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Article

Studies on the Synthesis of the Streptovaricins: Total Synthesis of 24,27-Dimethyl Dihydrodamavaricin D

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Neste trabalho é descrita a síntese total do 24,27-dimetil di-hidrodamavaricina D (**1**). O aldeído α–β insaturado (**3**) é obtido em alta diastereoseletividade, usando-se a tecnologia de crotil borato. O acoplamento de **3** com organoaril litro, gerado à partir de **2**, produz a enona **21**, que é transformada no ácido **2-6**. A macrolactamização de **26** via metodologia de Mukaiyama produz **27** em bom rendimento, que é transformado no produto desejado (**1**). A síntese é efetuada em 38 etapas à partir do composto comercial (R)-2-metil-3-hidroxipropionato de metila com uma esteresoseletividade global de 85%. Tentativas de conversão de **1** em Damavaricina D foram infrutíferas.

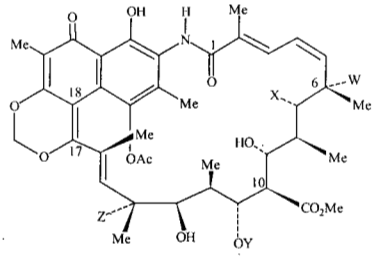
A total synthesis of 24,27-dimethyl dihydrodamavaricin D (**1**) is described. The synthesis features the highly diastereoselective synthesis of ansa chain α,β-unsaturated aldehyde **3** using crotylboronate technology for three of the four key C-C bond forming events. Coupling of **3** with the aryllithium reagent generated from **2** provides enone **21** which is smoothly elaborated to seco acid **26**. Macrolactamization of **26** via the Mukaiyama salt protocol provided **27** in good yield, which was smoothly deprotected to give the title compound. Overall, this synthesis proceeds in 38 steps via the longest linear sequence from commercially available methyl (R)-2-methyl-3-hydroxypropionate, with an overall stereoselectivity of 85%. Attempts to convert **1** to damavaricin D via oxidative demethylation have been unsuccessful owing to the unanticipated neighboring group participation of the carboxamide functionality (c.f., **27** → **28** and **29** → **30**).

Keywords: *streptovaricins, damavaricin D, macrolactamization*

Introduction

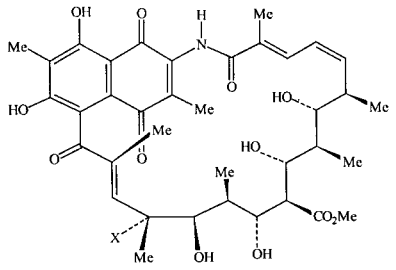
The streptovaricins are a family of biologically active ansamycin antibiotics isolated from *Streptomyces spectabilis*[1]. The stereochemistry of streptovaricin C was assigned by X-ray structure analysis of a derivative[2], while stereochemical assignments for all other members of the group are based on chemical and biosynthetic interconversions[3,4]. Interestingly, the ansa chain stereochemistry proposed for streptovaricin D is exactly the same as found in awamycin, the stereostructure of which is known unambiguously by X-ray structure analysis[5].

One of the unique structural features of the streptovaricins is the quinone methide unit, which is clearly strained according to the X-ray analysis[2]. This unit exhibits pronounced chemical reactivity, as illustrated by the facile degradation of the streptovaricins to damavaricins upon treatment with NH_3 in methanol[4]. Interestingly,



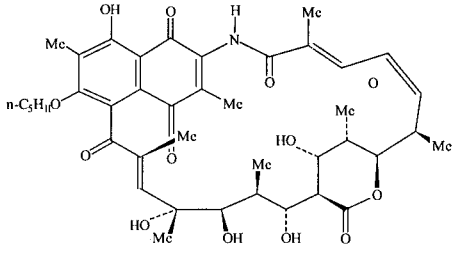
Streptovaricin	W	X	Y	Z
A	OH	OH	Ac	OH
B	H	OH	Ac	OH
C	H	OH	H	OH
D	H	OH	H	H
E	H	O=	H	OH
G	OH	OH	H	OH
J	H	OAc	H	OH
K	OH	OAc	H	OH

damavaricin D, the simplest member of this family, is a biosynthetic precursor of the more highly functionalized members of the streptovaricin group[1,4].



damavaricin C, X = OH
damavaricin D, X = H

The streptovaricins were studied originally for their anti-bacterial properties, but the toxicity of these agents limited their clinical success[1]. However, interest exists in streptovaricins and damavaricins as anti-viral agents owing to their ability to inhibit RNA-directed DNA polymerase (*i.e.*, reverse transcriptase)[6,7]. Indeed, Onodera and co-workers have demonstrated that *n*-pentyl damavaricin F_c (deriving from damavaricin C) has good activity against reverse transcriptase, and is potentially useful as an anti-viral agent and for treatment of adult T-cell leukemia[8-10].

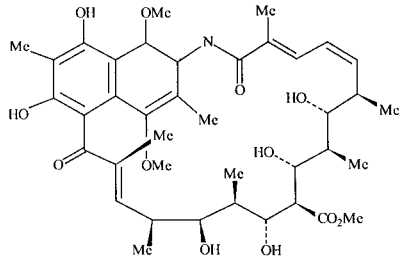


n-pentyl damavaricin F_c

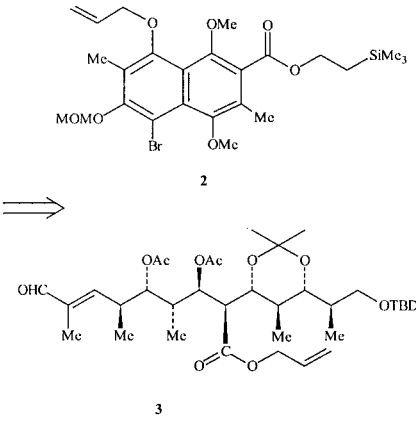
Several studies on the synthesis of the streptovaricins A and G have been reported[11-18]. We are pursuing an approach to streptovaricin D that proceeds by way of damavaricin D. Towards this end, we have reported a highly stereoselective synthesis of the C(1)-C(15) ansa chain segment, the fully elaborated naphthalene precursor, and a strategy for coupling of the two major fragments[19,20]. We report herein extensions of these studies, culminating in the total synthesis of 24,27-dimethyl dihydrodamavaricin D (**1**).

Synthesis of Naphthoate *2*

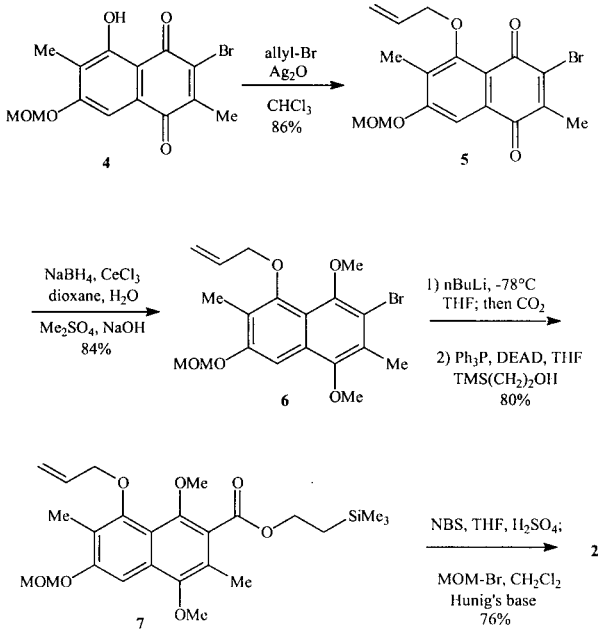
Naphthoate **2** was synthesized starting from the mono-protected bromo naphthoquinone **4**[12,20]. The principal modification of this synthesis relative to our previous publication[20] is that the C(21) phenol was protected as an allyl ether in order to simplify the deprotection sequence at the



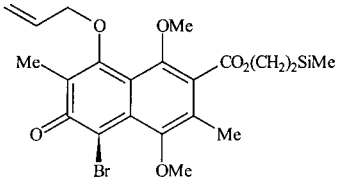
24,27-dimethyl dihydrodamavaricin D (**1**)



end of the synthesis. Thus, treatment of **4** with allyl bromide and Ag_2O in $CHCl_3$ provided allyl ether **5** in 86% yield. Reduction of the quinone under Luche conditions[12] followed by in situ methylation of the air sensitive hydroquinone with Me_2SO_4 and 50% aq. NaOH then provided **6** in 84% yield. Treatment of **6** with n-BuLi in THF at -78 °C followed by carboxylation of the aryllithium intermediate with dry CO_2 followed by Mitsunobu esterification of the



carboxylic acid with β-trimethylsilylethanol yielded naphthoate **7** in 80% yield[21]. Finally, bromination of **7** with NBS in THF containing catalytic H_2SO_4[22] and treatment of the crude product with MOM-Br and Hunig's base to reintroduce the MOM group that was lost during the bromination provided the targeted bromonaphthoate **2** in 76% yield. The bromination reaction proceeds by way of the benzocyclohexadienone intermediate **8**[23], which re-aromatizes when treated with Hunig's base. However, when MOM-Cl was used in the reprotection step, a mixture of bromo- and chloro-naphthoates was obtained, indicating that halide exchange at the stage of **8** is a facile process. Therefore, MOM-Br is used in the re-protection step to avoid this problem.



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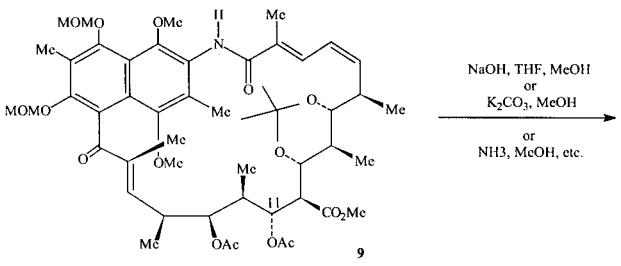
Synthesis of α,β -Unsaturated Aldehyde *3*

Our selection of **3** for use as the ansa chain fragment in this synthesis was predicated on the following considerations. First, examination of molecular models suggested that the macrolactonization would be difficult if both the C(7,9)- and C(11,13)-diols were protected as ketals, owing to strain that develops in the macrocycle. Supporting this assessment is the observation that acetonide derivatives of one of the C(7,9)- or C(11, 13)-diols of the streptovaricins have been prepared, but not both simultaneously in one structure[1]. Also, the C(11) and C(13) hydroxyl groups in the stereochemically related natural product awamycin adopt anti orientations in the crystal structure[5]. Second, the selection of acetates as the protecting groups for the C(11,13)-diol unit in **3**, which was dictated by functionality compatibility problems encountered in the synthesis, presented problems with their removal following the macrolactonization. Specifically, we were unsuccessful in all attempts to deprotect the advanced intermediate **9** under a variety of conditions owing to the facile β-elimination of the C(11) acetate unit. Accordingly, this dictated that **3** be functionalized so as to avoid this problem, and use of the C(10) allyl ester proved most advantageous.

One final issue that influenced the tactics employed in our synthesis of **3** concerns the stereoselectivity of formation of the C(11) and C(12) stereocenters. In our original synthesis[19], this was best accomplished by treatment of aldehyde **11a** with the Nozaki-Hiyama crotylchromium reagent, which optimally provided an 83:17 mixture of the desired diastereomer **12a**[24,25]. Unfortunately, the efficiency



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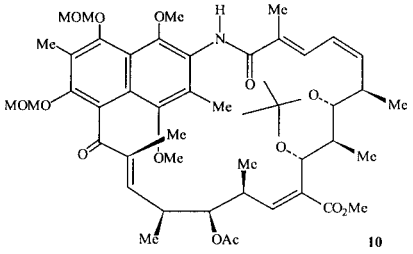

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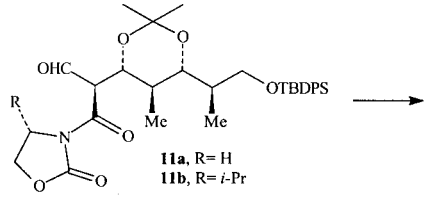
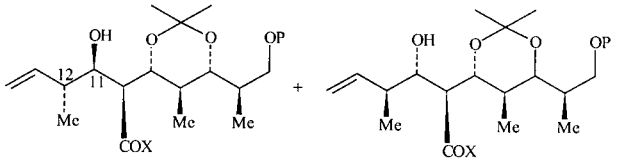
of this reaction was poor upon scale-up, and so an alternative means of establishing the C(11)-C(12) bond was required. As summarized in the accompanying equation, however, it was not possible to achieve better results by using our tartrate crotylboronate technology with either **11a** or **11b** as the substrate[26,27].



11a, R= H
11b, R= *i*-Pr

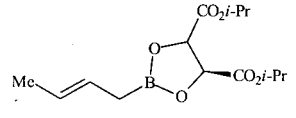


12a, R= H
12b, R= *i*-Pr

13a, R= H
13b, R= *i*-Pr

RCHO	Reagents	ratio 12 : 13
11a	crotylchromium[a]	83 : 17
11a	(S,S)-(e)-crotylboronate[b]	60 : 40
11b	crotylchromium[a]	50 : 50
11b	(S,S)-(e)-crotylboronate[b]	15 : 85

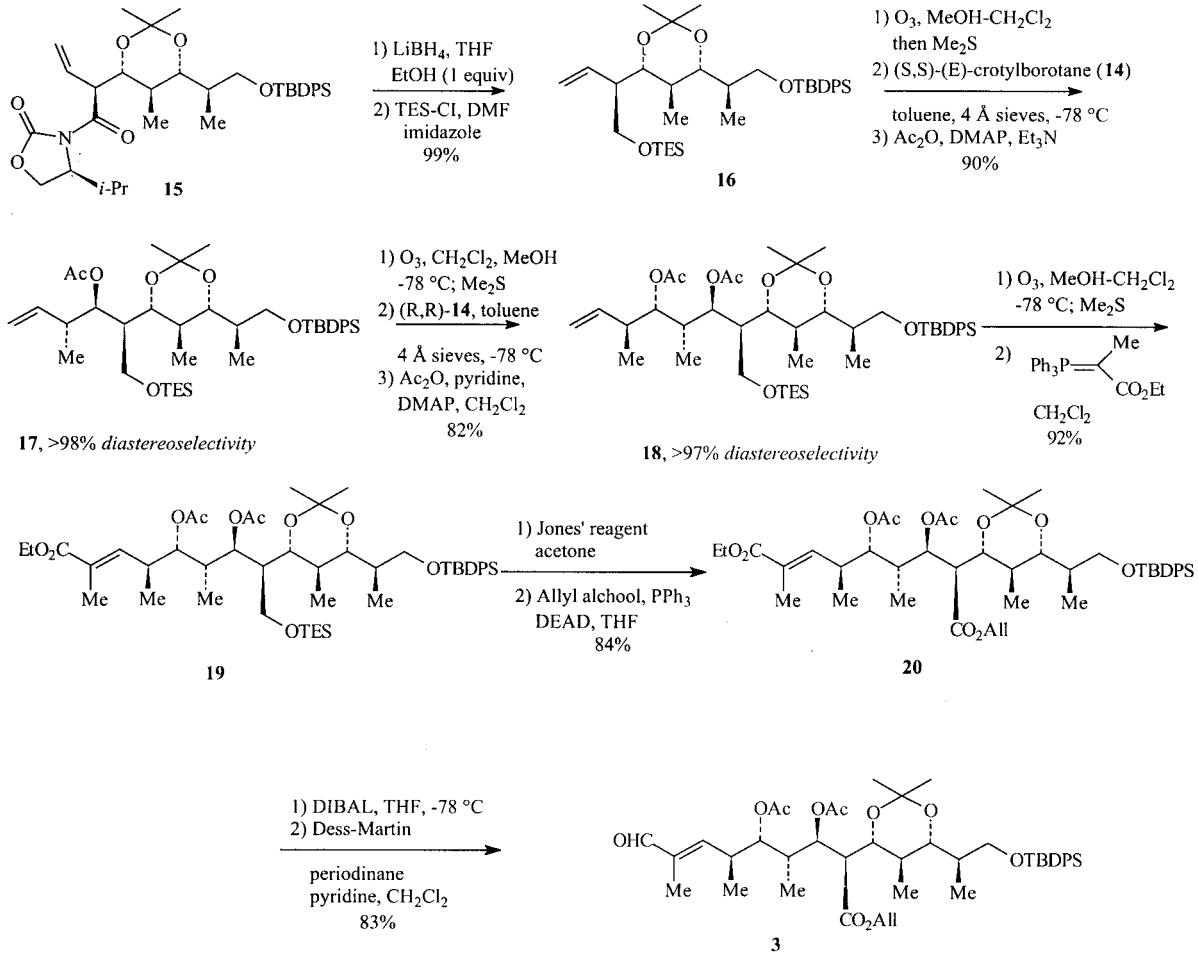
(a)THF, -25 °C; (b) toluene, 4 Å mol. sieves, -78 °C



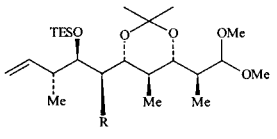
(S,S)-(e)-crotylboronate (**14**)

Our successful synthesis of the ansa chain α,β-unsaturated aldehyde is summarized in Scheme 1. Thus, reduction of **15**, which is available with 90% stereoselectivity according to our previously published route[19] with $LiBH_4$ in THF containing 1 equiv. of EtOH and protection of the resulting primary alcohol as a triethylsilyl ether provided **16** in 99% yield[28]. Ozonolysis of the vinyl group of **16** provided the corresponding aldehyde, which was subjected to our standard enantioselective crotylboration protocol with (S,S)-**14**[26,27]. Whereas the (E)-crotylborations of **11a** and **11b** proceeded with poor selectivity, the aldehyde derived from **16** behaved normally and provided the expected product with > 98% diastereoselectivity. After acylation of the C(11) hydroxyl, homoallylic acetate **17** was obtained in 90% overall yield. This intermediate was subjected to a second ozonolysis, crotylboration and acylation cycle, this time using (R,R)-**14** as the crotylborating agent, giving **18** in 82% yield. Enoate **19** was prepared from ozonolysis and Wittig reaction with (carboethoxyethylidene)triphenylphosphorane. At this stage, the oxidation state of the C(10) substituent was adjusted by treatment with Jones' reagent in aqueous acetone. These conditions are sufficiently acidic that the triethylsilyl ether hydrolyzes in situ, thereby avoiding a separate deprotection step. Esterification of the resulting carboxylic acid with allyl alcohol under Mitsunobu conditions then provided diester **20** in 84% yield[21]. Finally, selective reduction of the α,β-unsaturated ester unit of **20** by using 2.1 equiv. of DIBAL-H in THF at -78 °C (the two acetate esters and the allyl carboxylate are substantially more hindered) and oxidation of the resulting allylic alcohol with the Dess-Martin periodinane reagent then completed the synthesis of the targeted enal **3** (83%)[29].

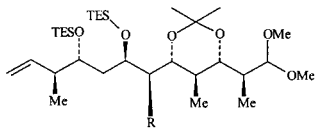
Although the synthesis summarized in Scheme 1 appears straightforward, the oxidation of **19** and related intermediates proved to be quite difficult. Although the oxidation of primary alcohols **21a** and **22a** to the corresponding C(10)-aldehydes **21b** and **22b** could be smoothly accomplished by using the Swern DMSO-$(COCl)_2$ protocol[30], we were unsuccessful in attempts to oxidize **21b** and **22b** to the corresponding carboxylic acids owing to steric crowding of the C(10) substituent[31]. These results contributed substantially to the decision to proceed with ansa chain intermediates with the C(11) and C(13) alcohols protected as acetates.



Scheme 1.



21a, R= CH_2OH
21b, R= CHO



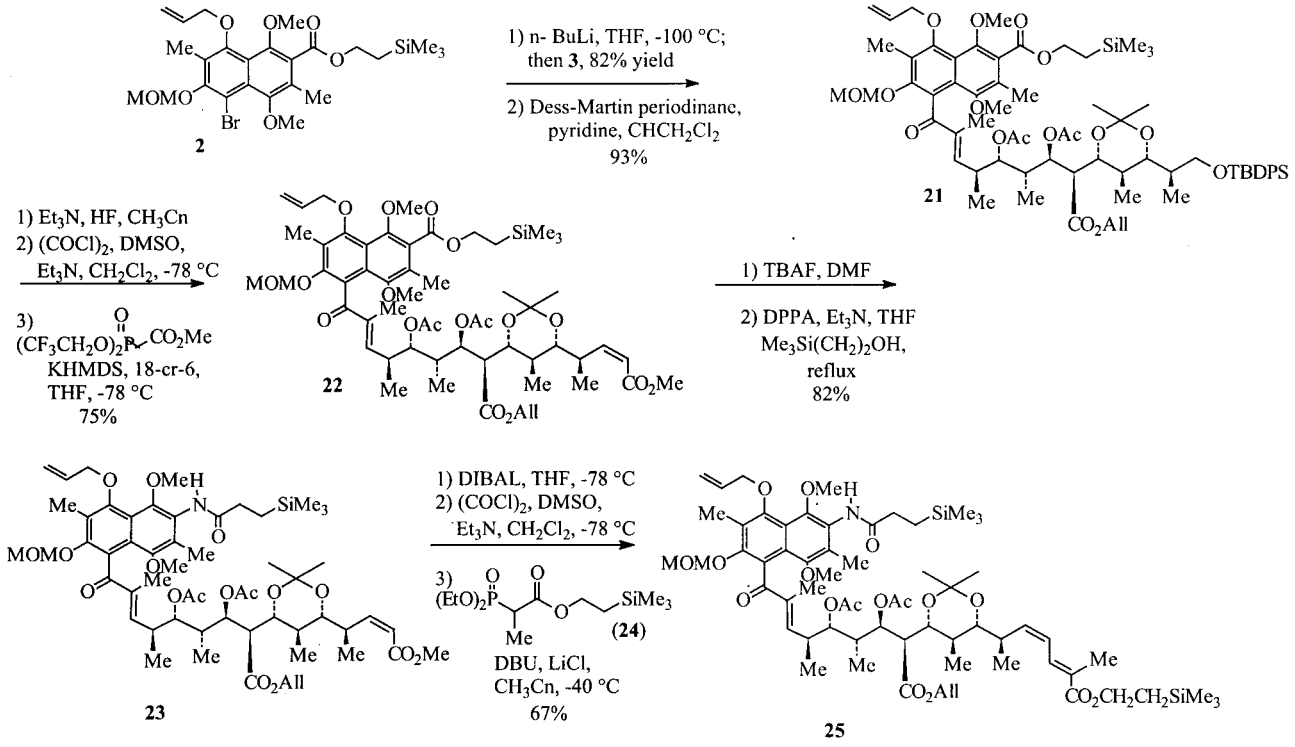
22a, R= CH_2OH
22b, R= CHO

Fragment Coupling; Synthesis of 24,27-Dimethyl Dihydrodamavaricin D

The coupling of fragments **2** and **3** and their elaboration to seco ester **25** is summarized in Scheme 2. Metallation of **2** (1.5 equiv.) with n-BuLi (1.0 equiv.) in THF at -100 °C followed by addition of α,β-unsaturated aldehyde **3** (1.0 equiv.) provided a diastereomeric mixture of allylic alcohols (82% yield) which, without separation, was oxidized by using the Dess-Martin periodinane to give enone **21**, a 1:1 mixture of atropisomers, in 93% yield[29]. The primary TBDMS ether was then removed by using Et_3N-HF in CH_3CN[32]. The resulting alcohol was oxidized via the Swern protocol[30] and the aldehyde was subjected to Still's (Z)-selective olefination procedure[33], thereby providing **22** in 75% yield as a 9:1 mixture of olefin isomers. At this stage, the aryl carbamate functionality of **23** was introduced by Curtius degradation (diphenyl phosphoryl azide, Et_3N, $Me_3SiCH_2CH_2OH$, THF, reflux)[34] of the carboxylic acidgenerated by fluoride mediated deprotection of **22**[35].

The next step of the synthesis involved selective reduction of the (Z)-enoate unit of **23**. While an analogous selective reduction was easily accomplished in the conversion of **20** to **3** (Scheme 1), the (Z)-carbomethoxyl group of **23** is more sterically hindered and consequently more careful control of the reduction conditions is necessary to achieve acceptable results. In the event, treatment of **23** with 6 equiv. of DIBAL-H in THF at -78 °C provided the desired (Z)-allylic alcohol in 63% yield, along with 20% of recovered **23** which can be recycled. The allylic alcohol was then elaborated to the (E,Z)-dienoate **25** by Swern oxidation and HWE condensation of the resulting (Z)-enal with β-ketophosphonate **24**, LiCl, and DBU[36]. The overall yield of **25** was 67% for this three step sequence (based on recovered **23**).

The carbamate and dienoate protecting groups of **25** were designed such that both could be removed in a single operation, in this instance by using TAS-F in DMF (Scheme 3)[37]. The seco amino acid **26** underwent smooth macrolactamization by using the Mukaiyama salt protocol (N-methyl-2-pyridinium iodide, Et_3N, CH_2Cl_2)[38,39] giving macrolactam **27** in 66% yield from seco ester **25**. It is also interesting to note that although all intermediates from the stage of **21** through **26** were ca. 1:1 mixtures of atropisomers, macrolactam **27** is predominantly (*ca.* 10:1) a single atropisomer. Atropisomerism in the streptovaricin series has been studied by Rinehart, who established that the naturally occurring isomer is usually the most stable one[32].



Scheme 2.

This suggests that the natural atropisomer can be obtained by thermal isomerization at the end of the synthesis, if indeed **27** and subsequent intermediates are in the unnatural atropisomeric series.

With **27** in hand, all that remained to complete the synthesis of 24,27-dimethyl dihydro-damavaricin D (**1**) was to remove all of the protecting groups. The aromatic MOM ether and the C(7,9) acetonide were smoothly removed by treatment of **27** with p-TsOH in MeOH (93% yield). The phenolic allyl ether and the C(10) allyl ester were then removed by treatment with catalytic $(Ph_3P)_4Pd$ and *n*-Bu_3SnH in toluene containing HOAc[40]. Treatment of the resulting C(10)-carboxylic acid with LiOH in an aqueous THF-MeOH mixture permitted clean removal of the two acetate protecting groups. Finally, esterification of resulting diphenolic tetrahydroxy acid with Me_3SiCHN_2[41] provided **1** in 38% overall yield from **27**.

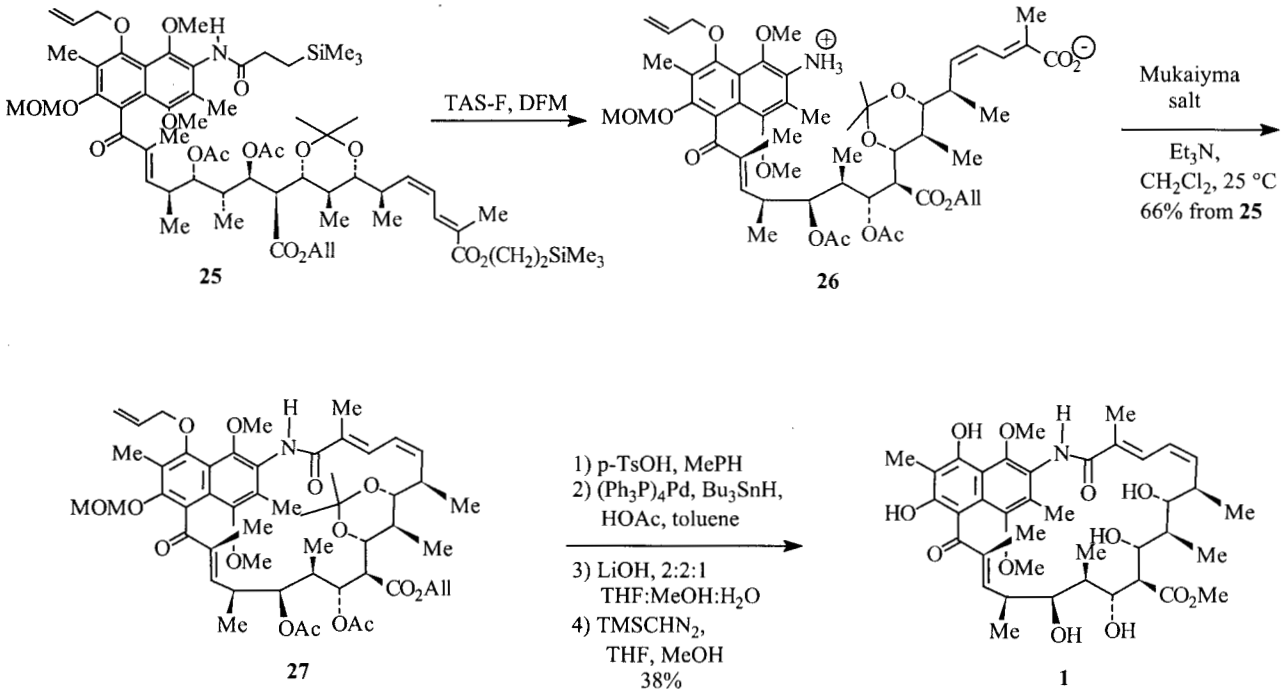
Attempted Synthesis of Damavaricin D

Our original target of this exercise was damavaricin D, and not 24,27-dimethyl dihydro-damavaricin D (**1**). Unfortunately, all attempts thus far to oxidize the 24,27-dimethoxy dihydronaphthoquinone unit of **27** or **1** to the quinone nucleus present in the damavaricins have been unsuccessful. Oxidation of **27** with ceric ammonium nitrate[42] in 10:1 CH_3CN-H_2O provides an unstable compound tentatively identified as the quinone hemiketal **28**. Unfortunately, this compound quickly decomposes to a another product that has not yet been conclusively identified. Product **28** is also observed when **27** is treated with AgO and HNO_3 in dioxane[43], or with nitric acid-impregnated MnO_2 [44]. Support for the assignment of **28** as the initial product of the CAN oxidation of **27** is provided by the analogous oxidation of **29** which provides **30** in 75% yield. This structure was assigned on the basis of NMR, IR and mass spectroscopic data. Attempts to demethylate **1** by treatment with BBr_3 were also unsuccessful (see Scheme 4).

The oxidative cyclization of **27**, **29** and related intermediates to products such as **28** and **30** was most unanticipated, particularly since oxidative demethylations of hydronaphthoquinone dimethyl ethers has been successfully accomplished in syntheses of other ansamycin antibiotics such as rifamycin W[45], macbecin I[46-49] and herbimycin A[50]. The main structural difference is that **27** possesses a C(25)-methyl group, whereas all the other systems cited above are unsubstituted at the analogous position. This causes the carboxamide unit of **27** and **29** to adopt a conformation perpendicular to the aromatic ring, thereby positioning the amide carbonyl above the plane of the aromatic unit where it is properly positioned to add to C(27) of the cationic intermediate generated during the oxidation reaction.

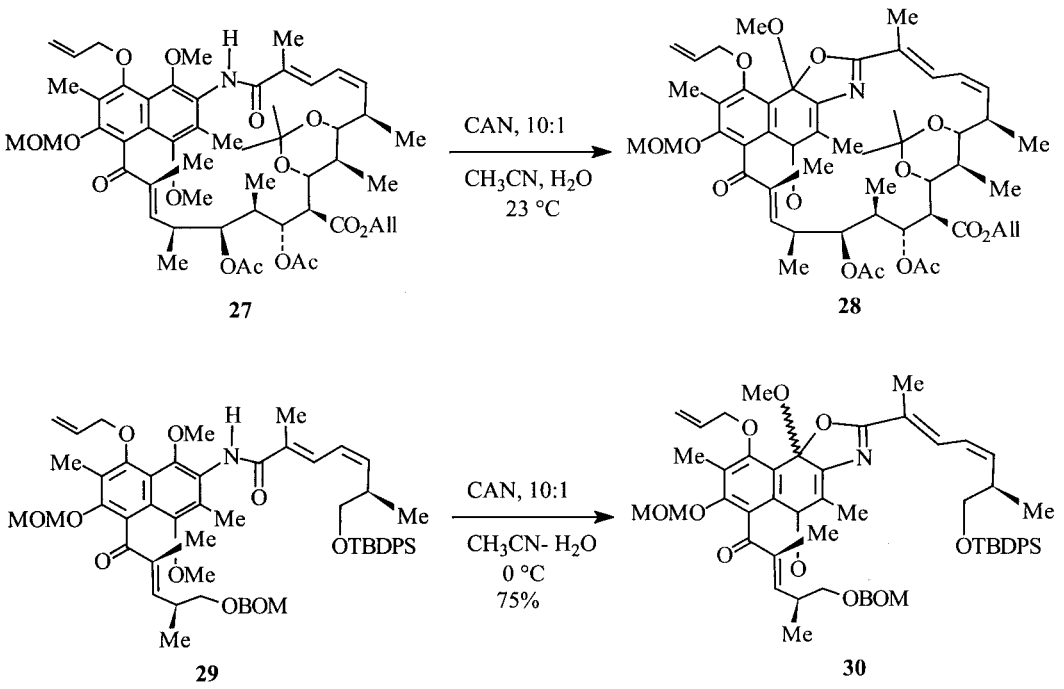
Conclusion

The present work defines a highly stereoselective entry to the damavaricin ring system represented by **27**. We anticipate that the strategies and tactics exemplified in the present work will ultimately lead to the successful conclusion of the first total synthesis of a naturally occurring



25 **26** **27** **1**

Scheme 3.



27 28

29 30

Scheme 4.

member of the streptovaricin family. Studies are currently in progress to design a solution to the final naphthoquinone oxidation problem, and in the process to complete the first total synthesis of damavaricin D which we will report in due course[51].

Acknowledgment

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