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Studies on the Synthesis of Bleomycin A_2: Observations on a Diastereoselective Imine Addition Reaction for C2-Acetamido Side Chain Introduction

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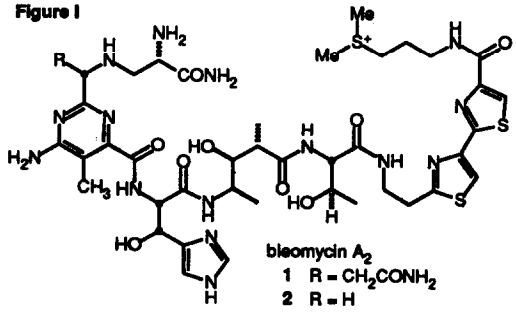
Abstract. A study of the diastereoselective addition of the stannous (Z)-enolates of optically active *N*-acyloxazolidinones with the prototype imine **5** is detailed and provides an approach to the stereocontrolled introduction of the C2-acetamido side chain of the pyrimidoblamic subunit of bleomycin A_2.

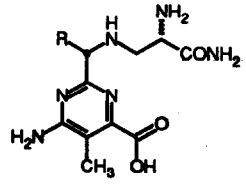
In recent studies, we have detailed an efficient synthesis of deglyco desacetamidobleomycin A_2 (**2**)[1] and related analogs[2] based on an effective approach to the heteroaromatic nucleus of the pyrimidoblamic acid subunit. The remaining strategic element required for the extension of the studies to the total synthesis of deglycobleomycin A_2 (**1**)[3] is the stereocontrolled introduction of the pyrimidoblamic acid C2-acetamido side chain. Prior studies directed at the total synthesis of pyrimidoblamic acid[4] and bleomycin A_2[5] have relied on nondiastereoselective introductions of the acetamido side chain requiring a separation of the resulting 1:1 mixture of diastereomers. In the conduct of our studies, we elected to examine the diastereoselective addition of optically active enolates with imines[6] as a potential solution to this problem. For this purpose, the addition reaction of a range of optically active enolates with the prototype imine **5** were examined. From the initial survey, the Evans' *N*-acyloxazolidinones[7] were selected for further study since both enantiomers of the diastereomeric imine adducts would be readily available through selection of the appropriate enantiomer of the chiral auxiliary. Herein, we report the results of this study which demonstrate the selected utility of the stannous (Z)-enolates of *N*-acyloxazolidinones in diastereoselective imine addition reactions.

Initial efforts to promote the reaction of the di-*n*-butylboronyl (Z)-enolate **6** with the imine **5** provided only a trace amount of the addition products and were expected to provide the Evans' syn addition product by reaction of the nonchelated enolate through a closed, chair transition state,[8] Scheme I and Table I. Consequently, the corresponding titanium enolates were examined with the expectation that the chelated enolate may react through a closed, chair transition state with imine complexation within the expanded titanium coordination sphere to provide the non-Evans' syn addition product.[9,10] Consistent with expectations, the imine addition products were obtained with a good level of diastereoselection but in modest conversions and efforts to improve the conversions through use of various protocols for titanium enolate generation were not successful. After considerable experimentation, it was found that the stannous (Z)-enolates[11-14] provided the same major imine addition products with a comparable level of diastereoselection and in excellent conversions. The expanded coordination sphere of tin(II), like that of titanium(IV), was anticipated to permit reaction of the chelated enolate with additional complexation of the reacting imine with tin(II). In the optimization of the reaction of **5** with the stannous (Z)-enolate **6**, the reaction was found to proceed with a minimal number of protecting groups on the imine provided 2 equivalents of the enolate and 2 additional

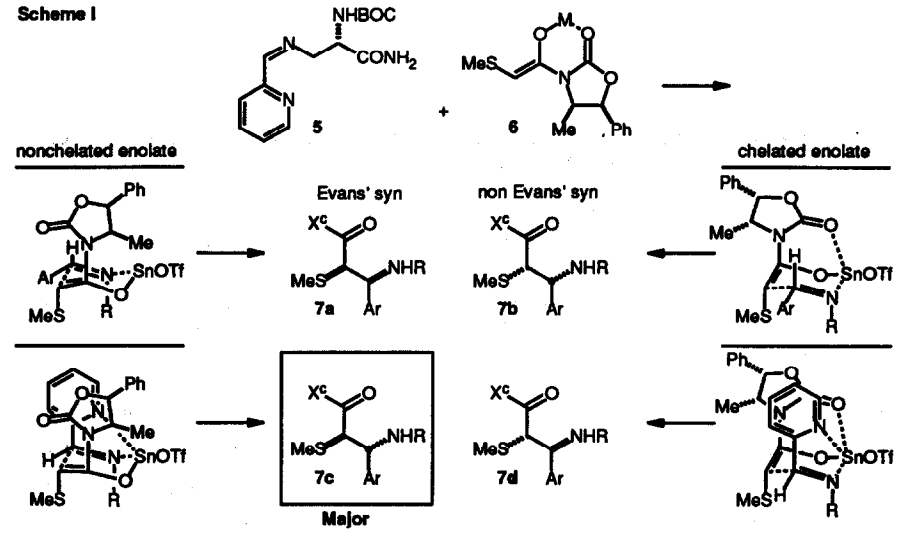
Figure I



bleomycin A_2
1 R = CH_2CONH_2
2 R = H



pyrimidoblamic acid
3 R = CH_2CONH_2
4 R = H



equivalents of $Sn(OTf)_2$ and iPr_2NEt were employed, Table I. Under such conditions, the major and minor products proved to be the unexpected anti adducts **7c** and **7d**, respectively. The major anti adduct **7c** is potentially derived from reaction of the nonchelated enolate through a closed, chair transition state in which the imine substituent occupies an axial position as a consequence of the additional pyridyl chelation with tin(II).[14] Although it is not possible to rule out the reaction of Sn(II)-**6** with imine **5** activated by coordination to the added Lewis acid and proceeding through an open transition state,[15] the lack of reaction of the di-*n*-butylboronyl (*Z*)-enolate **6** with **5** in the presence of added Lewis acid catalysts ($Sn(OTf)_2$, Et_2AlCl) would suggest that this is unlikely. Notably, the stereoinduction at the newly introduced amine center proved to be 83:17 (Σ **7b**, **7c** : **7a**, **7d**) and of a satisfactory level for incorporation into initial synthetic efforts on bleomycin A_2.

Similar, but not identical, observations were made with the enantiomeric enolate **8**, Table II and Scheme II. The major product of the reaction of **5** with the stannous (*Z*)-enolate **8** proved to be **9c** consistent with reaction of the nonchelated enolate through a closed, chair transition state with the imine pyridyl substituent occupying an axial position. However, the diastereoselectivity of the addition of **8** was reduced from that observed with **6** and the compostion of the minor diastereomeric

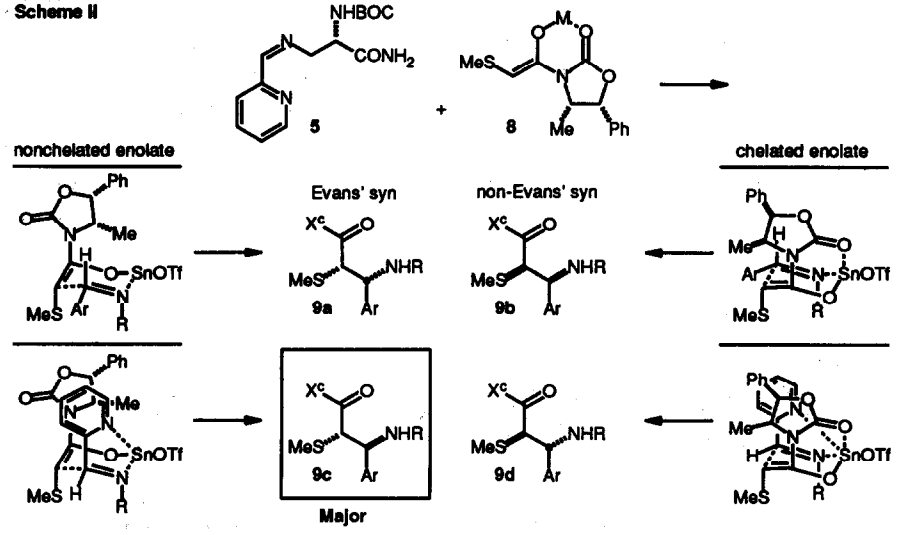


Table I. Representative Results of a Study of the Diastereoselective Addition of Enolates **6** with Imine **5**

Enolate (eq)	Reaction Conditions	7 Yield (%)	7a:7b:7c:7d
Bu_2B (2)	CH_2Cl_2, 0 to 25°C, 2 h CH_2Cl_2, -20 to 0°C, 10 h	0 trace	- -
Bu_2B (2)	CH_2Cl_2, 0°C, 12 h $Sn(OTf)_2$ (1 or 2 equiv) or Et_2AlCl (1 or 2 equiv)	0	-
$Ti(OiPr)_3$ (3)	CH_2Cl_2, -78 to 25°C, 12 h	0	-
$TiCl_3$ (1.4)	CH_2Cl_2, -20 to 5°C, 3 h	10	-:-:90:10[a]
$TiCl_3$ (2)	CH_2Cl_2, 0 to 5°C, 2 h	30	-:-:90:10[a]
Sn(OTf) (1)	THF, -5 to 0°C, 10 h	trace	-:-:80:20[a]
Sn(OTf) (2)	THF, -5 to 0°C, 10 h	33	-:-:80:20[a]
Sn(OTf) (2)	THF, -5 to 0°C, 10 h $Sn(OTf)_2$/iPr_2NEt (2 equiv)	86	4:12:71:13[b]

[a]Ratio of syn products not determined but less than anti.
[b]In situ epimerization of anti to syn adducts observed.

Figure II

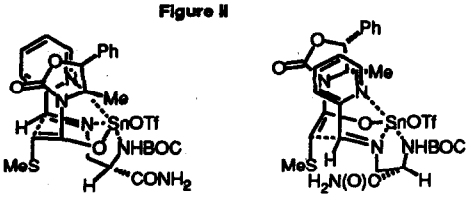
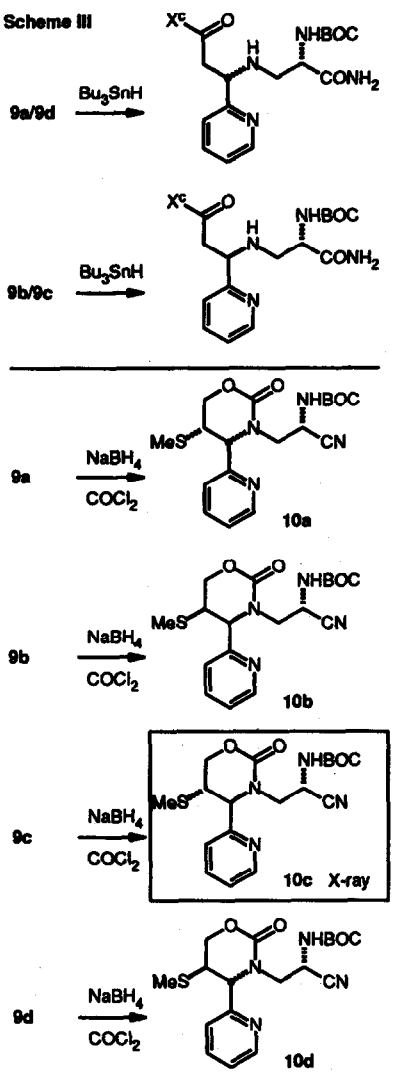


Table II. Representative Results of a Study of the Diastereoselective Addition of Enolates **8** with Imine **5**

Enolate (eq)	Reaction Conditions	9 Yield (%)	9a:9b:9c:9d
Sn(OTf) (2)	THF, -5 to 0°C, 10 h $Sn(OTf)_2$/iPr_2NEt (2 equiv)	72	33:9:50:8
Sn(OTf) (2)	THF, -5 to 0°C, 10 h $Sn(OTf)_2$/iPr_2NEt (2 equiv) TMEDA (4 equiv)	65	6:0:63:31
Sn(OTf) (2)	THF, -5 to 0°C, 10 h TMEDA (2 equiv)	21	-:-:75:25[a]

[a]Ratio of syn products not determined but less than anti.

Scheme III



addition products altered. This may be the consequence of the additional or competitive chelation of the imine side chain with Sn(II) disfavoring the addition to provide **9c** relative to that which provides **7c**, Figure II.

The tentative relative and absolute stereochemistry of the imine addition products was determined upon chemical correlation of **9a** with **9d** and **9b** with **9c** by reductive desulfurization as well as the conversion of **9a-d** to the cyclic carbamates **10a-d**, Scheme III, on the basis of characteristic ^1H NMR chemical shifts, coupling constants, and $w_{1/2}$ values in conjunction with 2D ^1H-^1H NOSEY NMR. Unambiguous confirmation of the stereochemistry of the major addition product **9c** was established in a single-crystal X-ray structure determination of **10c** which through chemical correlation unambiguously provided the relative and absolute stereochemical assignments for **9a-d** and **10a-d**. In particular, the cyclic carbamate portion of **10a** and **10b** or **10c** and **10d** exhibited ^1H NMR spectroscopic properties that indicated that they, and consequently **9a** and **9b** or **9c** and **9d**, possessed the same relative but opposite absolute configuration.

In additional studies, the reaction of the stannous (*Z*)-enolate of **8** with the corresponding benzaldehyde imine provided a nonselective mixture of imine addition products and the reaction of **5** with the stannous enolate of 4(*S*),5(*R*)-3-acetyl-4-methyl-5-phenyl-2-oxazolidinone provided a 1:1 mixture of the two possible imine addition products (58%) indicating that the presence of the pyridyl nitrogen and enolate substituent contribute in a significant fashion to the observed diastereoselection. The stannous enolate of 4(*S*),5(*R*)-3-(phenylthio)acetyl-4-methyl-5-phenyl-2-oxazolidinone provided the corresponding imine adducts **9** with comparable diastereoselectively (53%). 2-Bromo- and 2-chloroacetyloxazolidinone enolates were examined briefly and found to provide a lower imine addition diastereoselectivity and substituted 3-acetyl-1,3-thiazolidine-2-thiones failed to provide imine addition products although this was not investigated in detail. The implementation of the observations detailed herein in the total synthesis of deglycobleomycin A_2 and related analogs will be described elsewhere.

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