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Towards the Synthesis of Streptovaricin D: Synthesis of Fully Elaborated Aromatic Precursors and Coupling with Ansa Chain Fragments

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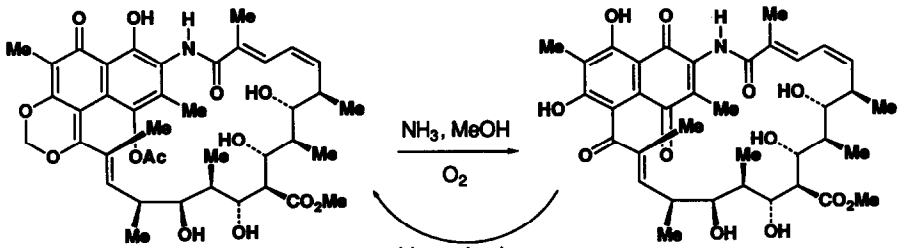
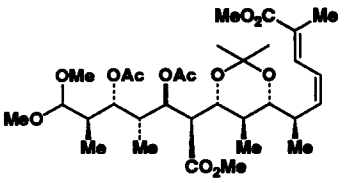
Abstract. The highly functionalized streptovaricin-damavaricin D aromatic precursors **12** and **15** have been prepared and coupled with propionaldehyde or unsaturated aldehydes **16** and **18** via aryllithium intermediates to give **2**, **3** and **19**.

The streptovaricins are a structurally complex group of biologically active ansamycin antibiotics isolated from *Streptomyces spectabilis*.[1] We are pursuing an approach to the total synthesis of streptovaricin D (SvD)[2,3] that proceeds by way of damavaricin D (DmD), a degradation product and a SvD biosynthetic precursor.[4] We have previously developed a highly stereoselective synthesis of the ansa chain segment **1**,[3] and are pleased to report herein syntheses of the first fully elaborated aromatic SvD or DmD precursors, ethyl ketone **2** and unsaturated ketones **3** and **19**. While preliminary attempts to perform aldol condensations of **2** and model aldehydes have not been fruitful,[5] the technology demonstrated by the synthesis of **3** is expected to be applicable to the synthesis of DmD.

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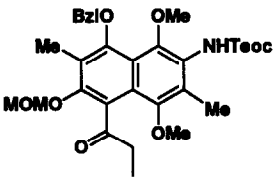
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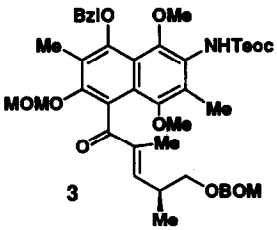
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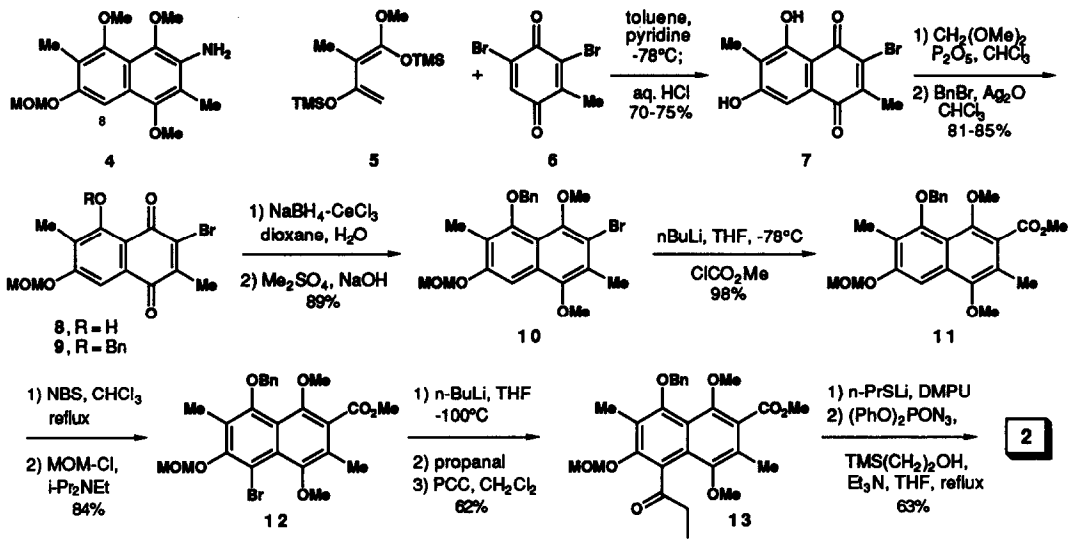
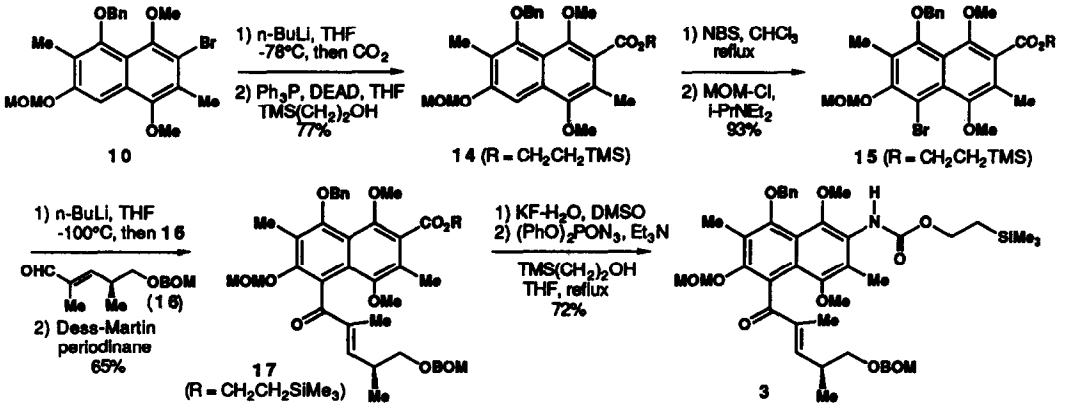
Diels-Alder reactions have been used to great advantage in several previous syntheses of the naphthalenic systems of the rifamycins and streptovaricins.[2b,6] Trost and Pearson, in particular, described an extremely brief synthesis of naphthyl amine **4**, but were not successful in attempts to introduce an ethyl ketone at C(8).[2b,7] Nevertheless, the Trost-Pearson work served as the starting point for our synthesis of ethyl ketone **2**. The cyclocondensation of diene **5**[2b,7] and 2,6-dibromo-3-methylbenzoquinone **6**[8] provided the known, highly crystalline cycloadduct **7** in 70-75% yield [m.p. 221-223°C (dec.); lit.[7] m.p. 226-228°C].[9] Treatment of **7** with a

large excess of dimethoxymethane and P_2O_5 in $CHCl_3$ according to Trost's procedure[2b,7] provided the highly crystalline C(7)-mono MOM ether **8**, m.p. 125-127°C, in 97% yield. The C(5) phenol was benzylated by using excess benzyl bromide and Ag_2O in $CHCl_3$, and then quinone **9**[10a,b] (m.p. 113-115°C, 90% yield) was reduced with $NaBH_4$ and $CeCl_3$ in dioxane and methylated in situ (Me_2SO_4, 50% aq. NaOH, with careful exclusion of O_2), to give **10**[10a,b] in 89% yield. After considerable experimentation, we determined that it was necessary to postpone the introduction of the C(3)-amine until after C(8) was functionalized. Thus, treatment of **10** with n-BuLi in THF at -78°C followed by addition of methyl chloroformate provided naphthoate **11**[10a,b] in 98% yield. As attempts to functionalize C(8) of **11** by Friedel-Crafts acylation with propionyl chloride and BF_3 or $AlCl_3$, or by Fries rearrangement of the propionate ester obtained following removal of the MOM ether, were unproductive, C(8) of **11** was brominated by exposure to NBS in $CHCl_3$ at reflux. The crude product was treated with MOM-Cl and Hunig's base to reintroduce the MOM group which was lost during the bromination reaction, thereby providing **12**[10a,b] in 84% yield. A solution of **12** in THF at -100°C was treated with n-BuLi for 3 min followed by propionaldehyde.[11] Oxidation of the intermediate benzylic alcohol (obtained in 80% yield) with PCC then provided ethyl ketone **13**[10a] in 77% yield. Finally, deprotection of the methoxycarbonyl unit (n-PrSLi, DMPU)[12] followed by Curtius rearrangement ($(PhO)_2PON_3$, Et_3N, THF, reflux)[13] of the resulting acid in the presence of 2-trimethylsilyl ethanol provided the targeted ethyl ketone **2**[10a,b] in 63% yield.

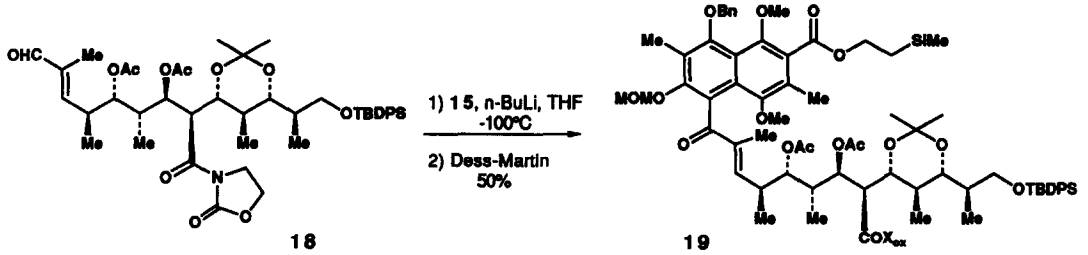


We originally planned to complete the damavaricin-streptovaricin carbon skeleton by performing an aldol condensation between **2** and the aldehyde corresponding to acetal **1**.[5] However, as preliminary attempts to perform aldol reactions of **2** or of keto ester **13** with simple model aldehydes were unpromising, we reconsidered our options for coupling of the aromatic and ansa chain segments. That we were already using a C(8) organolithium intermediate in the conversion of **12** to **13** suggested that it should be possible to use an ansa chain α,β-unsaturated aldehyde directly in this sequence. The synthesis of **3** therefore was developed to demonstrate the viability of this approach.



Naphthoate **14**,[10a,b] containing an easily removable β-trimethylsilylethyl ester, was prepared by carboxylation of the organolithium derivative of **10** with CO_2 (90% yield) followed by Mitsunobu esterification with β-trimethylsilylethanol (85% yield). Bromonaphthalene **15**[10a,b] was then prepared (93% yield) by using the procedure described for the synthesis of **12**, thereby setting the stage for the key coupling with α,β-unsaturated aldehyde **16**.[14] Thus, a -100°C solution of **15** (1.1 equiv) in THF was treated with 1.0 equiv of n-BuLi in hexane for 10 min, and then 0.8 equiv. of **16** was added. The reaction mixture was allowed to warm to 0°C and then was worked up in the usual manner. This provided a 1 : 1 mixture of the diastereomeric allylic alcohols[10a] in 75% yield (based on **16**). Also obtained were 12% of recovered **16**, 8% of recovered **15**, and 24% of **14** which can be recycled. The mixture of allylic alcohols was oxidized by using the Dess-Martin periodinane[15] (1.5 equiv) in CH_2Cl_2 with 1.5 equiv of pyridine to give enone **17**[10a,b] as an inseparable 1 : 1 mixture of atropisomers in 92% yield (69% from **16**).[16] Variable temperature ^1H NMR experiments revealed the coalescence temperature for the equilibration of the two atropisomers to be approximately 125°C, suggesting the barrier to rotation about the aryl-acyl bond to be on the order of 20 kcal/mol.[16] Finally, the triethylsilylethyl ester of **17** was cleaved by treatment with $KF•(H_2O)_2$ in DMSO (70 h, 23°C) and the resulting carboxylic acid[10a] was then subjected to a Curtius sequence ($(PhO)_2PN_3$, Et_3N, $TMSCH_2CH_2OH$, THF, reflux)[13] that provided **3**,[10a,b] also as an inseparable 1 : 1 mixture of atropisomers, in 72% yield.

As a final example of the aryllithium-unsaturated aldehyde coupling procedure, we are pleased to report that the coupling of **15** and the more fully functionalized ansa chain segment **18** has been successfully achieved. Further progress towards completion of a damavaricin D total synthesis from related intermediates will be reported in due course.



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