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Synthesis of the Oxazole- and Diene-Containing C_9-C_{23} Fragment of the Type A Streptogramin Antibiotics

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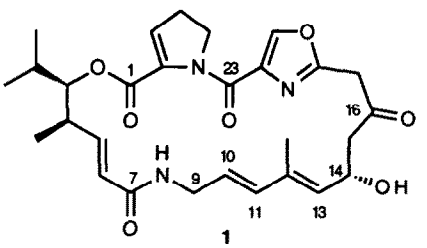
Abstract: The right-hand portion (**3**) of the type A streptogramin antibiotics was synthesized in non-racemic form through use of a Horner-Wadsworth-Emmons reaction for diene construction, an asymmetric aldol condensation, and a zinc-promoted oxazole addition reaction.

The streptogramin antibiotics have been known for the past four decades, and during this time, they have proven to have many useful applications. These antibiotics occur as two distinctly different classes of compounds. The type A streptogramins are complex macrocyclic lactam-lactones for which six structures have been reported to date. Virginiamycin M_1 (**1**) and madumycin I (**2**) are representative examples of type A.[1] The type B streptogramins, on the other hand, are cyclic hexadepsipeptides. Despite their quite different structures, the type A and type B compounds exhibit a strong synergism in their antibacterial action.



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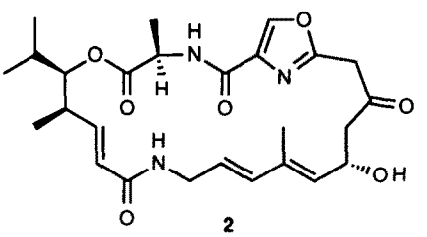

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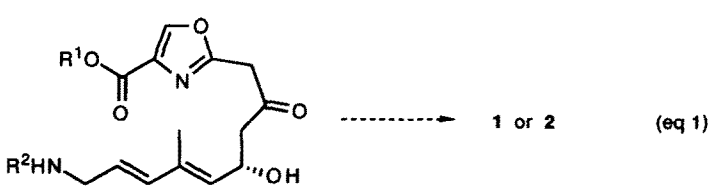
Considerable progress has been reported on the synthesis of the type A streptogramins during the past several years,[2] although a total synthesis has yet to be completed. An obvious building block that may serve as a common intermediate for several of these compounds, including the two shown above, would be an appropriately protected form of the C_9-C_{23} subunit **3** (*Chem. Abstr.* numbering scheme for virginiamycin) containing

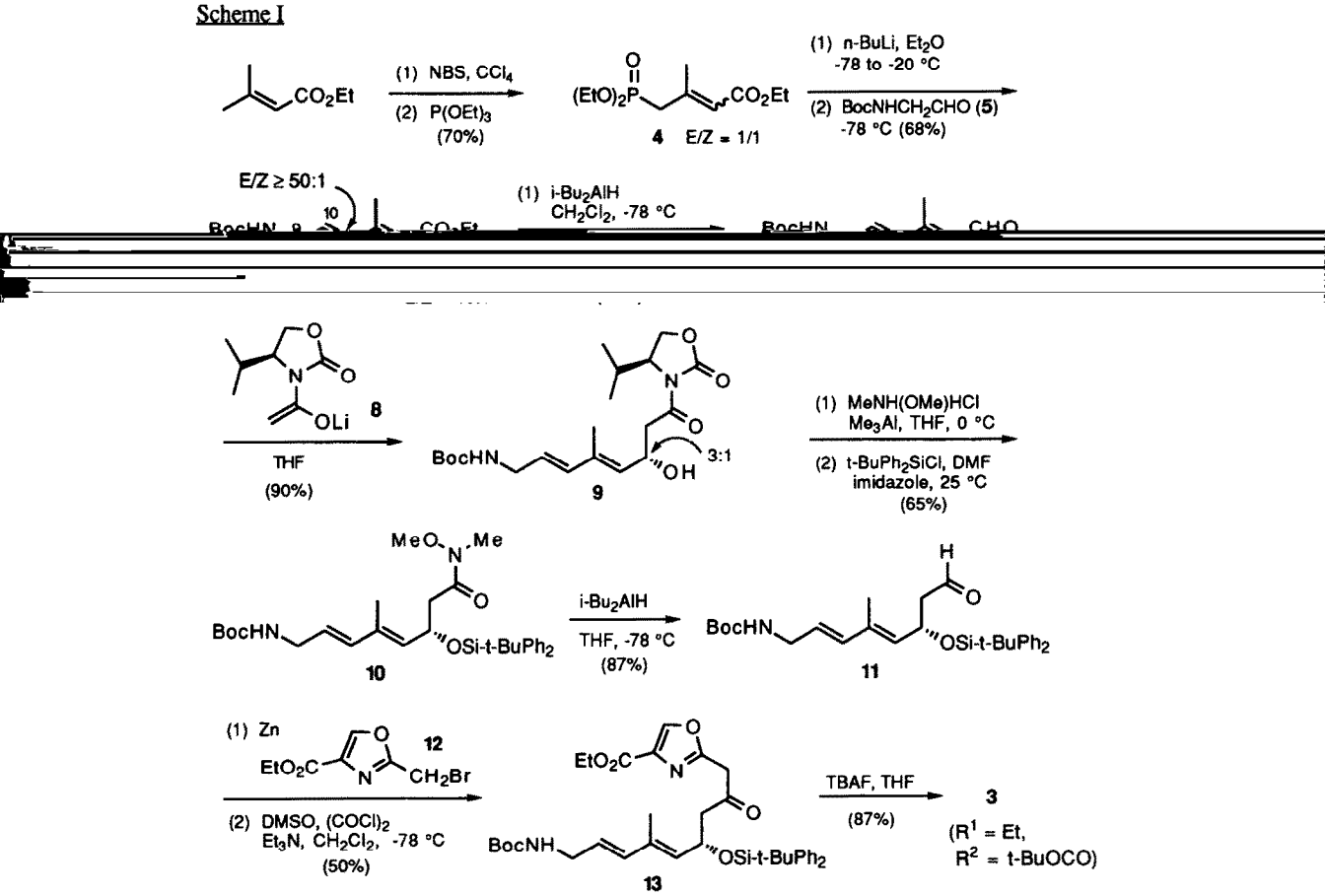


3

the key oxazole and diene functionality. Formation of two amide bonds between the terminal positions of this subunit and the previously synthesized left-hand portion[2d,e,h,j,k,n,o] would in principle complete the total synthesis (eq 1). Synthesis of other forms of subunit **3** have been reported by Meyers[2d,l] and by Fujita.[2h]

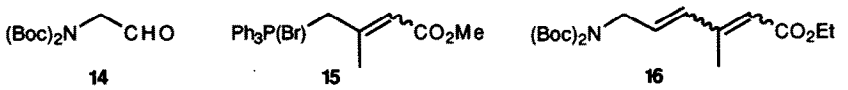
The synthesis of a suitable derivative of **3** is summarized in Scheme I. First, Horner-Wadsworth-Emmons condensation between the readily available phosphonate ester **4**[3] and *N-tert*-butoxycarbonyl (*N*-Boc) glycinal **5**[4] provided the protected methyl-substituted dieneamine ester **6** in 68% yield in which the newly formed C_{10}-C_{11} double bond was obtained as predominantly the *E*-isomer. Despite using a 1:1 isomer ratio of **4**, the *E*/*Z* ratio increased to 10:1 for the corresponding C_{12}-C_{13} double bond in the diene ester **6**. The lithium derivative was formed by adding n-BuLi in ether to **4** at -78 °C and then increasing the temperature to -20 °C and subsequently adding aldehyde **5** (1.1 equiv) at -78 °C. Equilibration of isomers is a plausible explanation for the stereochemical outcome under these conditions. By simple recrystallization from hexane, the *E*,*E*-isomer of **6** can be enriched to > 25:1.

Scheme I



Initially, the di-Boc aminoaldehyde **14** was employed as the diene precursor, but it provided no advantage over the mono-Boc derivative **5** since one of the Boc groups of **14** was cleaved under the Horner-Wadsworth-

Emmons conditions to give the same monoprotected diene product **6** in either case. In contrast, the corresponding Wittig reaction of **14** with the less reactive ylide derived from **15**[3b] (NaHMDS, THF) gave the fully protected diene ester **16** in 54% yield but with complete lack of *E,E*-selectivity.

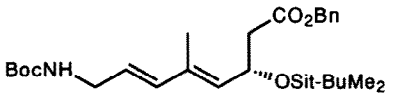


14 **15** **16**

Reduction of diene ester **6** to the corresponding alcohol occurred in nearly quantitative yield using i-Bu_2AlH (2.5 equiv). Swern oxidation[5] of the resulting allylic alcohol provided the key aldehyde **7** in greater than 90% yield. Diene aldehyde **7** was used in the next step immediately after purification since polyunsaturated aldehydes[6] are relatively unstable compounds; it was also noticed that some isomerization occurred after the oxidation.

The asymmetric aldol condensation methods of Evans[7a] and Thornton[7b] were applied in the next key step. Thus, aldehyde **7** reacted with the lithium enolate of (*S*)-*N*-acetyl-4-isopropyl-2-oxazolidinone (**8**)[8a] at -78 °C to yield 90% of **9** as two readily separable diastereomers. Analysis of the crude reaction mixture showed well-resolved ^{1}H-NMR signals of the two diastereomers in a ratio of 3:1. Somewhat low stereoselectivity was expected due to the lack of α-substituents in the chiral enolate.[7b] On the other hand, since the two diastereomers of **9** were easily separated by chromatography,[8b] the need for a "dummy group" such as an α-thioether[7a] or an α-halo[9] substituent was circumvented. Indeed, we were also successful in employing the corresponding boron α-chloro[9a,b] enolate which provided much higher stereoselectivity, but the more complex overall route was less attractive than the use of the simple *N*-acetyl oxazolidinone derivative.

The major isolated diastereomer of **9** (> 98% d.e.) was next transformed into amide **10**[10] by adding the imide to a solution of Weinreb's aluminum amide[11] ($AlMe_3$, MeONHMe.HCl, 3 equiv) and subsequently protecting the hydroxyl group as its silyl ether.[12] Amide **10** was then treated with i-Bu_2AlH (1.3 equiv, 1.5 h) to give 87% of the aldehyde **11**. An alternative method is first the protection of **9** as its silyl ether (TBDMSCl, imidazole, DMF, 18h, +20 °C) in 97% yield and then cleavage of the imide with $PhCH_2OLi$ (THF, 2h, 0 °C) to give the transesterified product **17** in 82% yield. Treatment of **17** with i-Bu_2AlH should give aldehyde **11**.



17

Introduction of the functionalized 1,3-oxazole onto the diene unit **11** was accomplished by employing a metalated derivative of **12** in a Reformatsky-type reaction. The use of this zinc organometallic in addition reactions with aldehydes and ketones has recently been reported from our laboratories.[13] The desired addition reaction was performed by adding **12** to a mixture of "activated" zinc[14] and aldehyde **11** in THF at 0 °C to give the product as the secondary alcohol. Subsequent Swern oxidation[5] furnished ketone **13** in 50% overall yield for the two steps. Despite use of widely varying amounts of **12** (1.25-2.5 equiv), the addition reaction gives consistently the same yield of the alcohol (ca. 50%) together with recovered aldehyde (30-40%) and the debrominated form of **12**. Adding catalytic amounts of $ZnCl_2$ (5-10 mol-%) to a mixture of zinc, oxazole **12**, and aldehyde **11** increased the rate of the addition reaction considerably but did not increase the yield. The recovery of unreacted aldehyde **11** could be due to steric hindrance by the large t-$BuPh_2Si$ group or the formation of a zinc

enolate of the aldehyde by exchange with the zinc derivative of **12** among other possible explanations. The final step of the synthesis is the straightforward deprotection of silyl ether **13** with tetrabutylammonium fluoride (THF, 4h, 25 °C) to give alcohol **3** in 87% yield.

In conclusion, subunit **3** should serve as a very flexible intermediate for the synthesis of the several type A streptogramins and their analogues. Furthermore, this route provides further demonstration of the utility of the methods employed for introduction of the diene and oxazole moieties.

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8. (a) The lithium derivative of **8** was generated using LDA in THF at -78 °C. (b) Major isomer, (*S*)-**9**: R_f 0.33 (30% ether in pentane); mp 103.5-104 °C; d.e. > 98% by ^{1}H NMR. Minor isomer, (*R*)-**9**: R_f 0.23.
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