We have shown that equilibrium constants are about 0.2 M^{-1} for association of phosphate monoanions with monocations; so all these results represent partial association ranging from approximately 20% association at 1 M to 50% association at 5 M. In addition, it must be kept in mind that ion exchange is fast so the data represent time averages for all states of $H_2PO_2^{-1/2}$

Figure 2 displays data for three tetraalkylammonium chlorides. There is a straight line correlation of ΔJ and $\Delta \delta$ for $(CH_3)_4N^+$, $(C_2H_5)_4N^+$, and $(C_4H_9)_4N^+$ solutions. In all cases decreases in chemical shifts and coupling constants are observed; the largest effects are observed with 3 M tetra-n-butylammonium chloride: $\Delta J = -29.4$ Hz and $\Delta \delta = -5.6$ ppm.

Since the more hydrophobic ammonium ions cause the largest decreases in ${}^{1}J_{PH}$, we propose that ${}^{1}J_{PH}$ decreases because of aggregation of the hydrophobic ions near $H_2PO_2^-$, thereby displacing water from the solvation shell and causing a large decrease in dielectric constant in the environment surrounding the H₂PO₂⁻ ions. The low dielectric constant will cause greater electrostatic repulsion between the two oxygen atoms in $H_2PO_2^-$ leading to a widening of the O-P-O bond angle. Since a larger bond angle demands more s character at phosphorus for the P-O bonds, there must be less s character at phosphorus in the P-H bonds and this will cause the observed decreases in coupling constants. The reverse effect with small metal ions² is consistent with this origin of the changes in coupling constants.

³¹P chemical shifts have been related to structure in phosphates: bond angle effects are thought to control ³¹P chemical shifts.^{6,7} Figures 1 and 2 show that there is direct correlation between decreased coupling constant and increased shielding. Some of the chemical shifts (Figure 2) are quite large. The decreased coupling constants are associated with larger O-P-O bond angles and larger bond angles are expected to cause deshielding.⁶ Consequently, the increased shielding observed here must be due to increased electron density at phosphorus; this would be expected from increased electrostatic repulsion between the two oxygen atoms because this effect will force electrons toward the phosphorus atom. Therefore, it seems clear that there can be cases where bond angle effects are less significant than effects involving redistribution of electron density. This is also true for metal ions; those metal ions which appear to have small effects on the PO₂⁻ bond angle² cause deshielding of the ³¹P nucleus.¹

Possible Application to Nucleic Acid Structure. $H_2PO_2^-$ is structurally similar to the phosphate monoanion groups in nucleic acids. Previously, discussions of nucleic acid structure have focused on conformational changes.⁸ Our results in this and the previous² paper indicate that there should be significant structural changes in nucleic acids if the phosphate monoanion groups change environment from association with metal cations² to a hydrophobic protein environment.9 This could have important functional consequences for genetic expression, for enzymes which act on nucleic acids, and particularly for DNA structural changes including supercoiling and the A, B, and Z helices. These electrostatic effects can be large and could easily drive the observed structural changes.^{10,11}

Acknowledgment. We thank Joyce Wilde for help with the NMR instrumentation. NSF and the Dreyfus fund contributed to purchase of the NMR instrument.

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Highly Diastereoselective Alkylation onto 4-Acetoxy-2-azetidinones Employing Tin(II) Enolates of C4-Chiral 3-Acyl-1,3-thiazolidine-2-thiones

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In the field of carbapenem syntheses, the carbon-carbon bond-formation methods at the 4-position of 2-azetidinones have been intriguing and the various fascinating reactions have been reported.⁵ However, there is no report on a facile and efficient method for the chiral alkylation at the 4-position of achiral 2azetidinones (e.g., 4-acetoxy-2-azetidinone (3)). We now report a new efficient methodology for the preparation of chiral 2-azetidinone intermediates applicable to the total synthesis of (+)-thienamycin and (-)-1- β -methylcarbapenem⁶ based on the highly diastereoselective aldol-type reaction employing C4-chiral 3-acyl-1,3-thiazolidine-2-thiones^{7,8} and 4-acetoxy-2-azetidinones.

To tin(II) enolate 2a,⁹ prepared from 3-acetyl-4(S)-ethyl-1,3thiazolidine-2-thione (1a) was added a THF solution of 4-acetoxy-2-azetidinone (3) at -40 °C. After being stirred at 0 °C for 1 h, the reaction mixture was subjected to the usual workup to afford a yellow mixture of 6a and 7a in a 95:5 ratio (HPLC analysis^{7a}). The major product **6a** was readily isolated in 82% yield by silica gel column chromatography (Scheme I). Other similar chiral alkylations of 3 by the tin(II) enolates of 1b-d gave, with high diastereoselectivity in the range of 90:10-98:2 ratios, the corresponding 4-alkylated 2-azetidinones 6b-d in 75-85% yields.10

Absolute configurations of the major products 6a and 6b were confirmed by their chemical conversion to the known compound 17 $[[\alpha]^{20}_{D} + 41.4^{\circ} (c \ 0.86, \text{ benzene}), \text{ lit.}^{11} [\alpha]^{20}_{D} + 43.2^{\circ} (c \ 0.37,$

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Scheme 1



a: $R^1 = H$, $R^2 = Et$; **b**: $R^1 = H$, $R^2 = i$ -Pr; **c**; $R^1 = Me$, $R^2 = Et$; **d**: $R^1 = Me, R^2 = i - Pr$

Scheme II⁴



-20 °C; 11a 35% from 10a. (f) LDA (2 equiv), THF, -40 °C; N-acetylimidazole, THF, -78 °C \rightarrow room temperature. (g) (*i*-Pr)₂NH-BH₃, (CF₃CO₂)₂Mg, Et₂O, -78 °C; 12a 60%, 12b 60% from 10b via f.

benzene)]. Stereochemistry of 6c and 6d was established by X-ray analysis¹² of the carboxylic acid 10b [mp 128-129 °C (CHCl₃-hexane), $[\alpha]^{26}_{D}$ -66.7° (c 0.6, CHCl₃)] which was derived from 6c (or 6d) by a sequential reaction shown in Scheme II.

This excellent re face selective alkylation into a presumed cyclic acyl imine derived in situ from 3 can be rationalized in terms of the most likely transition state 4. The contribution of the transition state 5 and/or 5' for si face selection of the imine group should be very minor due to steric repulsion between the C3- α proton of the cyclic imine miety and the C4- β and C5- β protons of the thiazolidine-2-thione moiety (5 in Scheme I) and/or steric repulsion between the imine moiety and the C4- α R² group of the thiazolidine-2-thione moiety (5' in Scheme I).

The major products 6a and 6c were successfully converted into the new useful compounds 12a [mp 75-77 °C (Et₂O-hexane), $[\alpha]^{25}_{D}$ -65.0° (c 0.4, CHCl₃)] and **12b** [mp 130-132 °C (Et₂Ohexane), $[\alpha]^{26}_{\rm D}$ -54.6° (c 0.5, CHCl₃)] as depicted in Scheme II.^{5a,13-15} During the synthetic course, direct conversion of **8a,b** into 10a,b by hydrolysis of the former in aqueous THF and MeOH

Scheme III



was attempted using weak bases such as K₂CO₃ and NaHCO₃. The reaction proceeded but the yields of the desired carboxylic acids 10a and 10b were less than 20%.

Subsequently, we investigated the reactions of racemic 3-substituted 4-acetoxy-2-azetidinones 13 with chiral tin(II) enolate **2a** derived from 3-acetyl-4(S)-ETT (1a).

To a solution of enolate 2a prepared in situ from the reaction of 1a (3.4 mmol) and N-ethylpiperidine (4.6 mmol) in THF (12 mL) at -50 to -40 °C for ca. 3-4 h, a solution of dl-2-azetidinone 13 (2.4 mmol) in THF (5 mL) was added at -40 °C. The mixture was stirred at 0 °C for 50 min and then treated as usual. Chromatographic separation of the yellow oily crude product afforded 15a (20% yield), 14a (42% yield), and 16a (9% yield) (Scheme III).¹⁰ Hydrolyses of active amides 14a-16a were carefully carried out in an aqueous THF solution containing 1 N NaOH for 10-30 min to give the each corresponding carboxylic acids 14b-16b in various yields (14b, 71%; 15b, 48%; 16b, 58%) (Scheme III).^{10,16}

The absolute configuration of 14b was confirmed by chemical correlation with the reported compound 18 [mp 126-127 °C (THF-Et₂O), $[\alpha]^{25}_{D}$ +21.3° (c 0.24, CHCl₃); lit.¹⁷ mp 123-124 °C, $[\alpha]^{25}_{D}$ + 21.0° (c 0.19, CHCl₃)]. Compound **15b** was confirmed to be the antipodal compound of 14b by the specific rotation and spectroscopic evidence. The stereochemistry of 16b was tentatively assigned on the basis of its ¹H NMR spectra [δ C4-H 3.97 (CDCl₃), J = 5-6 Hz (multiplet)] and the mechanistic consideration.18

The observed outcome of diastereofacial selectivity in the reactions of the chiral tin(II) enolate 2a with dl-3-substituted 4acetoxy-2-azetidinones 13 can be also rationalized, inspecting the similar transition state models like 4, 5, and 5'.¹⁸

Finally, optically active 13 was allowed to react with chiral tin(II) enolates 2c and 2d in THF at 0 °C for 1 h to afford the desired chiral azetidinones, **19** [80% yield, mp 85.5-86.5 °C (hexane-EtOAc), $[\alpha]^{25}_{D}$ + 233.9° (c 0.8, CHCl₃)], in a 90:10 (19/other isomers) ratio, and 20 [74% yield, mp 131.5–132.5 °C (hexane-EtOAc), $[\alpha]^{25}$ + 295.7° (c 0.9, CHCl₃)] in a 91:9 (20/other isomers) ratio, respectively.



Thus, we succeeded in the first aldol-type chiral alkylation of cyclic acyl imines by tin(II) enolates of C4-chiral 3-acyl-1,3-

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thiazolidine-2-thiones. This chiral induction proved to be strikingly effective for asymmetric syntheses of various C1- β -substituted carbapenems.

Supplementary Material Available: Tables of crystal data of compound 10b, atomic parameters for non-hydrogen atoms, fractional coordinates for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond length and valance angles, torsion angles, and observed and calculated structure factors in compounds 10b, the perspective view for the crystallographic structure of 10b, and experimental details and results in the reaction of 2 with 3 (or dl-13) (10 pages). Ordering information is given on any current masthead page.

Lewis Acid Mediated Condensation of Chiral Imide Enolates. A General Approach to the Synthesis of **Chiral Carbapenem Precursors**

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The search for carbapenem antibiotics possessing enhanced chemical and metabolic stability has generated considerable synthetic activity directed toward the synthesis of $1-\beta$ -methylcarbapenem carboxylic acids, such as (-)-(1R,5S,6S)-1methyl-2-[[2-(dimethylamino)-2-iminoethyl]thio]-6-[(1R)-1hydroxyethyl]-1-carbapenem (1).¹ The control of the stereo-



chemistry at the 1-position is a critical problem in the synthesis of this new generation of β -lactam antibiotics.^{1a}

In this paper we wish to report the results of a highly successful double-asymmetric synthesis leading to the 1- β -methyl carbapenem antibiotic precursor 2 in ≥98% enantiomeric excess from readily available optically active azetidinone $3.^2$ The key feature in the strategy is the utilization of chiral oxazolidone enolates³ in Lewis acid mediated carbon-carbon bond-forming reactions for the introduction of chirality at C-5 (2).

The structural analysis of the C-4 \rightarrow C-5 bond connection of 2 reveals that the coupling of two optically pure fragments 3 and 4 could be incorporated as a logical step in their synthesis.⁴ Recent investigations³ have demonstrated the utility of propionyloxazolidone carboximides in achieving high levels of diastereofacial selection. In direct analogy with prior report,^{3b} the illustrated

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carboximides 6 and 7 were transformed into their respective Zsilyl enol ethers⁵ 8 and 9 (1.05 equiv of LDA, 1.10 equiv of Me₃SiCl, THF, -78 °C \rightarrow room temperature). Reaction of 1.5 equiv of the enol ether 8 and 9 with the azetidinone 3 in CH_2Cl_2 (0.3 M in CH_2Cl_2 at room temperature) in the presence of a catalytic amount of ZnI_2 afforded the β -lactam carboximides 10α and 10β as illustrated in Scheme I. Although the chemical yields were generally quite high (78-93%), the diastereoselectivity of the process was only moderate (40-60%).6

Evans has extensively demonstrated the high level of efficiency of dialkylboryl enolates of carboximides in aldol condensations.³ We have found that the dialkylboryl enolates of carboximides react smoothly with the azetidinone 3 with a high degree of diastereoselectivity under Lewis acid conditions. The Lewis acid used determined the optimum stoichiometry of enol to azetidinone and the degree of diastereoselection. The diethylboryl enolates were selectively generated by treatment of the propionamide with ET₂BOTf⁷ and *i*-Pr₂NEt (0.3 M in CH₂Cl₂, -78 °C or room temperature)⁸ and to this solution was added the Lewis acid followed by the azetidinone 3 at room temperature. A \geq 95% mass recovery of products was obtained and the diastereomer analysis was determined by HPLC on the unpurified reaction products.9 Treatment of the crude product 10 with 1.0 M LiOH in THF at room temperature affords 2 in 73% isolated yield ($\beta/\alpha \ge 99$) based on 3.10,11



(5) Silyl enol ether Z/E mixtures have been prepared by using TMSOTf/Et₃N/CCl₄/room temperature. The stereochemistry of the silyl enol ether was confirmed by NMR. This is the subject of a separate report to be published.

(6) Independent generation of the zinc enolate via exchange of the lithium enolate with ZnBr₂ affords the β -lactam carboximides in a 10β : 10α ratio of 80:20.

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(8) The generation and the stereochemistry of the Si, Sn, and B enolates of the chiral carboximides is the subject of a separate report to be published. (9) HPLC assay: Altex Ultrasphere-Octyl, 5 μm, 25 cm × 416 mm i.d.; acetonitrile/water/H₃PO₄, 70:30:0.1, v/v; 1.1 mL/min; retention times (min) 8β 12.0, 8α 16.4.

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