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AN ASYMMETRIC SYNTHESIS FOR THE SYNTHETIC β-LACTAM INTERMEDIATE OF THIENAMYCIN VIA ISOXAZOLINE DERIVATIVE

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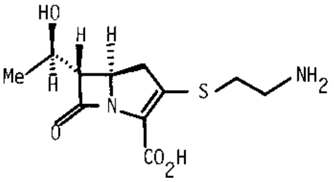
Abstract —— An asymmetric synthesis for the synthetic intermediate to thienamycin was examined *via* an isoxazoline derivative prepared by 1,3-dipolar cycloaddition between the nitrile oxide and menthyl crotonate. 3(R)-[1'(S)-Hydroxyethyl]-4(S)-(2',2'-dimethoxyethyl)-2-azetidinone (**6B**) and its derivative (**9B**) showed a positive Cotton effect at 214 ∿ 213 nm in the cd spectra, respectively.

Recently we have developed the efficient synthesis of thienamycin (**1**)[1], a potent and broad spectral antibiotic, through an isoxazoline derivative.[2-4] In continuation of this work, we further investigated an asymmetric synthesis of the antibiotic utilizing the isoxazoline strategy and wish to report here our interesting findings.

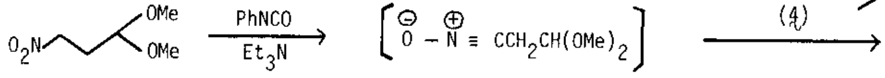
1,3-Dipolar cycloaddition of the nitrile oxide (**3**), generated *in situ* from 3-nitropropanal dimethyl acetal (**2**), and menthyl crotonate (**4**)[5] in benzene at 4°C for 6 days produced an epimeric mixture of *trans*-isoxazolines (**5A** and **5B**), $[\alpha]_D^{20}$ - 58.9° (c = 0.76, MeOH), in 40.3 % yield along with the corresponding *cis*-isoxazolines in 7.3 % yield and the regio isomers in 24.8 % yield. There was no sign for separation of the two isomers (**5A** and **5B**) by silica gel column and thin layer chromatographies using various solvent systems. The ratio of the two epimers was not estimated by nmr spectroscopy because no resolved signal based on diastereoisomeric properties was observed in the 100 MHz nmr spectrum ($CDCl_3$).

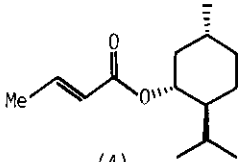
The mixture of *trans*-isomers (**5A** and **5B**) was converted into the enantiomeric mixture of β-lactams (**6A** and **6B**), $cd[\theta]_{214}^{25}$ + 2.357 x 10^3(MeOH), in 26.9 % overall yield by the established method,[3] namely catalytic hydrogenation with Adams catalyst, silylation, cyclization with ethylmagnesium bromide, and deprotection.

The ratio of enanthiomers (**6A** and **6B**) was determined by the transformation into two

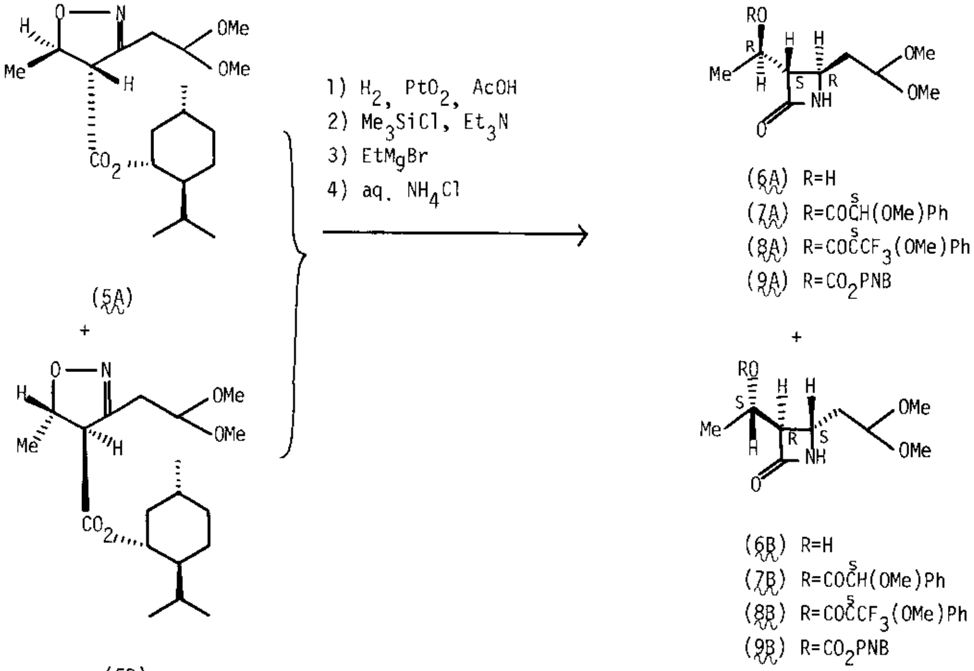


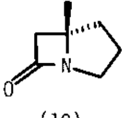
(1)


(2)
PhNCO
Et$_3$N
(3)



(4)


(5A)
+
(5B)
1) H$_2$, PtO$_2$, AcOH
2) Me$_3$SiCl, Et$_3$N
3) EtMgBr
4) aq. NH$_4$Cl
(6A) R=H
(7A) R=CO$\overset{S}{C}$H(OMe)Ph
(8A) R=CO$\overset{S}{C}$CF$_3$(OMe)Ph
(9A) R=CO$_2$PNB
+
(6B) R=H
(7B) R=CO$\overset{S}{C}$H(OMe)Ph
(8B) R=CO$\overset{S}{C}$CF$_3$(OMe)Ph
(9B) R=CO$_2$PNB



(10)

types of diastereoisomeric esters as follows by applying Mosher's nmr configuration-correlation method.[6] Reaction of the mixture (**6A** and **6B**) with (S)-(+)-*O*-methylmandelyl chloride in the presence of dimethylaminopyridine gave the diastereoisomeric esters (**7A** and **7B**). The signals due to methyls of the hydroxyethyl groups resonated at 1.27 and 1.41 ppm in the ratio of 2 : 3 as doublet with J = 6.4 Hz and the signals due to hydrogens at C_3-position were observed at 2.95 and 2.79 ppm in the ratio of 2 : 3 as double doublet with J = 8.6 and 2.3, and J = 9.3 and 2.3 Hz, respectively. The Mosher's model predicts that the signal due to the methyl group of (1'R)-(S)-isomer (**7A**) would appear at higher field than that of (1'S)-(S)-isomer (**7B**), while the hydrogen at C_3-position of **7A** would resonate at lower field than that of **7B**. Thus the above observation indicated that the product was about 20 % enantiomeric excess (ee) of the (1'S)-isomer (**6B**). Furthermore the nmr spectrum of the mixture of esters (**8A** and **8B**), which was prepared by the reaction with (S)-(-)-α-trifluoromethyl-α-methoxyphenylacetyl chloride, showed signals due to the methyl groups at 1.42 and 1.52 ppm in the ratio of 29 : 21 as doublet with J = 6.4 Hz; this result also suggested about 16 % ee of the (1'S)-isomer.

The circular dichroism (cd) of (5S)-1-carbapenam (**10**) exhibited a negative Cotton effect at 231 nm[7] and this observation was consistent with the prediction by calculation using semiempirical Extended Hückel and CNDO wave functions.[8] On the other hand, the mixture (**6A** and **6B**) exhibited a positive Cotton effect at 214 nm as shown above, which would be attributed to the chirality at the C_4 position of the (1'S, 3R, 4S)-isomer (**6B**), since the *p*-nitrobenzyloxycarbonyl-protected compounds (**9A** and **9B**) derived from the mixture (**6A** and **6B**), showed a positive Cotton effect, $[\theta]^{25}_{213}$ + 2.891 x 10^3(MeOH). It is noteworthy that monocyclic β-lactams alkylated at C_4 position have a reverse Cotton effect in constrast with the 1-carbapenam.

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