



## Higher-Order Cycloaddition Reactions in Synthesis. Asymmetric Assembly of the C5-C11 Segment of the Ansa Bridge of Streptovaricin D

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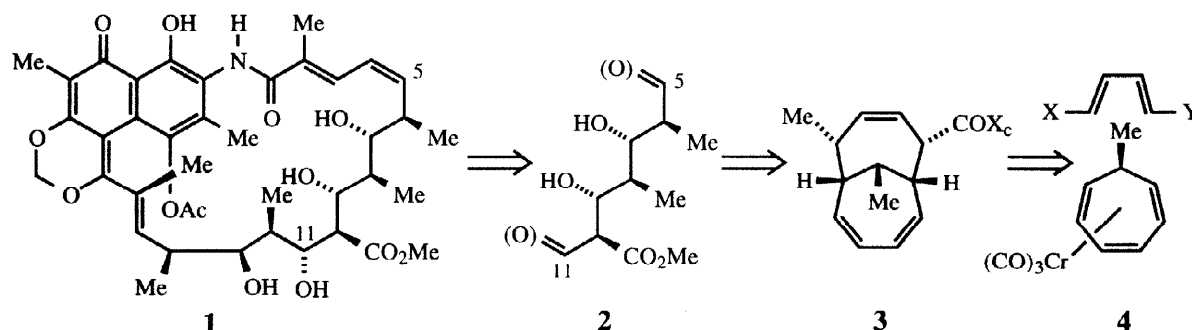
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**Abstract:** Auxiliary-controlled, asymmetric Cr(0)-promoted  $[6\pi+4\pi]$  cycloaddition followed by a ring fragmentation sequence afforded the C5-C11 segment of the ansa bridge found in the ansamycin antibiotics streptovaricin C, D and damavaricin D. © 1998 Elsevier Science Ltd. All rights reserved.

The streptovaricins are an intriguing family of antibiotics that are particularly rich in stereochemical information as well as in other structural features that present significant challenges to synthesis.<sup>1</sup> Many of these compounds are known to effectively inhibit reverse transcriptases<sup>2</sup> and, as such, have enjoyed renewed synthetic and medicinal interest in recent years.<sup>3,4</sup>

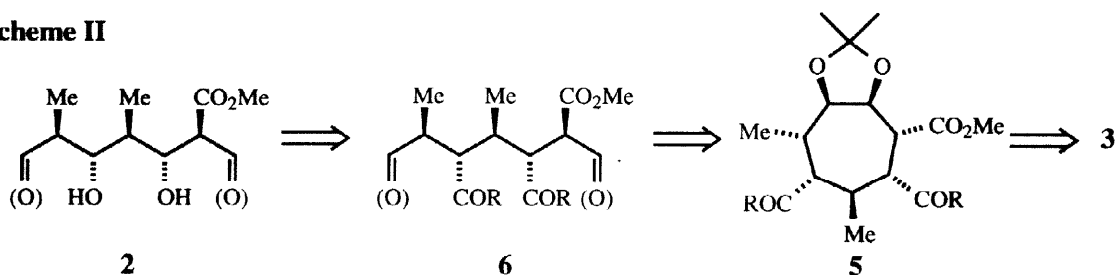
### Scheme I



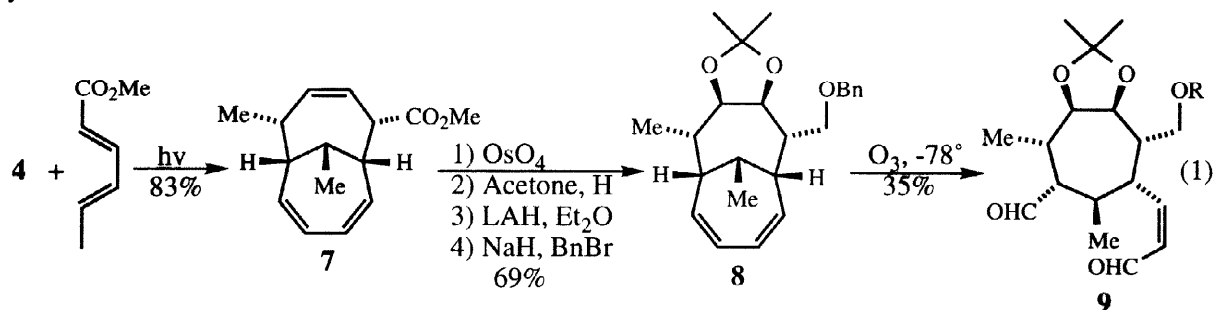
In this paper we describe a construction of the C5-C11 segment (2) of the ansa bridge moiety that is present in streptovaricin D (1) as well as in congeners, streptovaricin C and damavaricin D (Scheme I). It was envisioned that the entire carbon backbone of this substructure could be derived from the highly substituted bicyclo[4.4.1]undecatriene 3 that would be obtained from an auxiliary-controlled, asymmetric Cr(0)-promoted  $[6\pi+4\pi]$  cycloaddition of complex 4.<sup>5</sup>

The initial strategy for converting adduct 3 into intermediate 2 called for oxidative cleavage of the 1,3-diene function in a protected analog of cycloadduct 3 to give the highly substituted cycloheptane 5 (Scheme II). Oxidative cleavage of the unprotected cis-diol in 5 would then afford the fully deconvoluted acyclic intermediate 6. Finally, a Baeyer-Villiger or related oxidative bond reorganization would afford the target sequence of the ansa bridge. The viability of this approach was initially evaluated in a model study in the racemic series as depicted in equation (1).

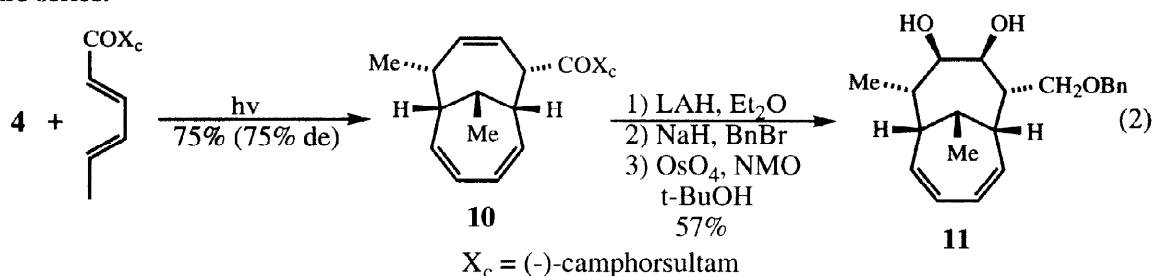
Scheme II



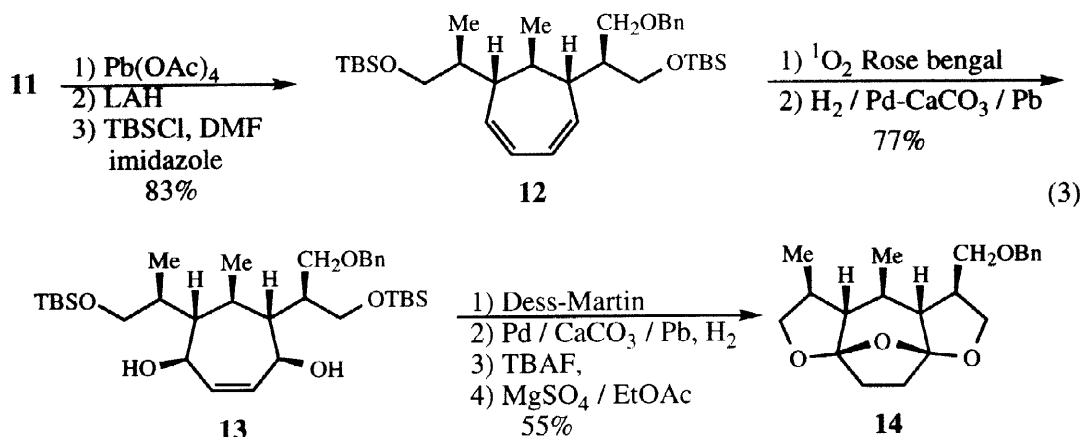
Irradiation of the readily available 7-*exo*-methylcycloheptatriene complex **4**<sup>6</sup> with methyl sorbate provided bicyclo[4.4.1]undecatriene **7**<sup>7</sup> in good yield. Cis-dihydroxylation, protection and reduction of the ester afforded **8**<sup>7</sup> after benzylation of the primary alcohol. Ozonolysis of **8** afforded only a modest yield



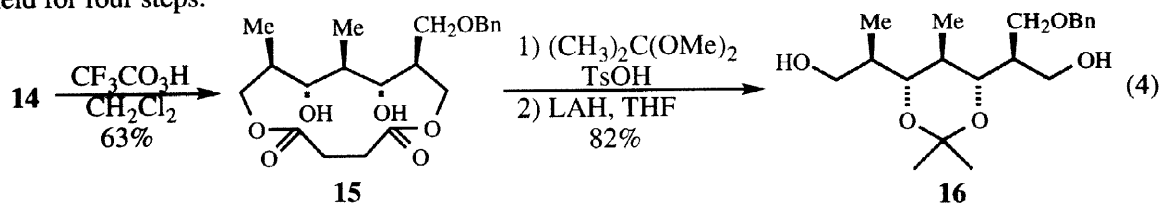
of a 1 : 1 mixture of the two possible enal-aldehydes **9**. Efforts to drive this cleavage reaction to the desired foreshortened dialdehyde species resulted in a complex mixture of products,<sup>8</sup> and several variations on this general strategic theme were attempted without success. In light of these results, a somewhat different tactic for unraveling the bicyclic system was then pursued in a related enantiomerically pure series.



Thus, irradiation of 7-*exo*-methylcycloheptatriene complex **4** in the presence of the N-sorbate derivative of (-)-camphorsultam<sup>9</sup> afforded the cycloadduct **10**<sup>7</sup> in 75% yield (75% de). The major cycloadduct diastereomer was easily separated and carried through the remaining steps of the sequence.<sup>10</sup> Routine reduction and protection of the side-chain in compound **10**, followed by cis-dihydroxylation afforded **11**<sup>7</sup> ( $[\alpha]_D^{20} = -82$ ) in a fashion completely analogous to that depicted in equation (1). Oxidative cleavage of the diol, reduction of the resultant aldehydes and protection as TBS ethers gave the highly-



substituted cycloheptadiene **12**.<sup>7</sup> Since direct oxidative cleavage of related dienes proved to be difficult (*vide supra*), the unsaturation in this compound was first modified in an effort to improve the prospects for successful ring cleavage. Therefore, highly face-selective cycloaddition of  ${}^1\text{O}_2$  across the diene of **12** was carried out, followed by reductive cleavage of the resultant peroxide linkage to provide the key syn-diol **13**<sup>7</sup> in excellent overall yield. Routine Dess-Martin oxidation of this material to the corresponding enedione followed by alkene reduction, disilylation and, finally,  $\text{MgSO}_4$ -mediated acetalization gave the interesting and stereochemically rich bisacetal **14**<sup>7</sup> ( $[\alpha]_{\text{D}}^{20} = +9.5$ ) as a single diastereomer in 55% overall yield for four steps.



The stage was now set for unveiling the *cis*-1,3-diol found in the target structure. The requisite oxidative ring cleavage designed to achieve this objective as well as to afford the fully intact C5-C11 substructure was ultimately brought to practice by treatment of bisacetal **14** with *unbuffered*  $\text{CF}_3\text{CO}_3\text{H}$ . This intriguing transformation represents a net double Baeyer-Villiger oxidation-*trans*-lactonization process that effected a one-pot transformation of the cycloheptane ring into **14** into a 13-membered bis-lactone **15**<sup>7</sup> ( $[\alpha]_{\text{D}}^{20} = +10$ ), the structure of which was assigned based on extensive decoupling studies.<sup>11</sup> Finally, the bis-lactone species that emerged from this intricate oxidation process was efficiently converted in straightforward fashion into the protected diol **16**<sup>7</sup> ( $[\alpha]_{\text{D}}^{20} = -18.9$ ), which exhibits the entire substitution pattern of the C5-C11 segment in protected and enantiomerically pure form.

Work on incorporating fragment **16** into a complete ansa bridge intermediate is currently underway.

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