agent. This finding matches the fact that potassium ion is implied in biological systems in the processes related to synthesis[6] and transfer[7] of the carbamate group. Among MY salts, the most active and selective of the halide ions is fluoride (100% selective in the organic carbamate), while other halides can afford other products derived from nucleophilic attack at the carbon dioxide moiety. Iodide yields the carbamoyl halide (eq 3) (ca. 20% yield), which

$$(R_2N)_2P(OOCNR_2) + NaI + R'X \rightarrow R_2NC(O)I + (R_2N)_2POR' + NaX \quad (3)$$

can be easily separated from the carbamate owing to the difference in physical properties. We have found that there is a correlation between the energy of the P–Y bond formed and the yield in carbamate.

When phosphacarbamate (3) was treated with an organic halide R'X (X = Cl, Br, I) in the presence of KF and of the 18,6-crown ether[8] we have observed quantitative formation of the organic carbamate R_2NCOOR' and of $(R_2N)PF_2$, which was isolated from the reaction mixture and characterized by means of IR spectroscopy and of ^1H, ^{13}C, ^{19}F, and ^{31}P NMR techniques. This fluorophosphine was quite unreactive and could not be recycled to afford the starting tris(dimethylamino)phosphine. Conversely, other halophosphines R_2NPY_2 (Y = Br, I) could be transformed into the starting aminophosphine. This fact was of interest as it permitted synthesis of carbamates under very mild conditions from quite safe reagents (amines, organic halides, and carbon dioxide), phosphorus halides being only promoters used in the synthesis of reactive intermediates. As the crown ether was also recycled the whole process can be summarized by eq 4 which represents the overall synthesis of carbamates from the reagents.[9]

$$R_2NH + CO_2 + R'X \xrightarrow{\text{base}} R_2NCOOR' + BaseH^+Y^- \quad (4)$$

Starting from metal carbamates R_2NCOOM (M = Li, Na, K) prepared by other routes, the organic carbamate could also be isolated in particularly good yield (>85%) when M = K^+ in the presence of 18,6-crown ether. Utilization of the coordinating crown ethers thus allows transfer of the carbamate group in high yield and represses nucleophilic attack at the carbon atom which yields ureas.

This transfer reaction appears to be of interest in a cyclic or a flow system. It represents one of the very few examples of an electrophilic attack at the carbon dioxide moiety mediated by a metal ion and the first example of a carbamate moiety transfer from a phosphacarbamate. It is relevant to other similar reactions in which the carbamate group is involved,[10-12] and may help in the understanding of common features.

Acknowledgment. This work was supported by CNR-Rome, Progetto Finalizzato I, Chimica Fine e Secondaria (Grant 84-931).

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(9) NMR data for $P(NMe_2)_3$ and its carbamate derivatives (mono and di) agree with those reported in the literature.[1-3] ^1H and ^{13}C data are referred to TMS, ^{31}P are referred to H_3PO_4, and ^{19}F data are referred to $(CF_3)_2CO$(hydrated). All spectra were run in CD_2Cl_2 at 273 K with a Varian XL 200 instrument. $P[N(CH_2CH_3)_2]_3$: ^1H NMR 2.74 (m, ^3J(H–P) = 8.47 Hz, CH_2), 0.84 ppm (t, ^3J(H–H) = 7.1 Hz, CH_3); ^{13}C NMR 38.94 (tdq, ^1J(C–H) = 133.7 Hz, ^2J(C–H) = 4.4 Hz, ^2J(C–^{31}P) = 19.3 Hz, CH_2), 13.57 ppm (qt, ^1J(C–H) = 125.0 Hz, ^2J(C–H) = 5.0 Hz, CH_3). $^{31}P\{^1H\}$ NMR 116.5 ppm. $P[N(CH_2CH_3)_2]_2$ [$OOCN(CH_2CH_3)_2$]: $^{13}C\{^1H\}$ NMR amino groups 39.67 (d, ^2J(C–^{31}P) = 20.2 Hz, CH_2), 13.78 ppm (s, CH_3); carbamate group 154.38 (d, ^2J(C–^{31}P) = 8.2 Hz, C(O)O), 41.43 (br s, CH_2), 14.57–14.50 ppm (s, CH_3). The two signals for the methyl groups show that the free rotation is restricted. This is true also at 300 K; $^{31}P\{^1H\}$ NMR 127.15 ppm. $P[N(CH_2CH_3)_2][OOCN(CH_2CH_3)_2]_2$: $^{13}C\{^1H\}$ NMR amino group 38.82 (d, ^2J(C–^{31}P) = 23.0 Hz, CH_2), 13.18 ppm (CH_3); carbamate groups 153.42 (d, ^2J(C–^{31}P) = 8.4 Hz), 41.81 (CH_2), 14.40 ppm (CH_3); $^{31}P\{^1H\}$ NMR 125.82 ppm. $(CH_3)_2NCOOCH_2CH{=}CH_2$: IR 1705 cm^{-1} (neat); *m/e* 129; ^1H NMR 5.48 (m, J(H–H_{trans}) = 17.25 Hz, J(H–H_{cis}) = 10.45 Hz, CH=), 4.82–4.72 m, J(H_{gem}) = 1.58 Hz, $=CH_2$), 4.10 (dt, J(H–C*H*=) = 5.41 Hz J(H–CH_2=) = 1.43 Hz, CH_2), 2.46 ppm (s, CH_3); ^{13}C NMR 155.97 (s, C(O)O), 133.03 (d, ^1J(C–H) = 152.4 Hz, C=), 116.69 (t, ^1J(C–H) = 156.6 Hz, $=CH_2$), 65.59 (t, ^1J(C–H) = 152.4 Hz, CH_2), 36.08 (q, ^1J(C–H) = 136.4 Hz, CH_3), 35.52 ppm (q, ^1J(C–H) = 136.8 Hz, CH_3). Yield, 95%. $(CH_3CH_2)_2NCOOCH_2(CH_2)_6CH_3$: IR 1695 cm^{-1}; *m/e* ^{13}C NMR 155.97, (t, ^3J(C–H) = 3.9 Hz, C(O)O), 64.94 (tt, ^1J(C–H) = 145.5 Hz, ^2J(C–H) = 3.8 Hz, OCH_2), 41.30, (t, ^1J(C–H) = 137.7 Hz, CH_2N), 31.78, 29.41, 29.17, 28.98, 25.88, 22.53 (m, CH_2), 13.90 (q, ^1J(C–H) = 122.8 Hz, CH_3N), 13.62 ppm (q, ^1J(C–H) = 126.0 Hz, CH_3). Yield, 98%. $(CH_3)_2NCOOCH_2C_6H_5$: IR 1700 cm^{-1} (neat); *m/e* 179; ^1H NMR 7.20 (m, phenyl protons), 5.00 (s, CH_2), 2.75 ppm (s, CH_3); ^{13}C NMR 156.36 (s, C(O)O), 66.92 (t, ^1J(C–H) = 147.0 Hz), 35.82 (q, ^1J(C–H) = 137.6 Hz), 36.36 (q, ^1J(C–H) = 137.9 Hz), 137.0 (s, C-1 phenyl), 127.35 (d, ^1J(C–H) = 159.2 Hz, C-2 and C-6 phenyl), 128.37 (d, ^1J(C–H) = 159.1 Hz, C-3 and C-5 phenyl), 127.83 ppm (d, ^1J(C–H) = 159.2, C-4 phenyl). Yield, 97%, based on the organic halide used in stoichiometric amounts. $(CH_3)_2NPF_2$: IR 1308, 990, 800, 740, 710 cm^{-1}; ^{19}F NMR 19.1 ppm (d, J(F–P) = 1193.7 Hz), ^{31}P NMR 154.2 ppm (doublet).

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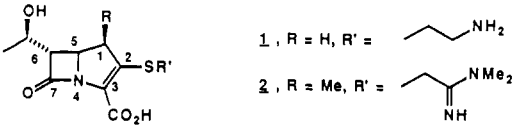
Enantioselective Synthesis of the 1β-Methylcarbapenems via Cycloaddition of 3-Siloxypentadiene and 4-Acetoxyazetidinone

Summary: The cycloaddition of a 3-siloxy-1,3-pentadiene and the 4-acetoxyazetidinone **3** followed by ring contraction and phosphorylation leads to the key precursor of 1β-methylcarbapenems (**11**) in a five-step process in 27% overall yield.

Sir: The huge success, both financially and medically, for thienamycin (**1**; Primaxin) since its introduction in 1985[1] has spawned considerable interest in analogues with either enhanced activity or greater stability. In 1984, the Merck group reported[2] the synthesis of the 1β-methyl analogue **2**, which exhibited greater stability and resistance to deactivation by renal dipeptidase-1 (DHP-1) and still retained the excellent broad spectrum antibacterial activity.



The 1α-methyl analogue, however, exhibited a marked decrease in antibacterial activity.[3] Furthermore, due to the concave environment in **2**, the β-methyl derivative is

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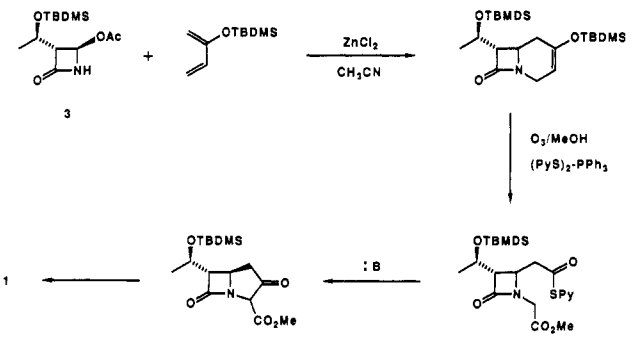
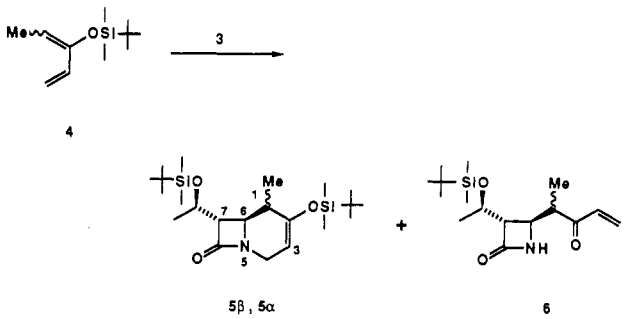
Scheme I



the least stable of the two epimers, with facile isomerization to the α-methyl site being the favored thermodynamic process.

In recent years there has been great emphasis on introducing the β-methyl substituent into the thienamycin system with high stereoselectivity. This has been successful, to varying degrees, by enolate alkylations[2] with methyl iodide, hydride reductions of prochiral olefins[4] or propargylic[5] precursors, chiral intermediates with the methyl group already in position,[6] and stereoselective aldol processes[7] using the readily available 4-acetoxyazetidinone **3**. We have recently reported[8] an efficient enantioselective approach to the thienamycin system (**1**) by cycloaddition of the siloxy diene with **3** (Scheme I). This sequence provided the thienamycin precursor in over 30% yield, based on **3**. The critical step for this approach was the cycloaddition of the azetidinone and the diene which we felt could be extended to the pentadiene and thus produce the biologically more significant β-methyl derivatives **2**. We now describe the successful implementation of this methodology, however, not without considerable difficulties and modifications.

In our previous cycloaddition, shown in Scheme I, the simple butadiene was employed. However, the homologous pentadiene **4** was required and concern over *E,Z* isomers and their ultimate effect on the stereochemistry of the β-methyl thienamycin was not trivial. The method to prepare **4** in sufficient quantity was patterned after a recent report[9] which gave the diene in 70–80% yield as a 75:25 mixture of *E,Z* isomers.[10] When the 3:1 mixture of the dienes was treated with the azetidinone **3** in acetonitrile and anhydrous zinc chloride as reported earlier,[8] a poor (20%) yield of **5** was obtained, although as a 70:30 mixture of 1-methyl epimers, along with 50% yield of the vinyl ketone **6** (also as methyl epimers). Repeated attempts to



improve the yield of **5** failed. Nevertheless, the 70:30 mixture[11] of β- to α-methyl epimers in **5** was encouraging. Since if reflected closely the 3:1 mixture of *E,Z* isomers in the diene, **4**, and this indicated that there was stereochemical consistency in the cycloaddition. Alter a large number of experiments which included varying Lewis acids, temperature, solvents, etc., it was found that the amount of acyclic enone **6** could be reduced to ~10–12% while the yield of cycloadducts **5** increased to 65% by simple use of toluene as the solvent. Furthermore, the ratio of β/α epimers in **5** remained relatively constant at 7:3. The efficacy of solvents form acetonitrile to toluene indicated that the transition state in this process is probably low in polar character. The fact that we were unable to transform **6** into **5** under a variety of conditions also indicates that these two products (**5**, **6**) do not arise from a common intermediate. If the production of $5\beta/5\alpha$ occurs via a concerted process, it would be expected that pure (*E*)-diene **4** wouuld give pure 5β, whereas pure (*Z*)-diene would produce 5α. However, when pure (*E*)-diene was employed (separated by flash chromatography, silica, hexane), **5** was obtained as an 80:20 mixture of β/α epimers. Conversely, pure (*Z*)-diene gave a 40:60 mixture of β/α epimers. This can be attributed to the isomerization of the dienes under the reaction conditions. In fact, excess diene **4**, recovered when pure (*E*)-diene was utilized, was shown to be a 75:25 mixture of *E/Z*. Furthermore a chloroform solution of (*Z*)-diene, containing traces of HCl, is transformed to the 75:25 (^{1}H NMR) equilibrium mixture on standing at room temperature for less than 1 h. Thus, pure (*E*)-diene leads to an 80:20 mixture of $5\beta/5\alpha$, whereas the diene mixture (75:25) provides $5\beta/5\alpha$ as a 70:30 mixture, indicating that separation of the dienes may be only of marginal importance.

The synthetic scheme was continued by ozonolysis of **5** as the 80:20 mixture (from pure (*E*)-diene) of α,β-methyl epimers. In order to obtain a useful intermediate for unmasking the carboxyl groups, the ozonolysis was carried out with benzyl alcohol as the cosolvent and oxidative workup[12] afforded the benzyl ester **7** in 85% yield. The epimeric mixture (80:20) had not changed, and with the benzyl ester in hand, it could be utilized as had been previously described by the Merck group.[13]

To carry out the ring contraction to the carbapenems (90%), the acid **7** was transformed into the thiopyridyl ester **8** according to Mukaiyama (Ph_3P, PySSPy, 25 °C). HPLC analysis of **8** (5 μM, silica gel, 30% ethyl acetate/hexane) confirmed that no epimerization had occurred (β/α, 80:20, β-epimer elutes first) either in ozonolysis or the thioester formation. Although the β/α epimers could have been separated at this stage, it was unnecessary since

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(9) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2089. Purification of the diene was performed by flash chromatography (silica-gel, hexane) rather than distillation. Modifications for large-scale preparations are presented as supplementary material.
(10) The method of Vedejs et al. (Vedejs, E.; Eberlein, T. H.; Mazor, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556) gave the pentadiene as an 82:18 mixture but in lower yields (30–40%) and was not as amendable to large scale-up as the French procedure (ref 9).
(11) The 70:30 ratio in **5** was determined from chemical shift nonequivalencies for H-6 and H-7 resonances. The β-methyl epimer was assigned from the H-1 and H-6 coupling (J = 5 Hz) compared to J = 10 Hz for the α-methyl epimer.
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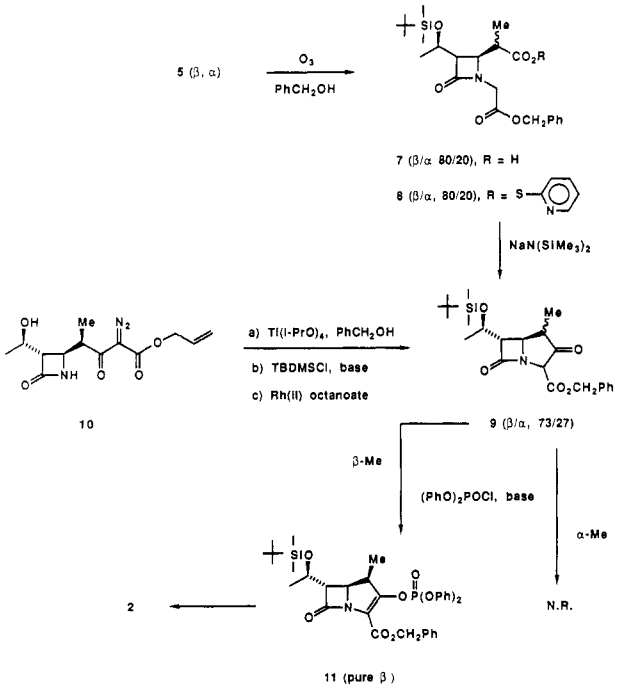
this would occur spontaneously at a later stage. The Dieckmann cyclization to **9** was performed by using exactly



2.0 equiv of sodium hexamethyldisilazide rapidly added to a THF solution of **8** at −30 °C. Lower temperatures, slow addition of base, and excess base all produced cyclic ketone **9**, but with 50–80% epimerization. The fast addition at higher temperature produced **9** in 85% yield in a 73:27 ratio of β- to α-methyl epimers. Thus, ~7% epimerization took place as evidenced by NMR integration of the C-1 proton. All attempts to purify the bicyclic ketone **9** by chromatography resulted in total epimerization to the 1α-methyl isomer. Proof of structure and stereochemistry for **9** was gathered by transforming the known β-lactam **10**[14] into **9** using the Merck protocol.[2] Although **9** from the present route was a 73:27 mixture, the pure material obtained from **10** coincided spectroscopically in every way with the major epimer in our mixture.

Due to the extreme lability of the C-1 methyl group when positioned on the β-face of **9**, this material was directly transformed[2] into the stable enol phosphonate and furnished only the pure β-methyl derivative **11**.[15] The Merck group had observed[3] this fortunate behavior regarding the relative rates of reaction for the α- and β-methyl epimers in the phosphorylation step. Thus, a kinetic separation of diastereomers was performed affording our target **11**, in 87% yield (based upon 73% of the β-epimer in **9**). Since further elaboration to a variety of thiovinyl derivatives is proprietary and involves many different side chains, we felt that the acquisition of **11** in five steps and 27% overall yield would be a prudent place to terminate this study.

Acknowledgment. We are grateful to Bristol-Myers for financial support of this study.

(14) Kindly supplied by Dr. R. A. Partyka of Bristol-Myers.

(15) Colorless oil, moisture sensitive; $[\alpha]^{22}_D$ +41.50° (*c* 1.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45–7.12 (m, 15 H), 5.25, 5.18 (AB q, *J* = 12.6 Hz, CH_2Ph), 4.21, (dq, 1 H, *J* = 12.3, 6.2 Hz, CH_3CHOSi), 4.14 (dd, 1 H, *J* = 10.3, 2.8 Hz, *H*-6), 3.44 (dq, 1 H, 5.4, 2.8 Hz, *H*-1), 3.25 (dd, 1 H, *J* = 6.1, 3.0 Hz, *H*-5), 1.22 (d, 3 H, *J* = 6.2 Hz), 1.18 (d, 3 H, *J* = 7.3 Hz), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); mass spectrum (Cl) *m/e* (relative intensity) 664 (M + 1, 5.4), 663 (M^+, 11.7), 500 (14.7), 432 (15.4), 286 (100). IR (neat) 2953, 2928, 2884, 2855, 1783 (C=O), 1724 (C=O), 1636, 1589, 1488, 1185, 1071, 1025, 971.

Supplementary Material Available: Complete experimental details and spectral data for all steps and products respectively (21 pages). Ordering information is given on any current masthead page.

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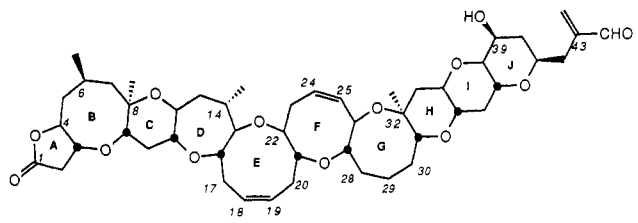
Assignment of ^{13}C NMR Peaks of Brevetoxin A: Application of Two-Dimensional Hartmann–Hahn Spectroscopy

Summary: Brevetoxin A, $C_{49}H_{50}O_{13}$ (BTX-A), the most potent toxin produced by the dinoflagellate *Gymnodinium breve*, consists of a 10 trans-fused oxacarbocyclic skeleton. The inherent problem when dealing with the NMR of molecules like BTX-A arises from the flexible nature of the molecule which is caused by the presence of medium-sized rings. This can be serious in terms of its lack of ^1H–^{13}C correlation in the spectra. A pulse scheme, Hartmann–Hahn (HOHAHA) type heteronuclear experiment for displaying RELAY cross peaks is described for direct detection of ^{13}C-nuclei. This pulse sequence leads to an improvement in resolution and sensitivity. The two dimensional (2D) ^1H–^{13}C correlation spectra which this pulse scheme produces has been applied in the assignment of carbon peaks in BTX-A.

Sir: Despite the numerous pulse sequences for obtaining 2D heteronuclear RELAY[1] as well as 2D heteronuclear chemical-shift correlation spectroscopy,[2] flexible molecules that cause severe broadening of peaks may lead to problems. This can be serious in terms of its lack of ^1H–^{13}C correlation, as exemplified by a molecule such as brevetoxin A (BTX-A, **1**).[3] In this paper, a pulse scheme for



BTX-A (1)

direct detection of ^{13}C nuclei which is superior in resolution and sensitivity to other currently available methods is described. The pulse scheme described here is a Hartmann–Hahn (HOHAHA)[4-6] type heteronuclear experiment

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