot Et_2O$ (0.2)	0.1	0	7	53
12	$Sc(OTf)_3$ (0.2)	0.1	rt	24	40
13	$In(OTf)_3$ (0.2)	0.1	rt	9	53
14	$B(C_6F_5)_3$ (0.2)	0.1	rt	9	57
15[c]	$B(C_6F_5)_3$ (0.2)	0.1	rt	0.5	58
16[c]	$B(C_6F_5)_3$ (0.2)	0.02	rt	1	64

[a] rt: 20−25 °C. [b] Isolated yield. [c] 400 mg/mmol of MS 4 Å was added.

diastereomerically pure compound (entry 3).[11] The yield improved to 62% when the reaction was carried out under dilute conditions to prevent the formation of dimers (entries 5 and 6). The use of $TsOH\cdot H_2O$ as an

Table 2. Substrate Scope

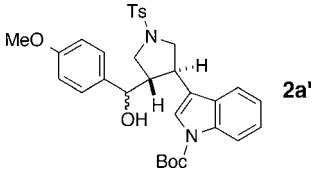
entry	product	results[a]	entry	product	results[a]	entry	product	results[a]
1		A: 62% yield B: 64% yield	2		A: 74% yield B: 83% yield	3		A: 71% yield B: 64% yield
4		A: 63% yield B: 60% yield	5		A: 53% yield B: 42% yield	6[b]		A: 99% yield[c] (dr = 6.7:1) B: 93% yield (dr = 5.7:1)
7		A: 85% yield C: 75% yield	8		A: 83% yield C: 73% yield	9		A: 76% yield C: 68% yield
10		A: 80% yield C: 75% yield	11		A: 92% yield C: 81% yield	12		A: 85% yield C: 72% yield
13		A: 90% yield C: 85% yield	14		A: 87% yield C: 80% yield	15		A: 51% yield C: 0% yield

[a] Isolated yield. [b] Product was isolated as a mixture of diastereomers. Diastereomeric ratio was determined by ^{1}H NMR analysis. We assumed that the minor diastereomer would be an epimer of the benzylic position in the ring junction moiety. See the Supporting Information. [c] Reaction was performed using 15 equiv of TFA.

acid-promoter slightly decreased the yield (entries 7 and 8). Reactions using more acidic promoters gave complex mixtures (entries 9 and 10). The same transformation was also examined using other Lewis acid catalysts, among which $B(C_6F_5)_3$[12] gave the best results. Using 20 mol % of $B(C_6F_5)_3$, **2a** was obtained in 57% yield (entry 14). Reactivity was dramatically affected by the addition of MS 4 Å (entry 15). Furthermore, the yield improved to 64% when the reaction was performed under dilute conditions (entry 16).

With optimum reaction conditions in hand (Table 1, entries 5 and 16), we next examined the scope and limitations of this cascade cyclization process (Scheme 2a and Table 2). In addition to 5-membered ring-fused tetracyclic cyclopenta[*b*]indoles **2a**, 6-membered ring-fused pentacyclic indole derivatives **2b**−**e** were obtained in moderate to good yield (entries 1−5). Product **2d** possesses a bisindole structural motif found in many natural products such as yuehchukene, as well as pharmaceutical compounds,

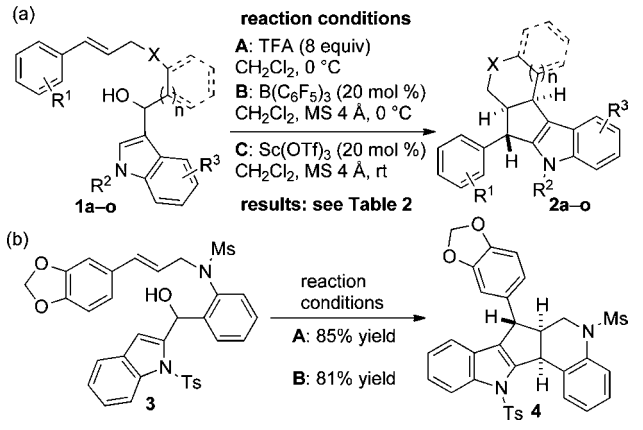
(11) The relative configuration **2a** was determined by NOE experiments. In addition to **2a**, **2a**′ was obtained as diastereomeric mixtures (35% yield in entry 6). See the Supporting Information for details.



2a'

(12) For selected reviews of $B(C_6F_5)_3$-catalyzed reaction, see: (a) Piers, W. E.; Chivers, T. *Chem. Soc. Rev.* **1997**, *26*, 345. (b) G. *Dalton Trans.* **2005**, 1883. (c) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (d) Piers, W. E.; Marwitz, A. J. V.; Mercier, L. G. *Inorg. Chem.* **2011**, *50*, 12252. For representative examples, see: (e) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440. (f) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090. (g) Blackwell, J. M.; Foster, K. L.; Beck, V. H.; Piers, W. E. *J. Org. Chem.* **1999**, *64*, 4887. (h) Gevorgyan, V.; Rubin, M.; Benson, S.; Liu, J. X.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 6179. (i) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921. (j) Oderinde, M. S.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 9834. (k) Bézier, D.; Park, S.; Brookhart, M. *Org. Lett.* **2013**, *15*, 496.

Scheme 2. Acid-promoted Cascade Cyclization



suggesting its potential utility in medicinal chemistry. Oxygen-tethered substrate **1e** was also converted into the corresponding pentacyclic indole derivative containing a chroman moiety **2e** in moderate yield (entry 5). Treatment of substrate **1f**, which has a $(CH_2)_2$ unit-longer than **1a**, with 15 equiv of TFA, led to a smooth reaction process, affording the corresponding product with a 7-membered ring **2f** in excellent yield with good diastereoselectivity (entry 6). It is particularly noteworthy that the present cascade reaction process was extremely effective for the synthesis of 8-membered ring-fused cyclopenta[*b*]indole derivatives (entry 7−15).[13] $Sc(OTf)_3$ was a more reactive promoter than $B(C_6F_5)_3$ for this purpose. Substrates with various protecting groups, such as *p*-toluenesulfonyl (Ts), Boc, benzyloxycarbonyl (Cbz), allyloxycarbonyl (Alloc) and benzoyl (Bz), on the nitrogen atom in the indole unit were applicable to this reaction and the corresponding products **2g**−**k** were obtained in good to high yield (entries 7−11). In addition, substrates bearing electron-donating and electron-withdrawing functionalities on the indole ring were tolerant to this reaction, giving the products **2l**−**n** in high yield (entries 12−14). Simple cinnamylamine-type substrate **1o** was also an effective substrate for this cascade cyclization, demonstrating the potential for broad substrate applicability of this method (entry 15). Furthermore, when the C-2-substituted substrate **3** was reacted under the optimized reaction conditions, the corresponding pentacyclic cyclopenta[*b*]indole derivative **4** was obtained in good yield (Scheme 2b). The polycyclic indole framework

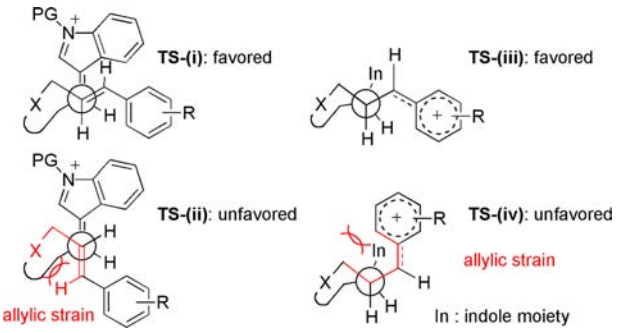


Figure 2. Transition state models.

of **4** is a ubiquitous structure in many natural products, as represented by paspaline.

The mode of diastereoselection of this process can be rationalized as follows (Figure 2).[14] First C−C bond formation: Transition state **TS-(i)** with minimum allylic strain is proposed as the transition state model for the intramolecular C−C bond formation. The *cis* configuration in the ring junction moiety is constructed during this process. Second C−C bond formation: Transition state **TS-(iv)** suffers from severe allylic strain because the C−C bond between the phenyl group and the cationic benzylic carbon has partial double bond characters. Therefore, the reaction proceeds through the more preferred transition state **TS-(iii)** to give the products with a *cis-trans* relative stereochemistry on the 5-membered ring core.

In conclusion, we developed an effective method for synthesizing polycyclic indole derivatives through an acid-promoted cascade cyclization. Structurally diverse polycyclic cyclopenta[*b*]indole derivatives were obtained in moderate to excellent yield. This reaction system was extremely effective for the synthesis of 8-membered ring-fused products. The present method provides access to polycyclic molecular frameworks that are of potential interest as scaffolds for drug design.

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Supporting Information Available. Experimental procedures, supplementary data, compound characterization, and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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