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A Novel Approach to the Synthesis of Bicyclic Lactones via an Interrupted Nazarov Reaction of *gem*-Divinyl Dihydrofurans†

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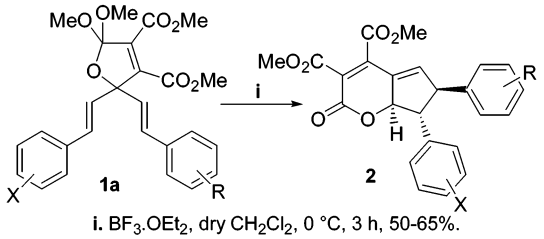
ABSTRACT



A facile Lewis acid induced interrupted Nazarov reaction of *gem*-divinyl dihydrofurans to bicyclic lactones is described.

The Nazarov reaction in its original form involves the cyclization of divinyl ketones to cyclopentenones under the influence of very strong acids. The recognition that it belongs to a general class of cationic electrocyclic reactions and that even mild Lewis acids can promote the cyclization has contributed significantly to the development of the reaction.[1] The scope and synthetic utility of the reaction was further broadened by the demonstration of Denmark that the strategic placement of a silyl group can direct the cyclization.[2] It may be noted that the crucial conrotatory electrocyclization of the pentadienylic cation that defines the Nazarov reaction creates a carbon−carbon bond and two stereocenters. Some or all stereochemical information is lost in the subsequent deprotonation or desilylation step. In the "interrupted Nazarov reaction", a variant of Nazarov cyclization investigated in detail by West, the stereochemical integrity is retained by trapping the oxyallyl zwitterion with pendant nucleophiles, and this has been efficiently applied for the diastereoselective synthesis of complex ring systems.[3] The participation of dihydrofuran derivatives in such interrupted Nazarov reactions, however, has not been reported so far. Herein we report the preliminary results of the interrupted Nazarov reaction of dihydrofurans substituted with a cross conjugated diene moiety.

The dihydrofurans that served as starting materials for our investigations were synthesized by a multicomponent reaction (MCR) between a dienone, acetylenic compound, and

† This paper is dedicated with best wishes to Professor Ian Fleming.
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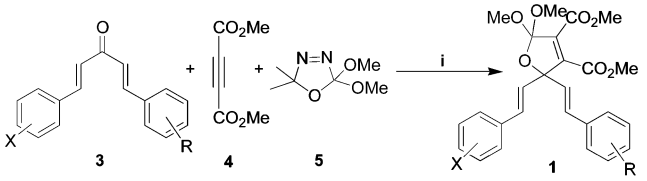
dimethoxy carbene.[4] When 1,5-bis(3-chloro-phenyl)-penta-1,4-dien-3-one is treated with dimethyl acetylene dicarboxylate (DMAD) and dimethoxycarbene, the latter being generated in situ by the thermolysis of 2,2-dimethoxy Δ^3-1,3,4-oxadiazoline in refluxing toluene following the Warkentin protocol,[5] a facile reaction leading to the dihydrofuran derivative in 70% yield occurred (Scheme 1). The product was characterized by spectroscopic analysis.

Scheme 1

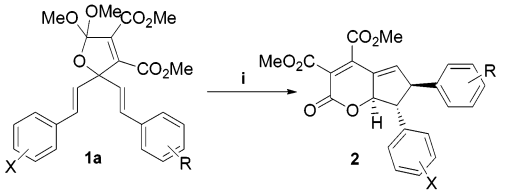


i. toluene, sealed tube, 110 °C, 24 h, 70 % **1b** X = R = 3-Cl

1a X = R = 2-Cl	91 %	1e X = R= 2-CF_3	81 %
1c X = R = H	73 %	1f X = R= 3,4-Cl	77 %
1d X = R = 4-CH_3	46 %	1g X = R= 3-OCH_3	41 %
1h X= R = 2-CH_3	53 %	1i X = H, R= CH_3	65 %

Our studies were set in motion by exposing the dihydrofuran derivative **1a** to a stoichiometric amount of $BF_3 \cdot Et_2O$ in dichloromethane. The reaction yielded a single bicyclic lactone derivative **2a** presumably resulting from an interrupted Nazarov reaction (Scheme 2). The product was

Scheme 2



i. $BF_3.OEt_2$, dry CH_2Cl_2, 0 °C, 3 h, 65 %. **2a** R = X = 2-Cl

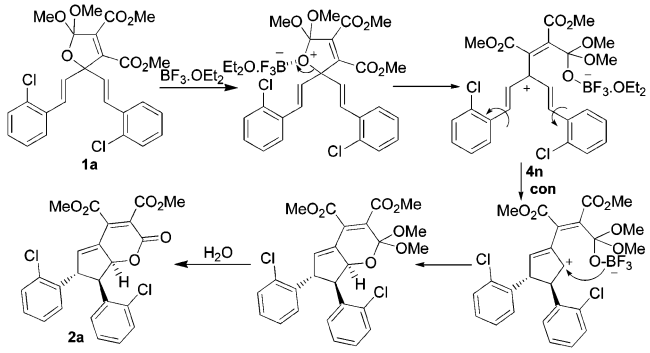
2b R = X = 3-Cl	65 %	2e R= X = 2-CF_3	60 %
2c R = X = H	60 %	2f R= X = 3,4 -Cl	79 %
2d R = X = 4-CH_3	81 %	2g R = X = 3-OCH_3	60 %
2 h R = X = 2-CH_3	62 %		

characterized by spectroscopic analysis.[6] Final proof of the structure assignment was derived from single-crystal X-ray analysis of **2a**.

The reaction was found to be general with other distyrenyl dihydrofurans and the cyclopentene derivatives were obtained in good yields (Scheme 1). Similar reaction occurred when $SnCl_4$ was employed as the Lewis acid.

A mechanistic rationale for this reaction is given in Scheme 3. Initial coordination of the Lewis acid to the

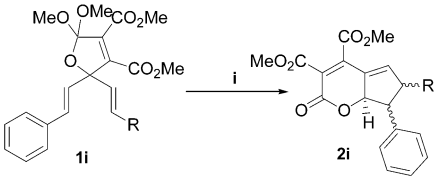
Scheme 3



dihydrofuran derivative **1a** yields the diallyl cation, which undergoes a facile 4π electrocyclic ring closure resulting in a new C−C bond, two new stereocenters, and an allyl cation. This allyl cation is trapped by the pendant ortho ester borate, establishing a new C−O bond and elimination of methanol, ultimately leading to the bicyclic lactone **2a**.

The rearrangement reaction of distyrenyl dihydrofurans with unsymmetrical substitution on the aromatic ring afforded an inseparable mixture of regioisomers (Scheme 4). Dihydrofurans with a nonstyrenyl substituent (Scheme 4, **2j** and **2k**) also gave the corresponding bicyclic lactone albeit in very low yields. This may be due to the relative instability of the cation formed in the reaction.

Scheme 4



i. $BF_3.OEt_2$, dry CH_2Cl_2, 0 °C, 3 h, 65% (1:0.8) 2i R = *p*- tolyl

2j R = H 10 %
2k R = CH_3 25%

It is interesting to note that the basic cyclopentanolactone moiety of **2** is a recurring structural motif in a number of biologically active monoterpenoids such as artemesia lactone **Ia**, vulgaris lactone[7] **Ib**, and ilexlactone[8] **II** (Figure 1). An

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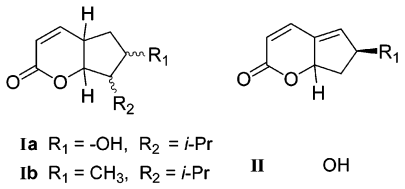
(5) Warkentin, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2161 and references therein.
(6) **Typical Experimental Procedure.** To 0.192 mmol of the dihydrofuran derivative dissolved in 15 mL of dry CH_2Cl_2 was added 0.22 mmol of BF_3. OEt_2 at 0 °C. The mixture was stirred for 3 h. When the reaction was completed, the reaction mixture was passed through a short pad of silica, the solvent was removed, and the residue was subjected to column chromatography on silica column using 70:30 hexanes−ethyl acetate solvent mixture to afford the bicyclic lactone. **Data for compound 2a:** colorless solid; mp 189−190 °C; IR (KBr) ν_{max} 3015, 2955, 2850, 1745, 1738, 1728, 1630, 1594, 1479, 1437, 1393, 1277, 1098, 1052, 993, 758, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$−CCl_4, v/v, 3:1) δ 3.88 (t, J = 8.3 Hz, CH), 3.91 (s, 6H, OCH_3), 5.02 (dd, J = 6.4 1H, CH), 5.94 (d, 1H, J = 7.9 Hz), 6.82 (s, 1H,). 7.19−7.35 (m, 8H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$−CCl_4, v/v, 3:1) δ 52.38, 52.95, 53.12, 59.42, 87.05, 127.06, 125.48, 128.57, 128.69, 128.92, 129.08, 129.54, 130.30, 130.52, 133.71, 134.06, 134.68, 135.34, 138.11, 141.63, 160.34, 162.75, 163.85. Anal. Calcd for $C_{24}H_{18}Cl_2O_6$: C, 60.90; H, 3.83. Found: C, 61.26; H, 3.93.



Ia R_1 = -OH, R_2 = *i*-Pr
Ib R_1 = CH_3, R_2 = *i*-Pr

II OH

Figure 1.

RCM approach to the synthesis of related core of α,β-unsaturated lactones has been described by Grubbs.[9]

In conclusion, we have uncovered a facile method for the synthesis of substituted dihydrofuran derivatives and it has been shown that the latter undergo an interrupted Nazarov reaction to give cyclopentanolactones, which resemble the structural framework of several monoterpenoid natural products.

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Supporting Information Available: General experimental procedures; IR, ^{1}H NMR, and ^{13}C NMR data for compounds **1a**−**h**, **2a**−**h**, **2i**, and **2k**; and single-crystal X-ray structure for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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