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Tunable Cyclization Strategy for the Synthesis of Zizaene-, *allo*-Cedrane-, *seco*-Kaurane-, and *seco*-Atesane-Type Skeletons

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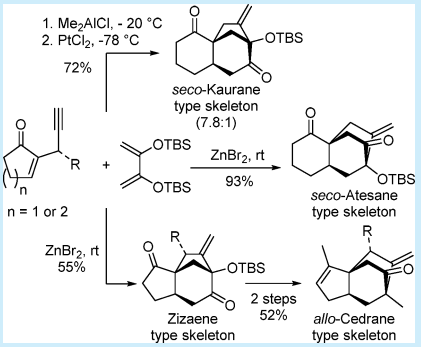
Supporting Information

ABSTRACT: A versatile Lewis acid-mediated cyclization strategy has been developed for selectively establishing zizaene-, *allo*-cedrane-, *seco*-kaurane-, and *seco*-atesane-type skeletons. The zizaene- and *seco*-atesane-type skeletons can be obtained in a cascade manner, which involves Diels–Alder reaction of cyclic enones with bis-silyloxy dienes and carbocyclization of yne–enolates through Lewis acid dependent 5- or 6-*exo*-*dig* modes. This cyclization strategy was also employed for the core synthesis of tashironin.



Bicyclo[3.2.1]octanes (**I**) and bicyclo[2.2.2]octanes (**II**) are common bridged ring systems found in natural products (Figure 1a).[1] When they are fused with a 5- or 6-membered ring, **I** will become a zizaene-[2] or *seco*-kaurane-type[3] skeleton, respectively, and **II** will become an *allo*-cedrane-[4] or *seco*-atesane-type[3] skeleton, respectively. These substructures are common motifs in the core structures of a variety of bioactive natural products. Our group has initiated a long-term project for developing a tunable cascade cyclization strategy for these bridged ring systems using dual-mode Lewis acids,[5] which could provide two different modes of activation for cyclization via σ- and π-complexation.[6] As shown in Figure 1b, we have previously reported a dual-mode Lewis acid induced Diels–Alder (DA)/carbocyclization cascade cyclization of enone **III** with diene **IV** for establishing the *seco*-kaurane-type skeleton **V**.[6c,d] However, this cascade cyclization strategy can only provide the 5-*exo*-*dig* cyclization products **V**, and the DA cycloaddition of diene **IV** with 5-membered enone **VI** (n = 1) under Lewis acid conditions has been reported to be difficult.[7] Instead of using Danishefsky's base-mediated "sequential Michael addition protocol",[7a] we decided to employ more electron-rich bis-silyloxy diene **VII** for cyclization with enone **VI** to overcome the limitation of our previous strategy (Figure 1c). By tuning the reaction conditions, the DA intermediate **VIII** could undergo either 5-*exo*-*dig* carbocyclization and lead to zizaene- and *seco*-kaurane-type skeletons **X** or 6-*exo*-*dig* carbocyclization and give *allo*-cedrane- and *seco*-atesane-type skeletons **IX**. Moreover, the cyclization products bear a hydroxyl at the ring junction, which could be useful for the synthesis of natural products, such as steviol glucosides,[8] gibberellic acid,[9] tashironin,[10] and platencin SL3.[11]

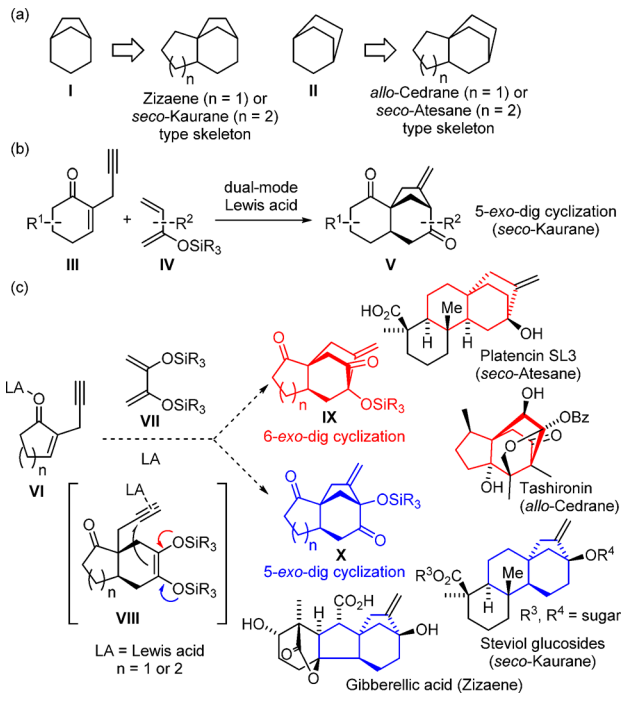


Figure 1. (a) Skeletons containing bicyclo[3.2.1]octanes (**I**) and bicyclo[2.2.2]octane (**II**). (b) Our previous work. (c) The goal of this work.

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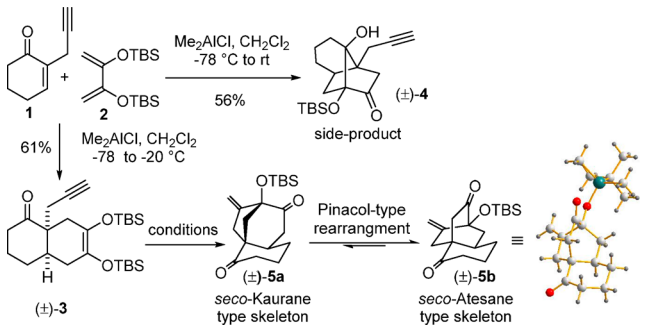
To study the selectivity of the carbocyclization, bis-silyloxy diene (±)-**3** was prepared by DA cycloaddition between enone **1** and 2,3-bis(*tert*-butyldimethylsiloxy)-1,3-butadiene (**2**) using Me_2AlCl in CH_2Cl_2. However, (±)-**3** underwent intramolecular Mukaiyama aldol reaction at rt and gave (±)-**4** as the major side product. This side reaction was suppressed by quenching the reaction at −20 °C. With (±)-**3** in hand, the effects of Lewis acids on the selectivity of the carbocyclization were studied. As shown in Table 1, dual-mode Lewis acids,[5] such as

Table 1. Effects of Lewis Acids on Cyclization of (±)-3[a]



entry	Lewis acid (equiv)/solvent	temp (°C)	yield[b] (%)	(±)-**5a**/**5b**[c]
1	$InCl_3$ (1)/CH_2Cl_2	rt		
2	$InBr_3$ (1)/CH_2Cl_2	rt		
3	$FeCl_3$ (1)/CH_2Cl_2	rt		
4	$ZnCl_2$ (1)/CH_2Cl_2	rt	43	1:9
5	$ZnCl_2$ (1)/CH_2Cl_2	rt[d]	46	(±)-**5b** only
6	$ZnBr_2$ (1)/CH_2Cl_2	rt[d]	98	(±)-**5b** only
7	ZnI_2 (1)/CH_2Cl_2	rt[e]	50	1:2.8
8	AuCl (1)/CH_3CN	rt	82	1.3:1
9	AuCl (1)/CH_3CN	−40	59	1.4:1
10	AuCl (1)/CH_2Cl_2	rt	46	3:1
11	AuCl (1)/CH_2Cl_2	−78	28	3:1
12	PPh_3AuCl (0.2)/toluene	0 or rt		
13	$AuCl_3$ (0.2)/CH_2Cl_2	0 or rt		
14	$Cu(OTf)_2$ (1)/CH_2Cl_2	0 or rt		
15	$Pd(OAc)_2$ (1)/THF	0 or rt		
16	$PdCl_2$ (1)/CH_3CN	0 or rt		
17	$PtCl_2$ (1)/THF	0 or rt		
18	$PtCl_2$ (1)/CH_3CN	rt		
19	$PtCl_2$ (1)/CH_3CN	0	10	(±)-**5a** only
20	$PtCl_2$ (1)/CH_2Cl_2	0	65	3.6:1
21	$PtCl_2$ (0.5)/CH_2Cl_2	0	62	5.1:1
22	$PtCl_2$ (0.2)/CH_2Cl_2	0	60	5:1
23	$PtCl_2$ (0.5)/CH_2Cl_2	−78	72	7.8:1

[a]The general procedures were followed (time = 30 min). [b]Isolated yield (%) after silica gel column chromatography. [c]The product ratios were determined by ^1H NMR signals of the exocyclic alkenes. [d]Reaction time = 20 h. [e]Reaction time = 40 h.

$InCl_3$, $InBr_3$, and $FeCl_3$, led to decomposition of the substrates (Table 1, entries 1−3). $ZnCl_2$ gave 43% of the cyclized products with a (±)-**5a**/(±)-**5b** ratio of 1:9 (Table 1, entry 4). Interestingly, only (±)-**5b** was obtained with an extended reaction time (20 h) (Table 1, entry 5), indicating Pinaol-type rearrangement of (±)-**5a** to (±)-**5b** occurred under the effect of Lewis acid. Finally, the formation of (±)-**5b** was optimized by using $ZnBr_2$ in CH_2Cl_2 at rt for 20 h (Table 1, entry 6), while ZnI_2 gave only 50% of the cyclized products with a ratio (±)-**5a**/(±)-**5b** at 1:2.8 (Table 1, entry 7). The *seco*-kaurane-type skeleton of (±)-**5b** was determined unambiguously by X-ray crystallography.[12]

After studying the effects of dual-mode Lewis acids, a variety of π-Lewis acids were investigated. Using AuCl[13] in CH_3CN gave 82% yield of the cyclized products with slightly higher selectivity for (±)-**5a** (Table 1, entry 8). Lowering the reaction temperature to −40 °C led to a lower yield (59%) with a similar product ratio (Table 1, entry 9). Switching the solvent to CH_2Cl_2 gave only 46% yield of the cyclized products with a higher selectivity for (±)-**5a** (3:1) (Table 1, entry 10). An attempt at increasing the product ratio by lowering the reaction temperature to −78 °C led to a much lower yield (28%) with a similar level of selectivity (Table 1, entry 11). PPh_3AuCl,[13] $AuCl_3$,[14] $Cu(OTf)_2$,[15] $Pd(OAc)_2$, and $PdCl_2$[16] did not provide any cyclized product at 0 °C or rt (Table 1, entries 12−16). $PtCl_2$[17] in THF led to hydrolysis of (±)-**3** and resulted in a mixture of α-silyloxy ketones (Table 1, entry 17). Using $PtCl_2$ in CH_3CN also led to decomposition of the substrate at rt (Table 1, entry 18) but surprisingly afforded (±)-**5a** in 10% yield at 0 °C (Table 1, entry 19). This encouraging result prompted us to study the effects of $PtCl_2$ under different conditions. Switching the solvent to CH_2Cl_2 afforded the cyclized products in 65% yield with a ratio (±)-**5a**/(±)-**5b** at 3.6:1 (Table 1, entry 20). After studying the effects of catalyst loading and reaction temperature, the optimal results was obtained by using 0.5 equiv of $PtCl_2$ in CH_2Cl_2 at −78 °C, which afforded 72% yield of the cyclized products in favor of the *seco*-atesane-type skeleton of (±)-**5a** (7.8:1) (entry 23). The results of this study indicated that π-Lewis acids generally favored the 5-*exo*-*dig* cyclizations and afforded the *seco*-kaurane-type skeleton preferentially.

Based on the results of the above study, $ZnBr_2$ could be a suitable dual-mode Lewis acid for the cascade cyclization between enone **1** and diene **2**. After a survey of different reaction conditions, the cascade cyclization was optimized by using 1 equiv of $ZnBr_2$ in CH_2Cl_2 at rt, which afforded 93% yield of (±)-**5b** in a single operation (Table 2, entry 1). With the above optimal conditions in hand, a series of dienes and enones with different steric hindrances were investigated. Cascade cyclization of enone **1** with diene **6** led to only 35% yield of the cyclized products (Table 2, entry 2) due to rapid hydrolysis of diene **6**. The selectivity for (±)-**7b** is low, and equilibration of (±)-**7a** to (±)-**7b** became unfavorable after hydrolysis of the TMS ethers of the cyclized products. The more bulky diene **8** gave a reasonable good yield of the cyclized product (±)-**9b**, but the equilibration of (±)-**9a** to (±)-**9b** is slow (Table 2, entry 3). These results indicated that diene **2** has the optimal size for balancing the stability and reactivity in the cascade cyclization. Cascade cyclization of enone **1** with cyclic diene **10** afforded 79% yield of (±)-**11a** (the structure was determined by X-ray crystallography)[12] as the only product (Table 2, entry 4). However, diene **12** gave only the Mukaiyama Michael side product **13** (Table 2, entry 5) due to its steric hindrance. Cascade cyclization of (±)-enone **14** with diene **2** gave 79% yield of (±)-**15b** as a single diastereomer (Table 2, entry 6), suggesting the possibility for developing an diastereoslective version via substrate-control. For synthesis of the zizaene- and *allo*-cedrane-type skeletons, 5-membered enone **16** was employed for the cascade cyclization with diene **2**, which resulted in 71% of a 4:1 mixture of (±)-**17a** (zizaene) and (±)-**17b** (*allo*-cedrane) (Table 2, entry 7). Interestingly, the ratio of the cyclized products remains unchanged upon heating with long reaction time probably

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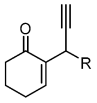
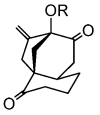
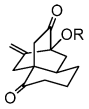
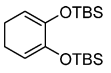
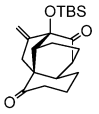
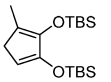
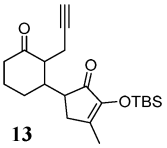
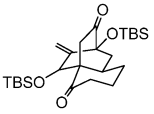
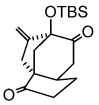
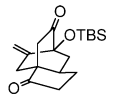
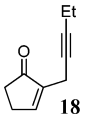
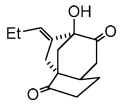
Table 2. Substrate Scope of the Cascade Cyclization[a]

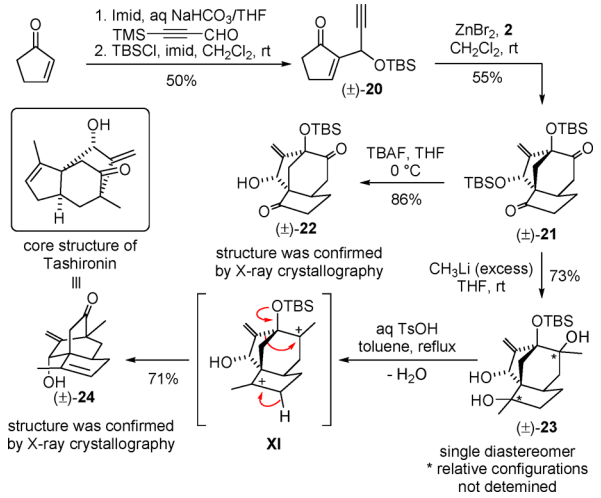
entry	substrates		product(s)		yield (%)[b]	product ratio (**a**/**b**)[c]
1					93	(±)-**5b** only
	1, R = H	**2**, R = TBS	(±)-**5a**, R = TBS	(±)-**5b**, R = TBS		
2	**1**, R = H	**6**, R = TMS	(±)-**7a**, R = H	(±)-**7b**, R = H	35	1:2
3	**1**, R = H	8, R = TIPS	(±)-**9a**, R = TIPS	(±)-**9a**, R = TIPS	78	1:16
4	**1**, R = H	 **10**	 (±)-**11a**[12]	-	79	(±)-**11a** only
5	**1**, R = H	 **12**	 **13**		35[d]	single diastereomer[d]
6	(±)-**14**, R = OTBS	 **2**, R = TBS	-	 (±)-**15b**	79	(±)-**15b** only single diastereomer[d]
7	 **16**	**2**, R = TBS	 (±)-**17a**	 (±)-**17b**[12]	71	4:1
8	 **18**	**2**, R = TBS	 (±)-**19a**	-	45	(±)-**19a** only single isomer[e]

[a]The general procedures were followed. [b]Isolated yield (%) after silica gel column chromatography. [c]The product ratios were determined by the ^{1}H NMR signals of the exocyclic alkenes. [d]The relative configurations of the OTBS group were not determined. [e]The geometry of the alkene was not determined.

due to the ring strain of the cyclized products. Introducing an ethyl group to the alkyne terminus (enone **18**) led to excellent selectivity for the zizaene-type-skeleton (±)-**19a** as a single isomer with moderate yields (Table 2, entry 8).

To demonstrate the utility of the cascade cyclization, a model toward the synthesis of tashironin[18] was studied. As shown in Scheme 1, Morita−Baylis−Hillman reaction of cyclopentenone with 3-(trimethylsilyl)propynal followed by silylation gave (±)-**20**, which underwent cascade cyclization with diene **2** using $ZnBr_2$ and afforded good yields of cyclized product (±)-**21** diastereoselectively. The structure of (±)-**21** was determined by X-ray crystallography of (±)-**22**,[12] which was obtained from by treating (±)-**21** with TBAF at 0 °C. Addition of excessive MeLi gave (±)-**23** as a single diastereomer. The relative configurations of the tertiary alcohols were not determined since the stereogenic centers will be destroyed in the subsequent step. Upon treatment of aq TsOH in refluxing toluene,[19] the carbocation (**XI**) generated in situ underwent elimination and Pinol-type rearrangement, which led to the *allo*-cedrane-type skeleton of (±)-**24**.[12] The model compound (±)-**24** contains the core structure of tashironin, which provides a foundation for developing a total synthesis for this natural product and related compounds based on this cascade cyclization strategy.

Scheme 1. Model Study toward the Synthesis of Tashironin



In summary, we have extensively studied the effects of Lewis acids on the selectivity of the carbocyclization of the DA intermediate (±)-**3** and developed a tunable cyclization strategy for establishing the zizaene-, *allo*-cedrane-, *seco*-kaurane-, and *seco*-atesane-type skeletons. Upon treatment of $ZnBr_2/CH_2Cl_2$

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at rt, the 6-membered enone **1** and diene **2** underwent cascade cyclization and afforded the 6-*exo-dig* cyclized product (bearing the *seco*-atesane-type skeleton) selectively in 93% yield. The 5-*exo-dig* cyclized product (bearing the *seco*-kaurane-type skeleton) can be obtained via carbocyclization of the DA intermediate (±)-**3** using $PtCl_2$ at −78 °C (72%, 7.8:1). On the other hand, the cascade cyclization between 5-membered enone (±)-**20** and diene **2** using $ZnBr_2$ favors the 5-*exo-dig* cyclization product (bearing the zizaene-type skeleton), which was converted to the *allo*-cedrane-type skeleton of (±)-**24** (the core of tashironin) with two steps in a model study. Development of an asymmetric version using chiral Lewis acids and a total synthesis of tashironin and related natural products using this cascade cyclization strategy are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02610.

Experimental procedures and characterization data for all new compounds (PDF)
X-ray crystallographic data for compound (±)-**5b** (CIF)
X-ray crystallographic data for compound (±)-**11a** (CIF)
X-ray crystallographic data for compound (±)-**17b** (CIF)
X-ray crystallographic data for compound (±)-**22** (CIF)
X-ray crystallographic data for compound (±)-**24** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC-1563450 ((±)-**5b**), CCDC-1563462 ((±)-**11a**), CCDC-1563456 ((±)-**17b**), CCDC-1563451 ((±)-**22**), and CCDC-1563457 ((±)-**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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