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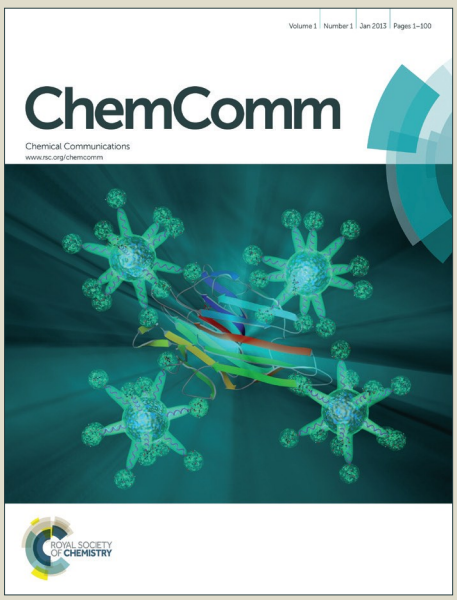

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Domino Intramolecular Diels-Alder Reactions to Construct the 6/6/5/5 Fused Tetracyclic Framework

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Domino intramolecular Diels-Alder (IMDA) reactions towards the 6/6/5/5 fused tetracyclic natural products were developed with satisfactory yield and high stereoselectivity. Four rings, six contiguous stereocenters and four C–C bonds were formed in a single operation. 4-*epi*-hydromitchellene B was also accomplished efficiently via this strategy.

Novel 6/6/5/5 fused tetracyclic framework exists in numerous bioactive natural products such as mitchellenes and pallavicinolides (Figure. 1).[1] Structurally, they shared a common fused tetracyclic muurolane skeleton embedded with seven or eight contiguous stereocenters, which makes them synthetically challenging. The first total synthesis of pallavicinolide A was reported by Wong and Dong in 2009 using a intramolecular Diels-Alder strategy.[2] However, the discovery and development of efficient and practical synthetic methodology to construct 6/6/5/5 fused tetracyclic skeletons was still a part of interest necessary.

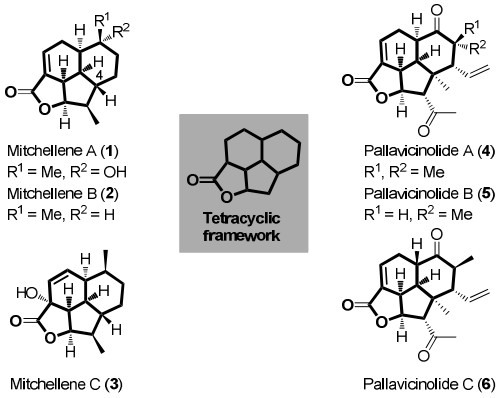
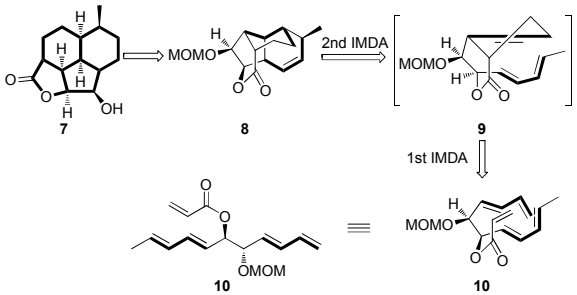


Figure1. Natural Products Share the 6/6/5/5 Fused Tetracyclic Framework.

The intramolecular Diels-Alder reaction (IMDA) is undoubtedly one of the most fundamental and useful reactions in organic synthesis, and it provides the regioselective and stereospecific multiple consecutive stereocenters on polycyclic adducts, which can be further transformed into useful scaffolds for the synthesis of complex natural products.[3] Especially, tandem IMDA reactions have showed their superiority in complex framework construction.[4] Herein, we describe our sequential IMDA reactions that can selectively generate the 6/6/5/5 fused tetracyclic framework and may allow for the rapid construction of the terpenoids family.

To establish this methodology, we selected the 6/6/5/5 fused tetracyclic framework **7** as a research target (Scheme 1). We envisioned that the sequential IMDA transformations without the isolation of intermediates permit the fast assembly of the bridged tetracyclic skeleton. The 6/6/5/5 fused tetracyclic framework **7** would be derived from the bridged tetracyclic skeleton **8** via an intramolecular translactonization. The key intermediate **8** could be obtained from linear polyene **10** using duble Diels-Alder reaction sequence. To the best of our knowledge, utilization of this domino IMDA strategy for synthesis of the 6/6/5/5 fused tetracyclic framework has not been reported in the literature.



Scheme 1. Domino IMDA Strategy for the 6/6/5/5 Fused Tetracyclic Framework.

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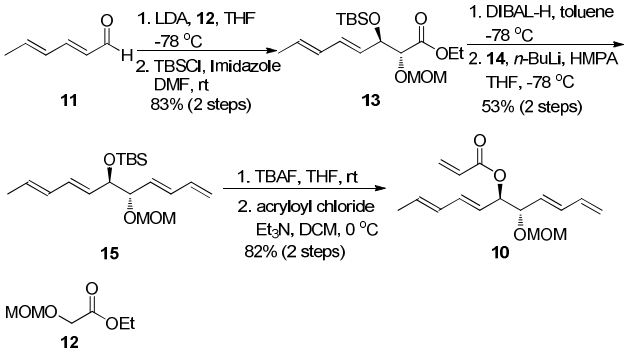
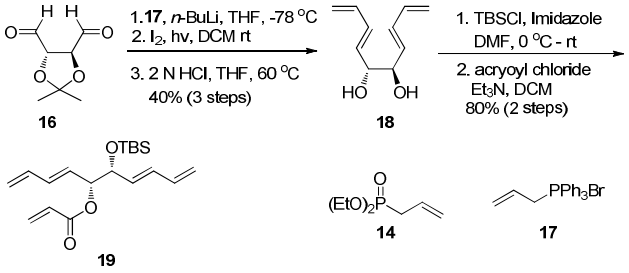
Our synthetic strategy began with the preparation of the IMDA precursors **10** and **19** to investigate the domino IMDA reactions. As shown in Scheme 2, aldol condenstation of ester **12** with aldehyde **11** and subsequent TBS protection of the secondary hydroxyl group gave ester **13** in 83% overall two steps. DIBAL-H reduction of ester **13** followed by Horner-Wadsworth-Emmons olefination provided the *E* diene **15** in 53% overall two steps.[5] Finally, removal of the TBS group and acrylation of the unmasked secondary alcohol produced the precursor **10** in 82% yield. Alternatively, terminal IMDA precursor **19** was prepared through a five step sequences from dialdehyde **16** (Scheme 3).[6]

With the two IMDA precursors in hand, we investigated the domino IMDA cycloadditions under various reaction conditions (Table 1). Initially, various Lewis acid was used to test the reactivity. The reactions were either totally decomposing under strong Lewis acid (Entries 1-5) or no reaction at all under mild Lewis acid (Entry 6). Lactone **9** was obtained with good yield by using thermo promoted IMDA (Entry 8). Increasing reaction temperature to 180 °C for 48 h, resulted in a mixture of the single/double cycloadducts **9** and **8** (Entry 10). When this reaction underwent in sealed tube at 180 °C for 120 hours, the major tetracyclic compound **8** was obtained in moderate yield with trace amount of related **9**. Moreover, lactone **9** could be further transformed into **8** in 60% yield with >95% conversion of starting material.

To determine whether there is a correlation between the product and its reactant, another different configuration precursor **19** was employed (Scheme 4). To our delight,

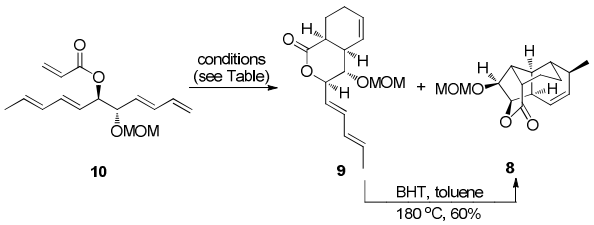


Scheme 2. Synthesis of Linear Precursor **10**.



Scheme 3. Synthesis of Linear Precursor **19**.

Table 1. Optimization of the Domino IMDA Reactions.[a]

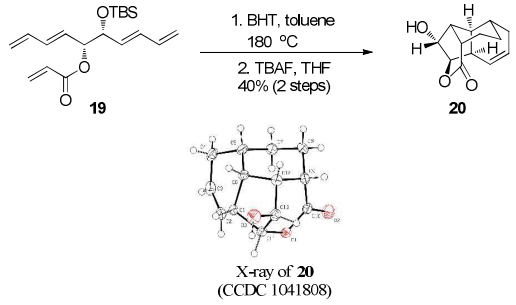


Entry	Lewis acid	Solvent	Temp (°C)	Time (h)	Yield(%)[b] 9	8
1	Et_2AlCl	CH_2Cl_2	-78	2	0	0
2	$EtAlCl_2$	CH_2Cl_2	-78	2	0	0
3	$BF_3{\cdot}Et_2O$	CH_2Cl_2	-78	2	0	0
4	$SnCl_4$	CH_2Cl_2	-78	2	0	0
5	$TiCl_4$	CH_2Cl_2	-78	2	0	0
6	$LiClO_4$	Et_2O	rt	4	NR	NR[c]
7	-	PhMe	80	24	14	0
8	-	PhMe	120	48	70	0
9	$AlCl_3$	PhMe	120	8	0	0
10	-	PhMe	180	48	27	35
11	-	PhMe	180	120	trace	51

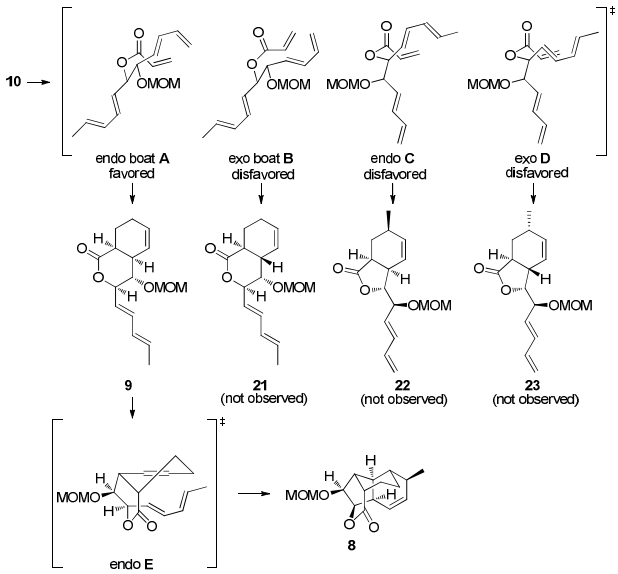
[a]Reaction were performed with 0.2 mmol of **10**, 0.22 mmol of Lewis acid in 4 mL of solvent. [b]Isolated yield after column chromatography. [c]No Reaction, starting material **10** recovered.

tetracyclic product **20** was successfully generated when **19** was heated in a sealed tube at 180 °C for 120 hours, followed by removal of the TBS protecting group. The relative configuration of **20** was then confirmed by X-ray crystallographic analysis. The relative configuration of the ester and hydroxy is also consistent with ene-**19**. These results indicated that this IMDA was preceded with high stereocontrol, giving ester and hydroxyl group *trans* to each other.

Based on the experiment results, we proposed that the first IMDA reaction to form [4,4,0] is preferred than [4,3,0],[7] and it proceeded via *endo*-boatlike transition state (*endo* boat **A**).[8] Once the first IMDA product **9** was generated, the subsequent transannular *endo* Diels-Alder reaction occurred via transition state **E** to produce the bridged tetracyclic product **8**.[9]



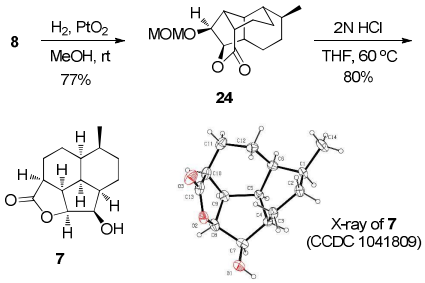
Scheme 4. Domino IMDA Reactions of Precursor **19**.



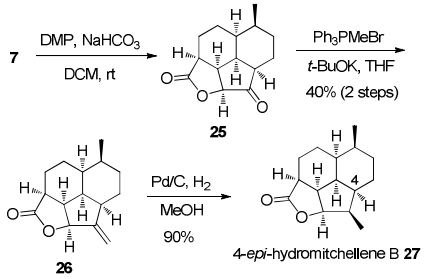
Scheme 5. Transition State of the IMDA Reactions.

The tetracyclic skeleton 7 was realized smoothly through PtO_2 catalyzed hydrogenation and acid promoted lactone transformation (Scheme 6). The structure of **7** was further confirmed by X-ray crystallographic analysis.

Finally, we turned our attention to the synthesis of 4-*epi*-hydromitchellene B (Scheme 7). Ene-**26** was then obtained through a sequence of Dess-Martin oxidation/Wittig olefination. Finally, 4-*epi*-hydromitchellene B **27** was accomplished with a high stereoselective hydrogenation in 90% yield.



Scheme 6. Synthesis of the 6/6/5/5 Fused Tetracyclic Framework.



Scheme 7. Synthesis of 4-*epi*-Hydromitchellene B.

In summary, a new strategy with high steric control and high step/atom economy towards the 6/6/5/5 tetracyclic skeleton was developed via thermally-promoted domino IMDA. Using this strategy, 4-*epi*-hydromitchellene B **27** was synthesized efficiently. Syntheses toward the natural products derivatives, such as alcohol **7**, ketone **25**, ene **26** and 4-*epi*-hydromitchellene B **27** further demonstrate the value of this IMDA technology, allowing significant functional flexibility to initiate structure-activity relationship studies.

Acknowledgements

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