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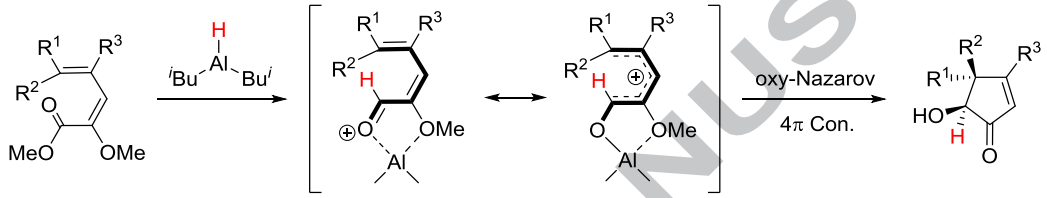

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ABSTRACT

Reduction of 2-methoxy-2, 4-hexadienoates with Dibal-H in toluene at –78°C resulted in a facile formation of 5-hydroxyl cyclopentenone derivatives. This novel transformation was proposed as a variant of the oxy-Nazarov cyclization of the corresponding 2-methoxy aldehyde intermediate via the cationic Al-chelate as depicted in Figure 2a.

Introduction

We reported in 2011 a facile and versatile reductive oxy-Nazarov (RON) cyclization of vinylalkylidene dioxolanone derivatives of type **I** structure (Figure 1a) by the action of Dibal-H under mild conditions leading to the 5-hydroxyl cyclopentenone product of type **II** in good to excellent yield.[1, 2] The synthetic application of this facile cyclopentenone annulation was demonstrated in a novel total synthesis of cephalotaxine as depicted in Figure 1b. Although we proposed

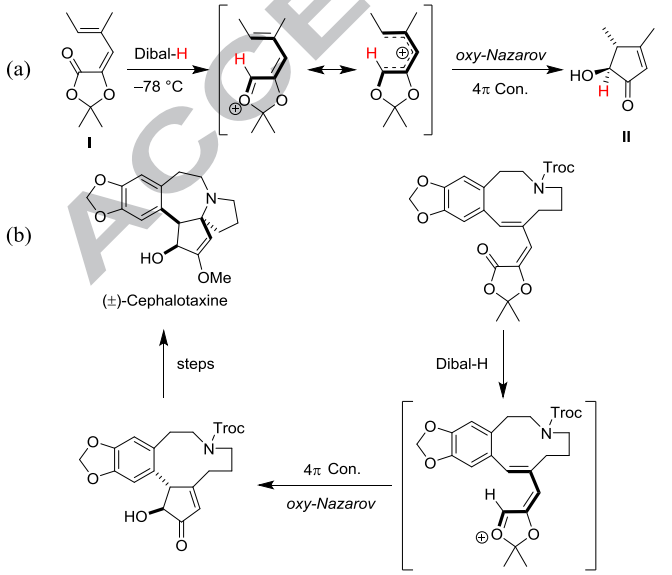
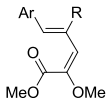


Figure 1 Reductive oxy-Nazarov cyclization of vinylalkylidene dioxolanones.

then a seemingly reasonable cationic intermediates as depicted in Figure 1 for this novel cyclopentenone annulation, we are wondering the reactivity of other analogous substrates, such as the 2-methoxy-2, 4-hexadienoates derivatives **III** toward the hydride reductant (such as Dibal-H).



III

We report in this letter the preliminary results of the reduction of 2-methoxy-2, 4-hexadienoates derivatives with Dibal-H.

Results and Discussion

Horner–Wadsworth–Emmons (HWE) olefination of aldehyde **1**[1, 3] with methoxylated phosphate **2**[4] afforded the *E*-product **3** (34%) along with the corresponding *Z*-product **4** (52%). As shown in Table 1, reduction of **3** with two equivalent of Dibal-H in toluene at –78°C produced a major product **5** and a small amount of **6** (2%). While with one equivalent of Dibal-H as the hydride reductant, 5-hydroxy cyclopentenone **6** was obtained as the major product along with 2% yield of **5** (Table 1, entry 4). Interestingly, oxidation of allylic alcohol **5** with IBX in DMSO at ambient temperature furnished a good yield of **6** (54%). It is also reasonable that reduction of the olefinic isomer **4** with Dibal-H (1.5 eq.) gave a good yield of **7**, which can be further oxidized to the corresponding aldehyde product **8** with IBX in DMSO. It is apparent that the reasonable intermediate in the formation of **6** would be the corresponding aldehyde in both the reductive cyclization of **3** → **6** and the oxidative cyclization of **5** → **6**. We thus suggested that the analogous cationic chelate species, as depicted in Figure 2, are responsible for the facile oxy-Nazarov cyclization under mild conditions. The reaction path might be

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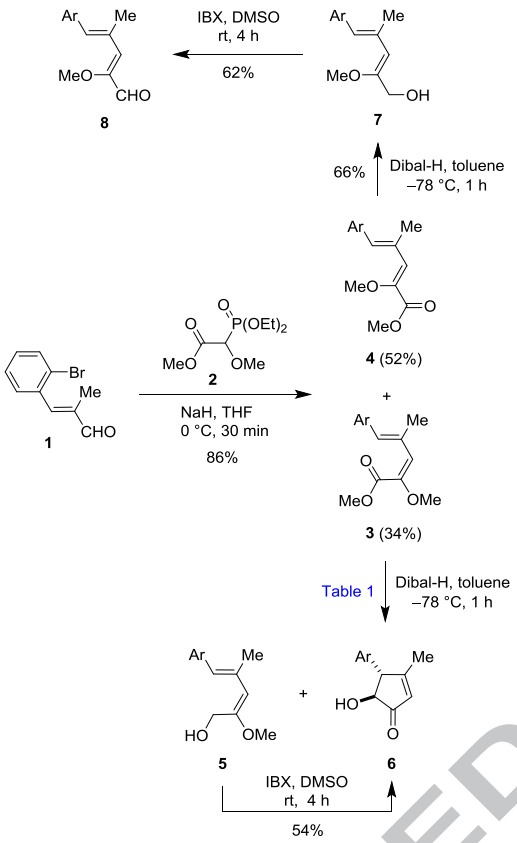
classified as the iso-Nazarov cyclization.[5] The relatively lower yield of **6** in the reactions of **3** with 1.2 or 0.8 equivalent of Dibal-H (Table 1, entries 3 and 5) could be explained by more effective further reduction of the corresponding pentadienal intermediate in the presence of excess Dibal-H than the oxy-Nazarov cyclization of the Al-chelate intermediate as depicted in Figure 2a.



Scheme 1 RON cyclization of **3.**

Table 1 Optimization of reaction conditions[a]

Entry	Dibal-H (equiv.)	Yield (%)[b] 5	6	Ratio (5: 6)	Conv.[c] (%)
1	2.0	50	2	25: 1	100
2	1.5	17	36	1: 2.1	100
3	1.2	43	37	1.2: 1	91
4	1.0	2	77	1: 39	80
5	0.8	23	30	1: 1.3	68

[a] Reactions were carried out with substrate **3** (1.6 mmol) in entry 1, 4.8 mmol in entries 2 to 4, 2.0 mmol in entry 5.
[b] Yields described herein are of isolated product after column chromatography.
[c] Conversion based on recovered starting material.

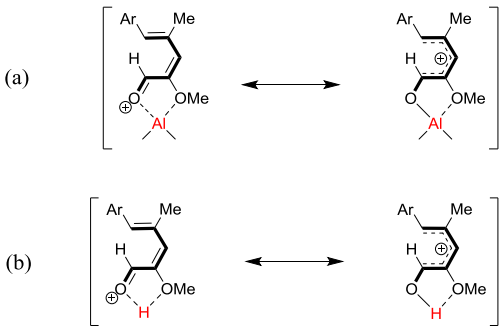
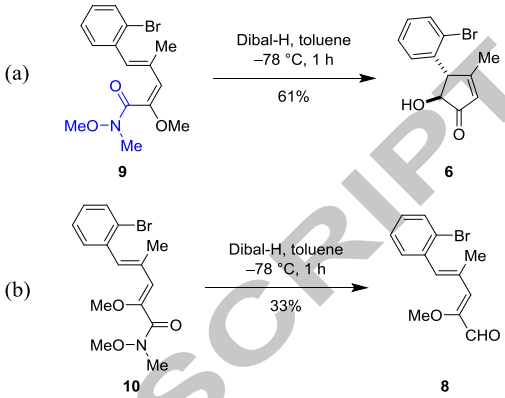


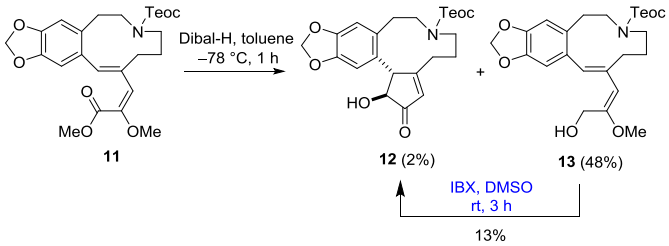
Figure 2 Reactive cationic chelates for oxy-Nazarov cyclization.

To further confirm the above mechanistic suggestion, the isomeric Weinreb amide analogs **9** and **10** were prepared following a reported protocol.[6] Reduction of **9** with one equivalent of Dibal-H produced a good yield of **6**, while reduction of **10** gave the corresponding aldehyde **8** solely in moderate yield (Scheme 2).

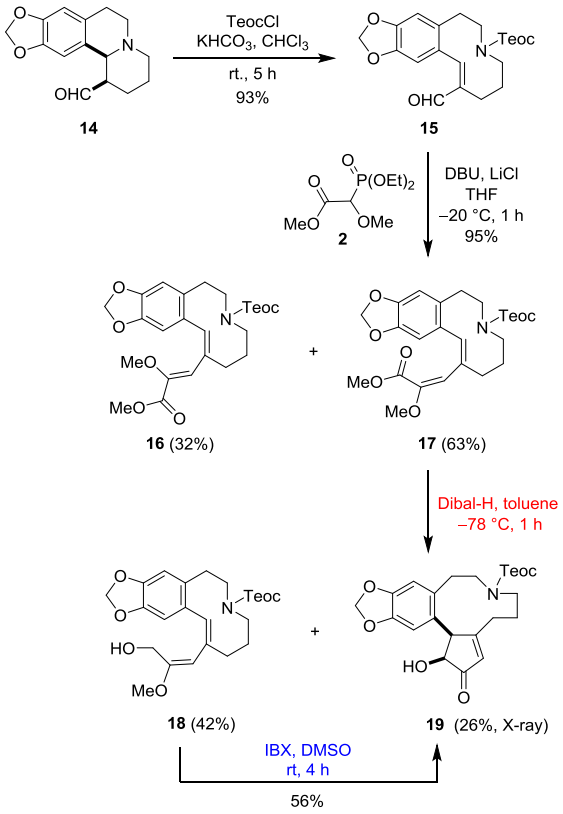


Scheme 2 RON cyclization of **9** and reduction of **10**.

The reductive cyclization reactivity of the 2-methoxy-2, 4-hexadienoate derivatives by the action of Dibal-H were further probed with more elaborated substrate, i.e. **11**[1]. Reduction of **11** with Dibal-H gave alcohol **13** as the major product and a small yield of **12**. Analogously, oxidation of **13** with IBX in DMSO afforded **12**, although in a relatively low yield (Scheme 3). It is obvious that the corresponding dioxolanone derivative (i.e. Figure 1b) is more effective substrate for the reductive oxy-Nazarov cyclization.



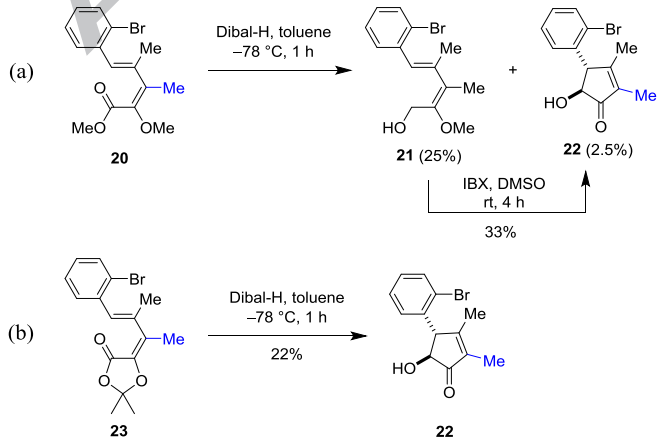
Scheme 3 RON cyclization of **11**.



Scheme 4 RON cyclization of **17**.

To our delight, the Dibal-H reduction of the isomeric precursor **17**, which was prepared analogously from the aldehyde **15** via the HWE olefination reaction as shown in Scheme 4, produced the cyclopentenone **19** in 26% yield along with 42% yield of alcohol product **18**, which was oxidized with IBX in DMSO effectively to give **19** in 56% yield (Scheme 4). The relative stereochemistry of compound **19** was further confirmed by X-ray crystallographic analysis.[7] Cyclopentenone product **19** serves as a key intermediate in the cephalotaxine total synthesis.[8]

Other 3-substituted 2-methoxy-2, 4-hexadienoates such as **20** can be cyclized by the action of Dibal-H to give cyclopentenone **22** less effectively (Scheme 5a). Intriguingly, it seems that proton chelate species of type b intermediate (Figure 2b) of the corresponding aldehyde of **21** underwent smooth oxy-Nazarov cyclization (**22** → **21**). In contrast, 3-methyl substituted dioxalanone analog of type **I**, such as **23**, undergo oxy-Nazarov cyclization in moderate yield (Scheme 5b). The above results imply that the reactivity of this novel variant of iso-Nazarov cyclization depends largely on the olefinic geometry and the nature of substituents which deserves further systematic study.



Scheme 5 RON cyclization of **20** and **23**.

Conclusion

In summary, we have shown that 2-methoxy-2*E*, 4-hexa dienonate derivatives are effective substrate type for the facile reductive oxy-Nazarov cyclization. This cyclopentenone annulation represents a new variant of the iso-Nazarov cyclization.[5] Some typical examples of iso-Nazarov cyclization of pentadienals leading to substituted cyclopentenones are illustrated in Figure 3.

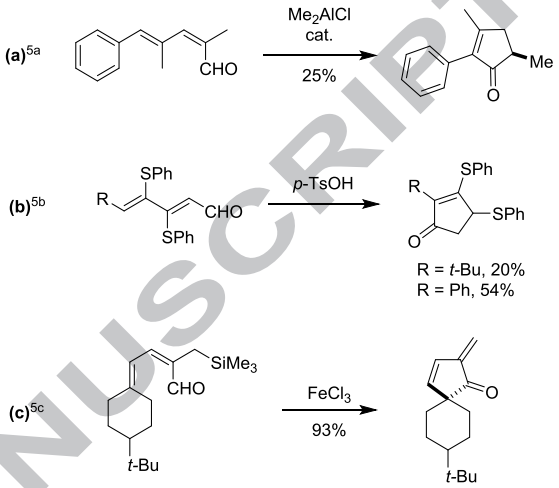


Figure 3 Typical examples of iso-Nazarov of pentadienals.

Further studies on the scope and application of this facile transformation in natural product synthesis will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at ____ (web link).

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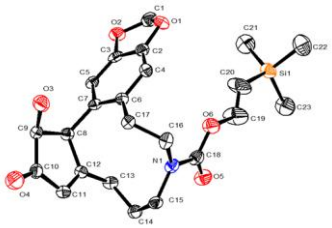
7. CCDC 1515005 contains the supplementary crystallographic data for compound **19**. X-ray crystallographic data of **19**: $C_{23}H_{31}NO_6Si$, FW 445.59, orthorhombic, space group *P2(1)2(1)2(1)*, a = 6.0550(3) Å, b = 16.1551(10) Å, c = 28.2228(17) Å, Volume/Å^3 = 2760.7(3), Z = 4, d_{calcd} = 1.072 g/cm^3. Final R indexes [$I>=2\sigma\ (I)$] R_1 = 0.1672, wR_2 = 0.4048. Final R indexes [all data] R_1 = 0.2108, wR_2 = 0.4372. See Supporting Information for details. The X-ray structure of compound **19**:



8. On-going work in our laboratory.

Highlights

A facile method for synthesis of 5-hydroxyl cyclopentenone derivatives was reported.

This transformation represents a new variant of the iso-Nazarov cyclization.

The approach has great potential application in natural product synthesis.