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## [3 + 2] Annulation of Allylic Silanes in Acyclic Stereocontrol: Total Synthesis of (9*S*)-Dihydroerythronolide A

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The [3 + 2] annulation reactions of allylic silanes are powerful methods for the stereoselective preparation of cyclopentanes and five-membered ring heterocycles.<sup>1</sup> These reactions have been used as key transformations for the syntheses of five-membered ring-containing natural products.<sup>2,3</sup> While evidently useful for the formation of cyclic compounds, these annulation reactions are not obviously suited for the synthesis of acyclic compounds.<sup>4</sup> In this communication, we demonstrate that annulation reactions of allylic silanes can be used in acyclic stereocontrol. We use this method as a key step in an enantioselective total synthesis of (9*S*)-dihydroerythronolide A (1), a molecule that has stimulated the development of a host of new reactions and concepts for C–C bond construction.<sup>5,6</sup>



To demonstrate the transfer of the stereochemical information introduced by the annulation reaction to an acyclic system, we performed a ring-opening reaction of the highly substituted tetrahydrofuran **3**. This heterocycle was obtained as a single diastereomer from the annulation reaction of allylic silane **2** with ethyl pyruvate (Scheme 1).<sup>2b</sup> Conversion of the carboethoxy group in **3** to the iodomethyl group followed by elimination formed the highly functionalized acyclic intermediate **5**.

If the tertiary silyl group, which was established during the annulation reaction, is considered as a tertiary hydroxyl group,<sup>7</sup> the synthetic utility of **5** becomes immediately apparent. This silane represents a motif that can be found twice in the natural product (9*S*)-dihydroerythronolide A (**1**). Disconnection of the seco acid **6** by an aldol reaction between the C8–C9 bond gives two similarly sized fragments **7** and **8** (Scheme 2).<sup>8</sup> These two fragments could be prepared from alkene **9**, which closely resembles silane **5**.

While the synthetic plan outlined in Scheme 2 was appealing in principle, the success of the aldol disconnection about the C8–C9 bond was not assured. Although the requisite stereochemistry of the aldol adduct can be anticipated from an  $\alpha$ -chelation-controlled aldol reaction of the (*Z*)-enolate of  $\alpha$ -benzyloxy ethyl ketone **8**, only a few examples of this transformation were reported with simple  $\alpha$ -oxygenated ethyl ketones.<sup>9</sup> Model studies with analogous substituted aldol partners suggested, however, that the key aldol reaction of **7** and **8** would proceed according to plan. Addition of the tin(II) enolate of the model ethyl ketone **10** to the model chiral aldehyde **11** proceeded with high diastereoselectivity, favoring the







product possessing the relative configuration required to complete the synthesis (eq 1).<sup>10,11</sup>

Encouraged by the result on the model aldol reaction, we began the total synthesis of (9*S*)-dihydroerythronolide A by assembling the aldol coupling partners **7** and **8** (Scheme 3). The annulation reaction of the racemic allylic silane **2** with (*S*)-pantolactone pyruvate ester followed by reduction afforded the chiral diol **13** with an ee greater than 98% (Scheme 3).<sup>2b</sup> The same diol **13** could also be obtained with comparable enantiomeric purity from the resolved chiral allylic silane (–)-**2** using (*R*)-pantolactone pyruvate ester.<sup>2b</sup> The derived iodide **14** underwent a ring-opening reaction to afford the key acyclic intermediate **15** after protecting group manipulations. Intramolecular hydrosilylation of allylic alcohol **15** followed by Tamao oxidation provided the desired diol **16** as a single diastereomer.<sup>12</sup> The C9–C15 fragment **7** was obtained from diol **16** in three steps. Condensation of **7** with the titanium enolate



Scheme 4



of (*R*)-4-benzyl-3-propionyloxazolidin-2-one afforded the desired aldol adduct as a single diastereomer.<sup>13,14</sup> Protection of the hydroxyl group by an anhydrous DDQ oxidation yielded a 4-meth-oxybenzylidene acetal, which could be converted to the C1–C8 fragment **8**.

With the two fragments in hand, efforts were focused on the key aldol coupling reaction. In accordance with the model system (eq 1), the aldol reaction of **7** and **8** gave the desired product **17** as a single diastereomer in 90% yield (Scheme 4). Although an excess of the aldehyde **7** (4.0 equiv) was used to consume all the ketone **8**, unreacted aldehyde was easily recovered without epimerization. The C7 oxygen atom was removed by a directed reduction<sup>15</sup> and protection of the C9 hydroxyl group followed by deoxygenation.<sup>6c,16</sup> Unmasking of the carboxylic acid and removal of the silyl group provided the seco-acid **6**. Macrolactonization<sup>17</sup> followed by global deprotection afforded (9*S*)-dihydroerythronolide A (**1**), whose subsequent conversion into erythronolide A and erythromycin A is known.<sup>18,19</sup>

This work demonstrates that the [3 + 2] annulation of allylic silanes can be a powerful method for the synthesis of highly substituted acyclic targets. Using this methodology, a convergent total

synthesis of (9*S*)-dihydroerythronolide A has been accomplished with the longest linear sequence of 29 steps and in 5.4% overall vield.

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**Supporting Information Available:** Full experimental and analytical data for all new compounds; the chiral HPLC traces of  $(\pm)$ -13, (-)-13, and (+)-13; and  ${}^{1}$ H and  ${}^{13}$ C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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