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TIN-DIRECTED NAZAROV CYCLIZATIONS: A VERSATILE ROUTE TO CYCLOPENTENOIDS

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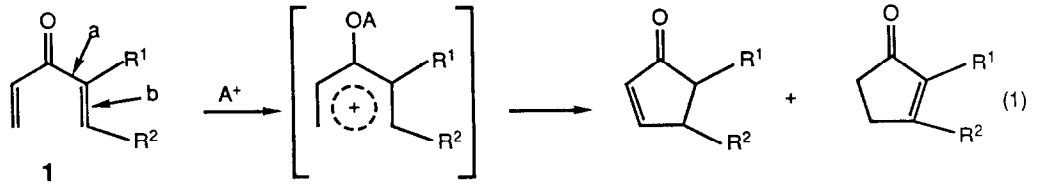
Summary - The preparation of 1-(tri-butylstannyl)-1,4-pentadien-3-ones and their efficient Nazarov cyclizations to cyclopentenones, including a PGA analogue, are described.

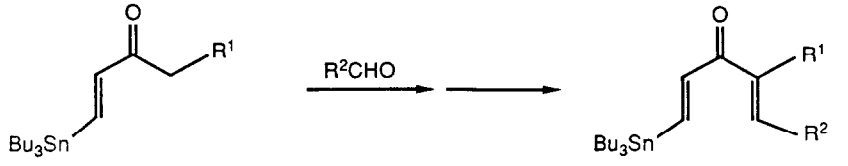
The continuing interest in the synthesis of cyclopentanoid natural products has resulted in the development of a wide variety of methods for the construction of substituted cyclopentanones and cyclopentenones.[1] Of the many methods, the Nazarov reaction[2] involving acid-catalyzed cyclization of divinyl ketones **1** to give cyclopentenones (eq 1) is attractive due to its simplicity.



1 (1)

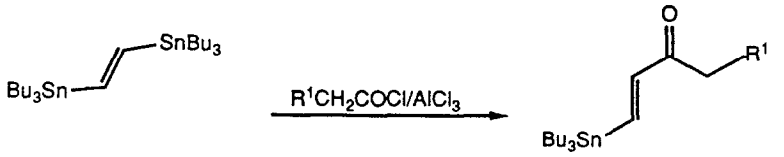
The classical Nazarov reaction has received considerable attention over the last twenty years.[3] The reaction, however, has several drawbacks which have limited its use as a general tool for organic synthesis, including (1) a lack of positional control of the double bond, (2) strong acidic conditions are generally required and (3) the preparation of highly functionalized divinyl ketones is far from simple. Recently the problem of regiocontrol of the double bond was overcome by Denmark[3e,g,h] by use of a trimethylsilyl group to direct the position of unsaturation. However the convenient preparation of appropriate functionalized divinyl ketones presents a considerable challenge. The most common route to compounds of type **1** involves the addition of a vinylic nucleophile to an unsaturated acid or aldehyde derivative with formation of bond a (see **1**).

In this communication we show that the aldol reaction (eq 2) between enolate anions derived from tin-substituted enones **2** and various aldehydes, followed by dehydration, represents a flexible route to tin-substituted divinyl ketones *via* formation of bond b (see **1**).



2 (2)

Tributylstannyl-substituted enones such as **2** (R = H) have been prepared in our laboratory and were found to be useful precursors to [4.1.0.] bicyclic systems using a Diels-Alder-cyclopropanation sequence.[4] These compounds are readily prepared by acylation of *trans*-1,2-bis(tri-n-butylstannyl)ethylene[5] in the presence of aluminium chloride (eq 3).



(3)

2

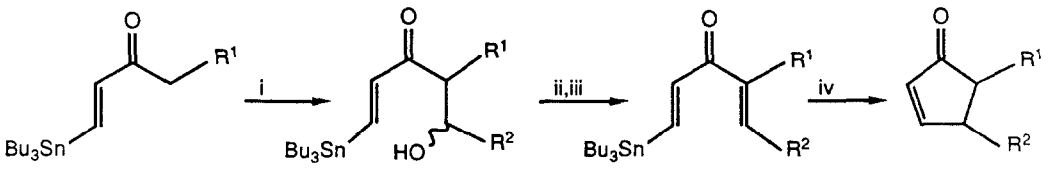
R^1 = H 58%

R^1 = n-C_4H_9 60%

R^1 = n-C_7H_{15} 65%

Sequential treatment of these tin-substituted enones with lithium diisopropylamide followed by a variety of aldehydes resulted in clean formation of hydroxy ketones **3** which were smoothly dehydrated via a mesylation-elimination sequence. The tin-substituted divinyl ketones **4** were treated with boron trifluoride etherate complex at room temperature to effect Nazarov cyclization to cyclopentenones (Scheme 1).

Scheme 1



2 **3** **4** **5**

i) LDA, -78°C,THF, R^1CHO; ii) Et_3N, MsCl, CH_2Cl_2; iii) DBU, CH_2Cl_2; iv) $BF_3.OEt_2$(4eq), CH_2Cl_2, 20°C

R^1	R^2	3 (%)	4 (%)	5[6] (%) (trans/cis)
H	n-C_7H_{15}	83	71	47
H	Ph	63	70	44
H	(E)-CH=CH	65	68	21
n-C_4H_9	Me	69	68	93 (1.7:1)
n-C_4H_9	n-C_7H_{15}	61	65	87 (1.4:1)
n-C_4H_9	Ph	69	61	92 (1.4:1)
n-C_4H_9	(E)-CH=CH	66	76	88 (1.3:1)
n-C_4H_9	(E)-PhCH=CH		42*	83 (1.5:1)

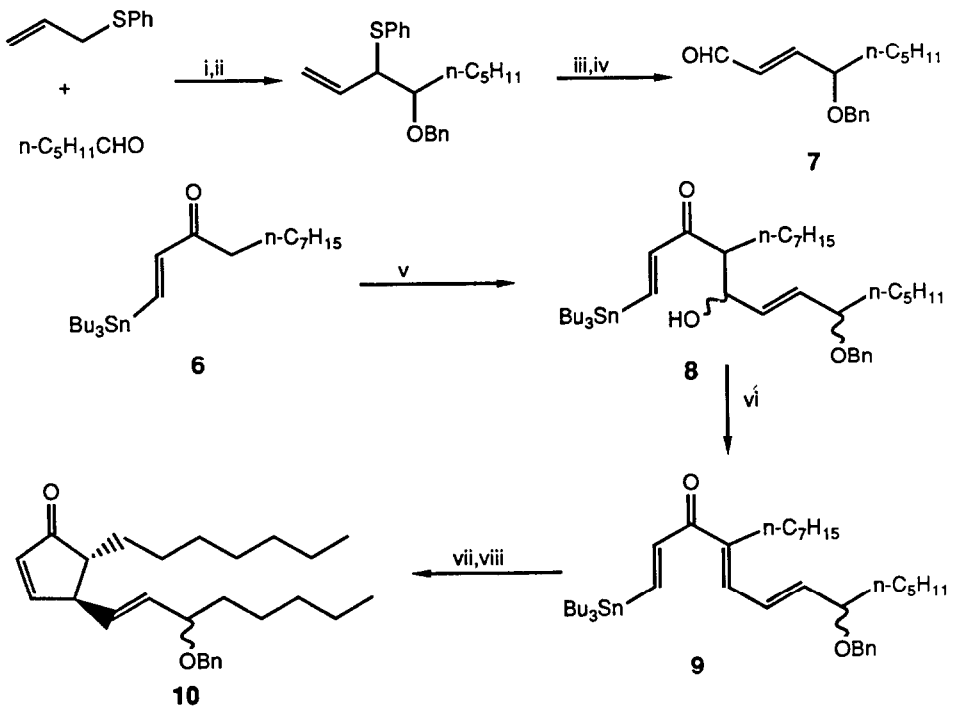
* Yield from starting enone

In many reports concerning the Nazarov reaction it has been noted that the Lewis acid of choice varies from substrate to substrate; in our experience, boron trifluoride was found to be a superior choice for Nazarov reactions involving tin-substituted precursors. The main advantage was that it gave extremely clean results, presumably due to the *in situ* formation of insoluble tin fluoride polymers,[7] which made the isolation of the products very simple.

We believe that this approach to divinyl ketones and cyclopentenones represents a convenient and flexible method for the preparation of more complex cyclopentanoid natural products. In order to demonstrate this point we have completed a convergent synthesis of a simple PGA_1[8] analogue **10** using the tin-directed Nazarov methodology described above.

The aldehyde **7** which was ultimately to become the lower side chain of the prostaglandin was readily prepared from allyl phenyl sulphide and hexanal as outlined in Scheme 2. The enolate derived from tin-substituted enone **6** added smoothly to aldehyde **7** to give the hydroxy ketone **8** (67% yield) which was dehydrated in the normal manner to give the divinyl ketone **9**. Cyclization of **9** using boron trifluoride afforded a PGA derivative as a mixture of four diastereoisomers. Equilibration of this mixture (basic Al_2O_3) gave the thermodynamically favoured trans isomer **10** as a mixture of epimers at C-15.

Scheme 2



i) n-BuLi, $AlEt_3$, THF, -78°C,[9] (72%); ii) BnI, NaH, THF, 0°C, (81%); iii) mCPBA, EtOAc, -40°C, then Et_2NH, MeOH, R.T., (58%); iv) PCC, CH_2Cl_2, R.T., (60%); v) LDA, -78°C, (7), (67%); vi) MsCl, Et_3N, R.T., (85%); vii) $BF_3.OEt_2$, CH_2Cl_2, R.T., (56%); vii) Basic Al_2O_3, CH_2Cl_2, R.T., 24h.

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6) Yields for cyclopentenones refer to clean (^{1}H NMR and HPLC) material. The ratios were determined from the ^{1}H NMR spectrum of the mixture of isomers, and the major isomer was confirmed as the trans isomer by equilibration of a selected example to its more stable trans configuration. All compounds were characterized by ^{1}H, ^{13}C NMR and IR spectra; high resolution MS or C,H analysis were obtained for key compounds.

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