

## Synthesis of Nine-Membered Carbocycles via Sequential Higher-Order Cycloaddition--Pinacol Rearrangement

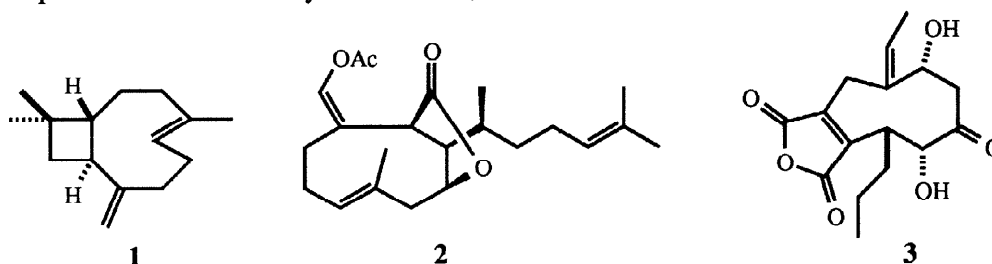
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Received 12 December 1997; revised 2 January 1998; accepted 5 January 1998

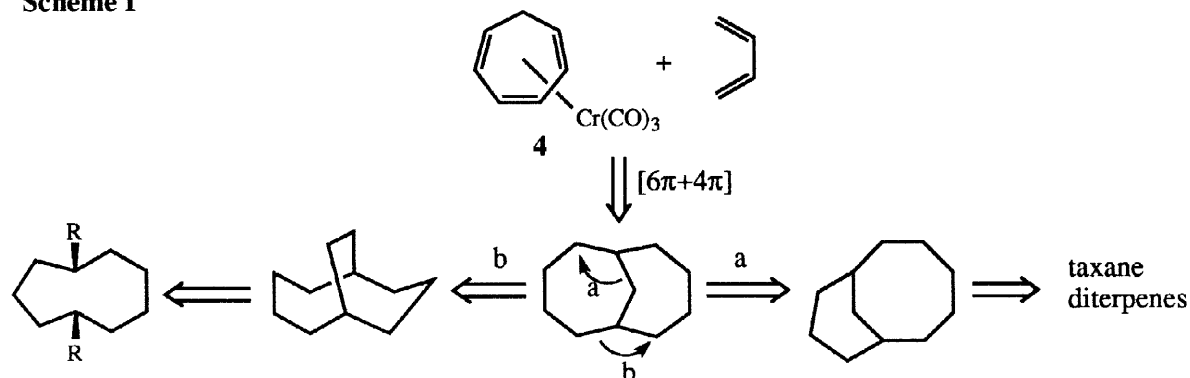
**Abstract:** Chromium(0)-promoted  $[6\pi+4\pi]$  cycloaddition followed by pinacol rearrangement and ring cleavage of the resultant bicyclo[4.3.2]undecane system affords functionalized nine-membered carbocycles. © 1998 Elsevier Science Ltd. All rights reserved.

The number of natural products known to possess nine-membered carbocyclic substructures continues to grow. Typical examples that illustrate the structural diversity of these compounds include the well-known sesquiterpene, caryophyllene (1),<sup>1</sup> the xenicane diterpene, dilopholide (2)<sup>2</sup> and the nonadride, cornexistin 1 (3).<sup>3</sup> In recent years, even more structurally elaborate nine-membered ring containing compounds have been isolated,<sup>4</sup> including the important antitumor enediyne antibiotics, kedarcidin<sup>5a</sup> and neocarzinostatin.<sup>5b</sup>

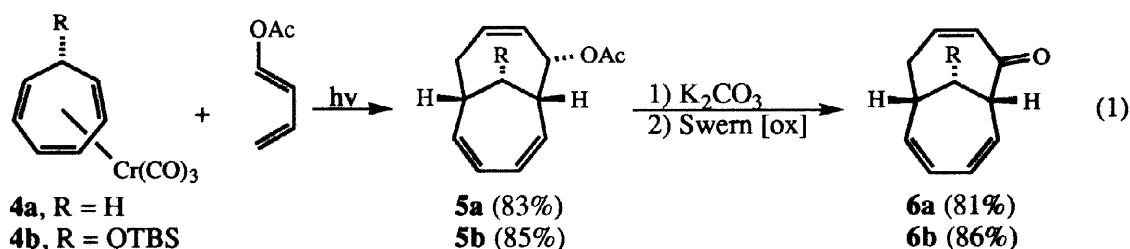


Numerous strategies have been employed for the construction of nine-membered rings including fragmentation,<sup>6</sup> annulation,<sup>7</sup> rearrangement<sup>8</sup> and ring expansion-ring contraction methods.<sup>9</sup> Direct cycloaddition has also been explored briefly.<sup>10</sup> We now wish to report a novel chromium(0)-promoted  $[6\pi+4\pi]$  cycloaddition<sup>11</sup>-pinacol rearrangement strategy that delivers substituted nine-membered carbocycles with complete control of substituent stereochemistry.

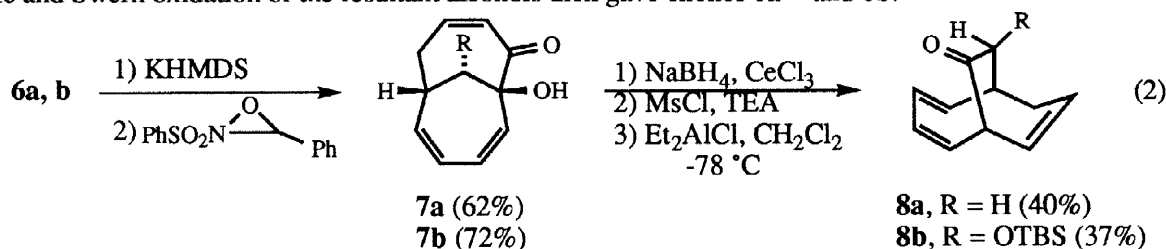
Scheme I



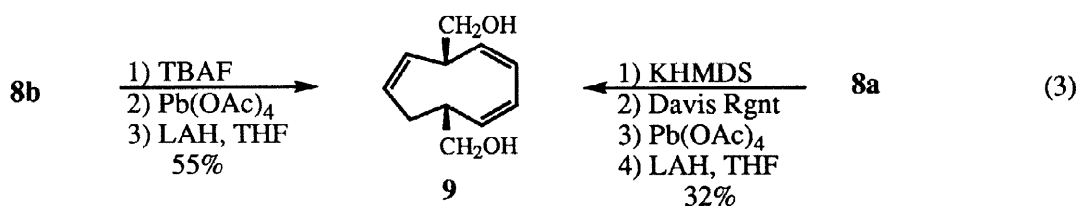
Previously, it had been recognized that the readily available bicyclo[4.4.1]undecane ring system that emerges from the metal-promoted higher-order cycloaddition process could be selectively isomerized to either the bicyclo[5.3.1]undecane system that comprises the AB-ring substructure of the taxane diterpenes (Scheme I, bond migration a), or to the corresponding bicyclo[5.4.0]undecane system characteristic of the tiglianes (not shown).<sup>12</sup> It can be further envisioned that a functionally modified bicycle could undergo yet another productive bond reorganization to deliver a bicyclo[4.3.2]undecane, which upon cleavage of the two-carbon bridge would afford a substituted nine-membered ring (Scheme I, bond migration b). The results of this investigation are described below.



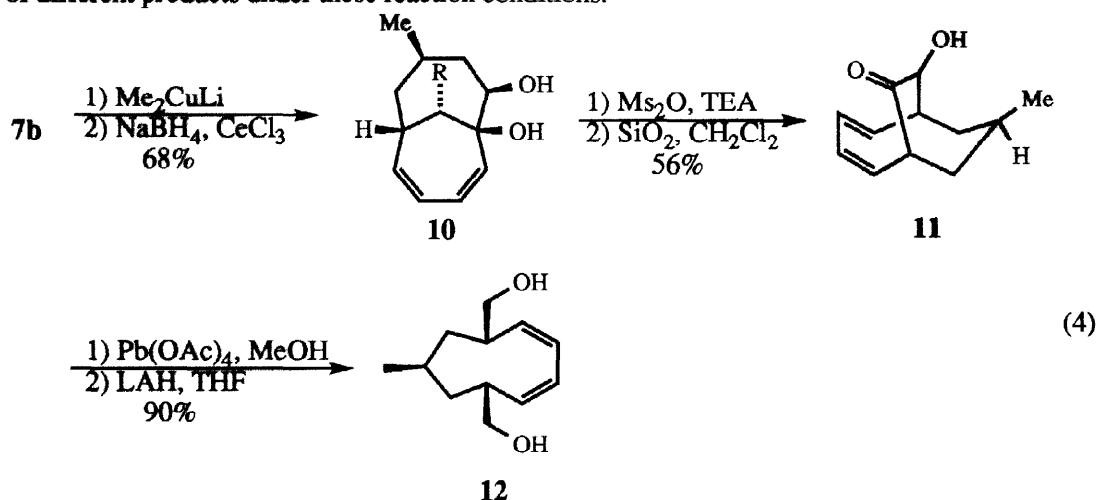
Irradiation of either the parent ( $\eta^6$ -cycloheptatriene)tricarbonylchromium(0) (**4a**) or the corresponding *endo*-*t*-butyldimethylsilyloxy derivative (**4b**)<sup>13</sup> in the presence of 1-acetoxybutadiene afforded cycloadducts **5a**<sup>14</sup> and **5b**,<sup>14</sup> respectively in excellent yields and in diastereomerically homogeneous form. Saponification of the acetate and Swern oxidation of the resultant alcohols then gave enones **6a**<sup>14</sup> and **6b**.<sup>14</sup>



Critical to the success of the projected bond reorganization strategy was the ability to efficiently introduce a hydroxyl function at the bridgehead position adjacent to the carbonyl group in compounds **6a,b**. Closely related bridgehead enolates in the bicyclo[4.4.1]undecane series have been shown previously to be well-behaved and useful intermediates for alkylation and hydroxylation.<sup>15</sup> Thus, treatment of each of these enones in turn with KHMDS followed by the Davis oxaziridine reagent<sup>16</sup> provided the requisite ketols **7a,b**<sup>14</sup> in good yields. Reduction of the resultant  $\alpha$ -hydroxy enones afforded the corresponding syn-diol in each case, setting the stage for performing the crucial rearrangement step. In this case, the Tsuchihashi version of the pinacol rearrangement proved to be the method of choice.<sup>17</sup> In the event, mesylation under standard conditions followed by exposure to  $\text{Et}_2\text{AlCl}$  at  $-78^\circ\text{C}$  yielded the desired bicyclo[4.3.2]undecanes **8a**<sup>14</sup> and **8b**<sup>14</sup> in serviceable yields.



Conversion to the corresponding nine-membered carbocycle was completed by processing compounds **8a** and **8b** in routine fashion as shown in Equation (3) to provide diol **9**<sup>14</sup> in good yield. While stereoelectronic effects may play a role in dictating the course of this rearrangement, the efficiency of the process may be more reflective of the migratory aptitude of the proximate vinyl group, since the corresponding saturated system affords a variety of different products under these reaction conditions.



More substitutionally elaborate systems can also be accessed using this protocol. Addition of  $\text{Me}_2\text{CuLi}$  exclusively from the more accessible exo-surface of **7b**<sup>11</sup> followed by cerium-mediated reduction afforded primarily the diol **10**<sup>14</sup> (14 : 1, cis : trans) in good yield. In this instance, pinacol rearrangement of the corresponding mesylate could be effected by simply stirring the substrate with a suspension of silica gel in  $\text{CH}_2\text{Cl}_2$  at room temperature to provide bicycle **11**.<sup>14</sup> It is noteworthy that the silyl protecting group had been severed during this event as well to afford the  $\alpha$ -ketol directly. Cleavage of this  $\alpha$ -hydroxy ketone and reduction of the resultant dicarbonyl product as before afforded the all-cis cyclononadiene **12**<sup>14</sup> in excellent yield.

In summary, a new method for the synthesis of substituted nine-membered carbocycles has been developed. Application of this chemistry to the synthesis of a member of the xenicane family of diterpenes will be reported in due time.

**Acknowledgment.** The authors wish to thank the National Institutes of Health (CA-36543) for their generous support of this research.

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