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A Highly Convergent Cascade Cyclization to cis-Hydrindanes with All-Carbon Quaternary Centers and Its Application in the Synthesis of the Aglycon of Dendronobiloside A

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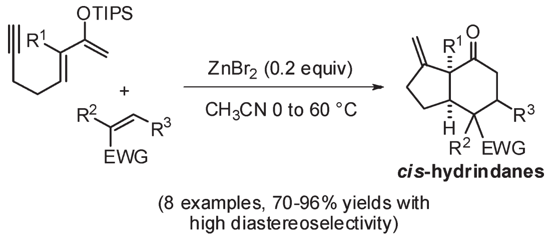
ABSTRACT



An efficient and versatile ZnBr$_2$-catalyzed Diels−Alder/carbocyclization cascade reaction has been developed for construction of highly functionalized cis-hydrindanes (70−96% yields with high diastereoselectivity), and it has been successfully utilized in the synthesis of the aglycon of dendronobiloside A.

The *cis*-hydrindane skeleton with an all-carbon quaternary center at the ring junction is a common motif in many biologically active natural products (Figure 1).[1] Developing efficient and stereoselective methods for this type of skeleton with the appropriate functionalities already in place would provide a quick synthetic entry to *cis*-hydrindane-containing natural products. One of our major research interests is to develop convergent and versatile cascade cyclization reactions for the construction of various types of fused ring systems.[2] We herein reported a highly convergent Diels−Alder/carbocyclization cascade reaction for the construction of the *cis*-hydrindanes and its application in the synthesis of the aglycon of dendronobiloside A. As shown in Scheme 1, our strategy involved a Lewis acid catalyzed Diels−Alder (DA) cycloaddition of a silyl enol ether diene with an electron-deficient dienophile. The silyl enol ether moiety of the resulting DA adduct is expected to undergo an intramolecular carbocyclization with the

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[1] (a) **Dendrobine**: Wang, H.; Zhao, T. *J. Nat. Prod.* **1985**, *48*, 796–801. (b) Dendronobiloside A: Zhao, W.; Ye, Q.; Tan, X.; Jiang, H.; Li, X.; Chen, K.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1196–1200. (c) Aplykurodinone-1: Gavagnin, M.; Carbone, M.; Nappo, M.; Mollo, E.; Roussis, V.; Cimino, G. *Tetrahedron* **2005**, *61*, 617–621.

[2] (a) Peng, W.; Lee, C.-S. *Synlett* **2008**, 142–146. (b) Li, Wei; Liu, X.; Zhou, X.; Lee, C.-S. *Org. Lett.* **2010**, *3*, 548–551.

[3] For reviews, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (c) Hayashi, Y. *Cycloaddit. React. Org. Synth.* **2002**, 5–55. Selected references for Lewis acid catalyzed DA cycloaddtions:(d) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400. (e) Ge, M.; Stoltz, B. M.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1927–1929. (f) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390. (g) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387–4390. (h) Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539–2541. (i) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082–7085. (h) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649–1651. (j) Wu, W.; He, S.; Zhou, X.; Lee, C.-S. *Eur. J. Org. Chem.* **2010**, 1124–1133.

10.1021/ol102781p

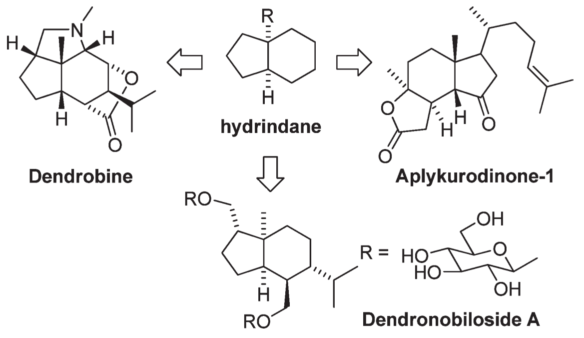
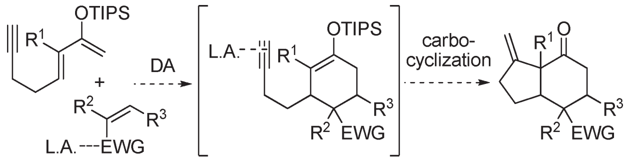


Figure 1. Examples of *cis*-hydrindane-containing natural products.

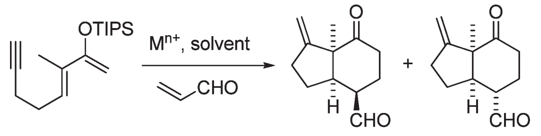
terminal alkyne and afford the *cis*-hydrindane cycloaddition products in a one-pot manner (Scheme 1). This cascade cyclization required a bifunctional Lewis acid catalyst which can form both σ- and π-complexes with the substrates and intermediates.

Scheme 1. DA/Carbocyclization Cascade Cyclization Approach to *cis*-Hydrindanes



DA cycloaddtion catalyzed by Lewis acids that can form strong σ-complexes with the dienophiles has been studied extensively.[3] In contrary, reports on catalytic carbocyclization via nucleophilic addition of silyl enol ethers to unactivated alkynes are still limited.[4] This type of reaction was first reported by Drouin and Conia in 1985 using a stoichiometric amount of $HgCl_2$ which can form strong π-complexes with the unactivated alkynes.[5] The first catalytic carbocyclization of ω-acetylenic silyl enol ethers was reported by Iwasawa's group in 1998 using $W(CO)_5 \cdot THF$ as the catalyst, which required 3−5 days with 10−30 mol % of the catalyst.[6] In 2005, the same group reported a photoirradiated tandem carbometalation reaction using $[ReCl(CO)_5]$ as the catalyst.[7] And a year later, Toste's group reported mild and efficient conditions using $AuClPPh_3/AgBF_4$ as the catalyst[8] and then an asymmetric version with a Pd catalyst in 2007.[9] Since some of the transition metal salts have been shown to be able to function as both σ- and π-electrophilic Lewis acids,[10] we have decided to employ a transition metal salt as the bifunctional catalyst in our cascade cyclization reactions.

Table 1. Optimization of the DA/Carbocyclization Cascade Reaction[a]



1 2a: *endo* 2d: *exo*

entry	M^{n+}	solvent	time	yields[b]	*endo*/*exo*[c]
1[d]	$AuClPPh_3/AgBF_4$	CH_2Cl_2	1 h	-	-
2	$PtCl_2$	toluene	5 h	-	-
3	$PdCl_2(PPh_3)_2$	toluene	24 h	-	-
4[e]	$AgBF_4$	DCE	24 h	42	6:1
5[f]	$InCl_3$	DCE	24 h	40	3:1
6	ZnI_2	DCE	24 h	50	4:1
7	ZnI_2	toluene	24 h	trace	-
8	ZnI_2	THF	72 h	trace	-
9	ZnI_2	dioxane	72 h	-	-
10	ZnI_2	CH_3CN	36 h	92	4.8:1
11	$Zn(OTf)_2$	CH_3CN	36 h	68	5.3:1
12	$ZnCl_2$	CH_3CN	36 h	90	7.4:1
13	$ZnBr_2$	CH_3CN	24 h	96	12:1

[a] The general procedures: To a stirred solution of $ZnBr_2$ (25 mg, 0.10 mmol) in anhydrous acetonitrile (2.0 mL) was added freshly distilled acrolein (0.20 mL, 3.0 mmol) at 0 °C. After 15 min of stirring at 0 °C, the reaction mixture was treated with a solution of silyl enol ether **1** (2 mL of a 0.25 M solution in CH_3CN, 0.50 mmol) slowly over 15 min. The resulting mixture was stirred at 0 °C for 5.5 h and then stirred at 60 °C for 12 h. [b] Isolated yields (%) after silica gel column chromatography. [c] The *endo*/*exo* ratios were determined by the isolated yields or by comparison of the signal at δ_{endo} 5.13 ppm and δ_{exo} 4.72 ppm in ^1H NMR. [d] Similar results were obtained in CH_2Cl_2 with 10% water. [e] Other Ag(I) salts including AgOTf, $AgBF_6$, and $AgClO_4$ gave similar results. [f] $In(OTf)_3$ led to rapid hydrolysis of **1**.

To this end, the cascade cyclization reaction between silyl enol ether **1**[11] and acrolein was first studied with the transition metal salts that had been used as a catalyst for carbocyclization. As shown in Table 1, $AuClPPh_3/AgBF_4$ in either dry or wet dichloromethane[8] resulted in the complete hydrolysis of **1** (entry 1). Switching to $PtCl_2$ in toluene[7] led to a similar result (entry 2). $PdCl_2(PPh_3)_2$ in toluene[9] gave the DA intermediate as the major product along with a minor unidentifiable side product (entry 3).

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(4) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366–2447.

(5) Drouin, J.; Boaventura, M. A.; Conia, J.-M. *J. Am. Chem. Soc.* **1985**, *107*, 1726–1729.

(6) (a) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. Other references using $W(CO)_5 \cdot THF$ as the catalyst:(b) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871–3873. (c) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569–2571. (d) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463–4466.

(7) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468–470.

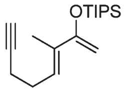
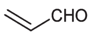
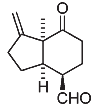
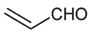
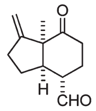
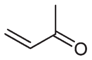
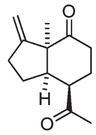
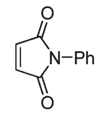
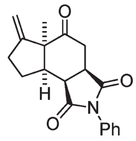
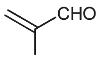
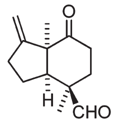
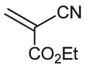
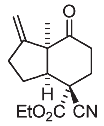
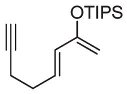
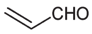
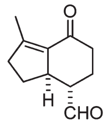
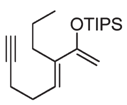
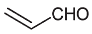
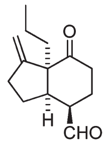
(8) (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991–5994. Other references using Au(I) as the catalyst:(b) Lee, K.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2092–2096. (c) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236–4238.

(9) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764–2765.

(10) (a) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831. (b) Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161–17167.

(11) The procedures for preparation of **1** are available in the Supporting Information.

Table 2. Scope of the DA/Carbocyclization Cascade Reaction[a]

entry	diene	diene no.	dienophile	product[b]	product no.	yields[c]	*endo*/*exo*[d]
1[e]		**1**			**2a**	96	12
2[f]					**2b**	89	*exo* only
3					**3**	92	6.0
4					**4**	93	*endo* only
5					**5**	85	17
6					**6**	91	2.3[g]
7[h]		**7**			**8**	70	*exo* only
8		**9**			**10**	88	5.6

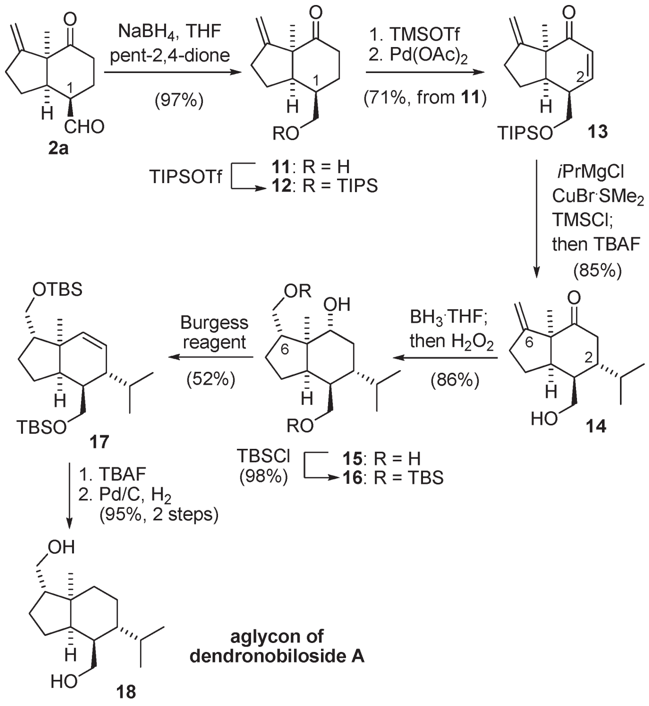
[a] The general procedures were followed. [b] The relative configurations of the cyclized products were determined by 2D NMR experiments. [c] Isolated yields (%) after silica gel column chromatography. [d] The *endo*/*exo* ratios were determined by the isolated yields or by comparison of the signals at δ_{endo} 4.95−5.16 ppm and δ_{exo} 4.70−4.73 ppm in ^{1}H NMR. [e] The catalyst loading can be reduced to 5 mol % in a 10 mmol scale with comparable yields and selectivity. [f] 0.1 mL of NEt_3 was added after the cyclization reaction. [g] The *endo* product was defined with respect to the cynao group. [h] 5 mol % of triflic acid was added after the cyclization reaction.

After surveying some of the late transition metal salts that are known to be potential bifunctional catalysts, we found that the cascade cyclization proceeded smoothly with $AgBF_4$, $InCl_3$ or ZnI_2 in 1,2-dichloroethane (DCE) and gave the expected bicyclic product (**2**) in modest yields along with the side products that resulted from hydrolysis of **1** and the DA intermediate (entry 4−7). The bicyclic products were separable by silica gel flesh column chromatography and were fully characterized by ^{1}H, ^{13}C NMR and HRMS. The major product was found to be the *endo* product by 2D NMR experiments. These encouraging results promoted us to further optimize the reaction conditions with ZnI_2. When toluene, THF, or 1,4-dioxane was used as the solvent, the hydrolysis of **1** and the DA intermediate became a serious problem and led to only a trace amount of the expected products (entry 7−9). Surprisingly, **1** was found to be very stable in CH_3CN. The cascade cyclization proceeded smoothly under the reaction conditions and gave 92% of the cyclized products with *endo*/*exo* equaling 4.8:1 (entry 10). Various Zn(II) salts provided modest to excellent yields of the bicyclic products with modest to very good *endo* selectivity (entry 11−13). The optimal conditions included using 0.2 equiv of $ZnBr_2$ in CH_3CN, which afforded 96% yields of the cyclized products with the *endo*/*exo* ratio equaling 12:1 (entry 13).

With the optimized conditions in hand, the scope of this cascade cyclization reaction was studied and the results are summarized in Table 2. In the presence of Et_3N, the cascade cyclization gave only the *exo* product in 89% yield (entry 2). The *exo* product could be formed via epimerization of the aldehyde moiety. This condition could be a very useful complementary tool for obtaining the corresponding *exo* product efficiently. Cascade cyclizations of **1** with a variety of dienophiles were investigated, and they all gave the expected cyclized products (**3**−**6**) in very good yields (85−93%) with modest to excellent *endo* selectivity (entry 3−6).

Among the dienophiles being tested, *N*-phenylmaleimide provided the best *endo* selectivity (entry 4). Cyclization of silyl enol ether **7** with acrolein led to a mixture of double bond isomers, which can be completely converted to the α,*β*-unsaturated ketone by addition of a catalytic amount of triflic acid, which also induced the epimerization of the aldehyde moiety and gave the *exo* product (**8**) in 70% yields (entry 7). Replacing the methyl group of **1** with an *n*-propyl group also afforded a very good yield of the cyclized products (**10**) with modest *endo* selectivity (entry 8).

Scheme 2. Synthesis of the Aglycon of Dendronobiloside A



To demonstrate the utility of this cascade cyclization reaction, **2a** was employed as the building block for the synthesis of the aglycon of dendronobiloside A, which is a sequiterpene glycoside isolated from the stems of *Dendrobium nobile* (a plant used in traditional Chinese medicine) with immunomodulatory activity.[1b] As shown in Scheme 2, attempts of selective reduction of the aldehyde moiety of **2a** with $NaBH_4$ alone led to the over-reduction product and epimerization at C1. These problems were solved by the addition of a stoichiometric amount of 2,4-pentanedione before the addition of $NaBH_4$. This additive would act as a proton source as well as a scavenger for excess hydrides. To the best of our knowledge, this is the first example of utilizing 2,4-pentanedione in a selective reduction. This condition completely suppressed the over-reduction problem and epimerization at C1 and gave **11** in 97% yields. After TIPS protection of the resulting alcohol, the ketone moiety was oxidized to the α,*β*-unsaturated ketone via Saegusa oxidation.[12] Cuprate addition to enone **13** successfully installed the isopropyl group with the desired stereochemistry at C2. After removal of the TIPS ether, hydroboroation/oxidation of the exocyclic alkene of **14** gave triol **15** with the desired stereochemistry at C6. Interestingly, hydroboroation of **12** (a model with TIPS on the hydroxy group) gave the same stereochemical results as that of **15**. This result suggested that the diastereoselectivity of this reaction could be induced by coordination of the borane to the ketone moiety prior to hydroboroation of the alkene. After selective protection of the two primary alcohols of triol **15**, the remaining secondary alcohol was first mesylated (85%) and was intended to be displaced by super hydride. However, only a trace amont of the elimination product (**17**) resulted along with some unidentifiable side products. Thus **17** was obtained directly from dehydration of **16** using Burgess reagent.[13] Finally, TBS deprotection and hydrogenation of the alkene finished the synthesis of the aglycon of dendronobiloside A (**18**). The spectral data of **18** were found to be consistent with those reported in the literature.[1b]

In conclusion, we have successfully developed a new class of highly convergent cascade cyclization reactions for the construction of highly functionalized *cis*-hydrindanes with an all-carbon quaternary center(s) and have demonstrated its utility in the synthesis of the aglycon of dendronobiloside A. With 0.2 equiv of an environmentally friendly and less expensive bifunctional catalyst, $ZnBr_2$, in CH_3CN, **1** reacted with a variety of dienophiles and gave the bicyclic products in very good yields with high selectivity. We are currently investigating the utility of this cyclization strategy for the construction of other bicyclic fused ring systems and exploring their utility in natural product synthesis.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(13) (a) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224–5226. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.