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DOUBLE CYCLIZATION OF AMINOPHOSPHONOACETATE DERIVED ß-HYDROXYACIDS TO BICYCLIC ß-LACTAMS

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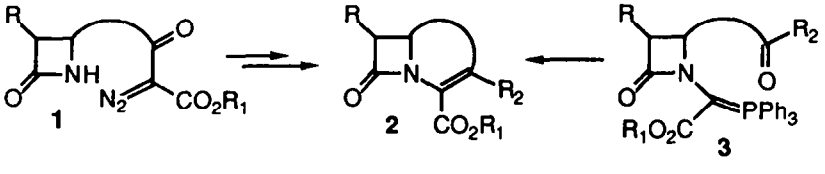
Abstract: The carbon framework for carbapenems was constructed by an asymmetric aldol condensation and subsequent direct coupling of the resulting β-hydroxy acid equivalent with an aminophosphonoacetate. Cyclization to the monocyclic β-lactam **20** was followed by oxidative elaboration to the penultimate aldehyde **22** which was converted to carbapenem **23** by an intramolecular version of a Horner-Emmons cyclization.

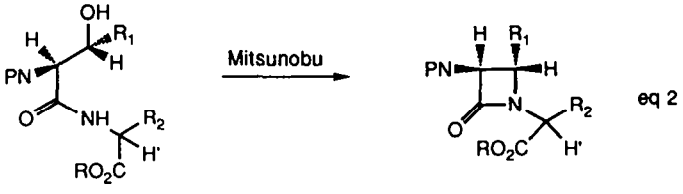
INTRODUCTION

Most asymmetric syntheses of bicyclic ß-lactam antibiotics begin with construction of an optically active monocyclic ß-lactam. Incorporation of appropriate functionality for eventual elaboration to the bicyclic ring system is often a multistep process that diminishes the practicality of total synthesis as a production process. For the formation of the second ring of penems, carbapenems, cephems and carbacephems, two different, but complementary, methods have been most widely used - a carbene insertion (**1** → **2**) developed by the Merck group[1] and an intramolecular Wittig process (**3** → **2**) devised by Woodward.[2] The latter process requires several steps to incorporate the key phosphorane. Thus, development of a synthesis of optically active monocyclic ß-lactams with direct incorporation of comparable functionality remains an important goal. Herein we report that appropriately substituted aminophosphonoacetate derived ß-hydroxyacids can be directly cyclized to the corresponding ß-lactams under modified Mitsunobu conditions. The utility of the methodology is also demonstrated by asymmetric synthesis of the carbapenem nucleus.



eq 1

The Mitsunobu reaction has been shown to be quite useful for the chemical cyclization of several peptides to ß-lactams (eq 2).[3] The efficiency of the process is quite dependent on the peptide substituents as well as the choice of azodicarboxylate and phosphine or phosphite used as the Mitsunobu reagents. We had previously shown that the yields of the cyclization products improved with increased α-hydrogen acidity (H' in eq 2) of the C-terminal amino acid component in the peptide substrate.[3a] For example, cyclization of serylaminomalonates **8** under the Mitsunobu conditions proceeded nearly quantitatively, while the same reaction of serylglycine derivatives **6** produced the corresponding ß-lactam in lower yield. Cyclization of serylaminophosphonates **10** and related derivatives was expected to parallel the amino malonate process, yet provide products with more versatile functionality. We have described preliminary tests of the feasibility of aminophosphonate facilitated cyclizations by the preparation of monocyclic ß-lactams **11** from the serine and threonine derived peptides **10** (R_1 = H, Me, respectively).[4] Since neither of these peptides (**10**) or ß-lactams contained the appropriate carbon framework or functionality suitable for elaboration to a bicyclic ß-lactam precursor, our attention focused on the development of an efficient asymmetric synthesis of a substrate which would allow us to test the proposed double cyclization route to bicyclic ß-lactams. Details of the successful application of this approach to the synthesis of a representative carbapenem are presented in this paper.



eq 2

4 PN = Ft, R_1 = H, R_2 = p-RO-C_4H_6: ref 3b **5**
6 PN = Ft, R_1 = H, R_2 = H: ref 3a **7**
8 PN = Ft or Ox, R_1 = H, R_2 = CO_2R: ref 3a **9**
10 PN = Ox, R_1=Me, R_2 = $P(O)(OR)_2$: ref 4 **11**

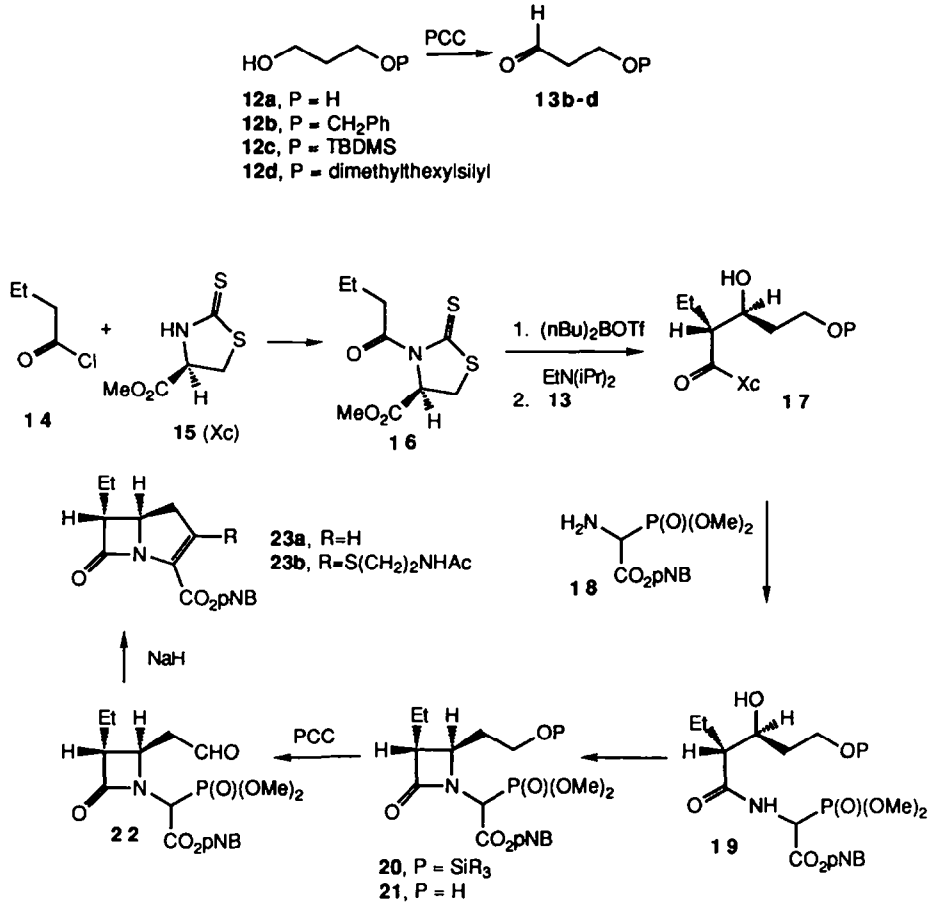
RESULTS AND DISCUSSION

The nucleus of the carbapenem **PS-5** (**23b**, Scheme 1) was chosen as the first bicyclic target since the carbapenems in general are such potent antibiotics[5] and use of an intramolecular Horner-Emmons reaction was expected to allow direct formation of the unsaturated five membered ring. Realizing that a suitably protected form of an aminophosphonoacetate **18** (Scheme 1) would provide the nitrogen and two carbons of the carbapenem system, the next requirement was the asymmetric construction of the rest of the carbapenem carbon framework. The key reaction planned for this part of the synthesis was an asymmetric aldol condensation.

1,3-Propanediol (**12a**, P = H) was treated with 100 mole percent of sodium hydride followed by reaction with benzylbromide, t-butyldimethylsilylchloride, or dimethylthexylsilylchloride to give the monoprotected diols **12b-d**. Separate PCC oxidation[6] of **12b-d** produced the corresponding aldehydes **13b-d**. Acylation of butyryl chloride (**14**) with the cysteine derived thiazolidine thione

(**15**)[7] produced the optically pure aldol substrate **16**. Enolization of **16** with di(n-butyl)boryltriflate and diisopropylethylamine[7] followed by separate reaction with aldehydes **13b-d** produced the *syn* β-hydroxy acid equivalents **17b-d** diastereoselectively (> 10:1 routinely and, as a single detectable diastereomer in the case of **17d** when performed exactly as described in the Experimental Section). This process established the two asymmetric centers for the PS-5 nucleus.

Scheme 1



As reported earlier, the acylthiazolidinethiones are also effective active esters.[7,8] However, direct treatment of **17b-d** with aminophosphonoacetate **18** produced the desired amides **19b-d** in low yields as mixtures of diastereomers because racemic phosphonoacetate **18** was used in the coupling reaction. Since the chiral center associated with the aminophosphonoacetate was eventually to be lost, no attempt was made to separate the diastereomers. The only problem with characterization and subsequent reactions of the mixture of diastereomers was the increased complexity of the corresponding NMR spectra. Addition of N-hydroxybenzotriazole, pyridine and / or

DMAP improved the isolated yields of coupled products somewhat (40-60%). At this point **19d** was chosen as the most appropriately protected form, since problems were encountered with the hydrolytic sensitivity of the TBDMS group of **19c** and removal of the benzyl group of **19b** was incompatible with utilization of the PNB ester. Treatment of **19d** with Di-(t-butyl)-azodicarboxylate[9] and triphenylphosphine produced the β-lactam **20** cleanly, but the isolated yield was only 66% because the product was difficult to separate from the triphenylphosphine oxide produced from the Mitsunobu reaction. Removal of the silyl protecting group with tetrabutylammonium flouride produced the alcohol **21** in 62% isolated yield. Oxidation of alcohol **21** with PCC / alumina provided the desired aldehyde **22** in 50% purified yield. As expected, treatment of the aldehyde with sodium hydride generated the optically active carbapenem nucleus **23** in 41% yield. Like other relatively unsubstituted carbapenems, **23** was quite unstable and decomposed upon storage at low temperature within a few days. However, as described in the experimental section, the optically active carbapenem **23** was fully characterized and the data corresponded to that reported for racemic **23** which was reported previously.[10] Most noteworthy were the infrared absorption at 1780 cm^{-1} and the 2.9 Hz coupling constant in the NMR spectrum for the β-lactam ring protons which clearly demonstrated the expected and correct *trans* substitution pattern of the β-lactam ring. This sequence clearly demonstrated the utility of the amino-phosphonoacetate mediated double cyclization approach for the synthesis of bicyclic β-lactams.

In summary, the direct cyclization of β-hydroxy amide derivatives of aminophosphono-acetates provides a direct route to β-lactams with appropriate functionality already incorporated for the direct construction of important bicyclic antibiotics. Use of this and related methodology for the synthesis of other natural and unnatural bicyclic β-lactam antibiotics is being studied.

Experimental section

General Comments: Melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum-backed silica gel 60 F-254, 0.2 mm plates (MCB). Proton NMR spectra were obtained on MagnaChem A-200, Nicolet NB-300 or General Electric GN-300 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ-units). Infrared (IR) spectra were recorded on a Perkin-Elmer 1420 spectrometer. Mass spectra were recorded on DuPont DP102 and FInnigan MAT Model 8430 spectrometers. Solvents used were dried and purified by standard methods.

Monodimethylthexylsilylpropanediol 12d. To a suspension of sodium hydride (3.2 g, 60% dispersion in oil) in 100 mL of THF at room temperature was added 6 g (78.9 mmol) of neat 1,3-propanediol (**12a**). The mixture was stirred for 1 h. Dimethylthexylsilylchloride (15.6 mL) was added and a mildly exothermic reaction ensued. After 2 h, the reaction mixture was diluted with 300 mL of diethylether. The mixture was washed successively with 100 mL of 10% sodium carbonate and 100 mL of brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was distilled under vacuum (94-98°C at 0.9 torr) to give 15 g (75%) of liquid **12d**. ^1H NMR

(200 MHz, $CDCl_3$) δ 0.0 (s, 6H), 0.73 (s, 6H), 0.75 (d, 6H, J = 6.9 Hz), 1.54 (m, 1H), 1.68 (m, 2H), 3.70 (m, 4H); ^{13}C NMR δ -2.979, 18.319, 20.260, 25.099, 34.190, 34.924, 61.772, 61.978; IR (neat film) 3350, 2950, 2865, 1300, 1085, 825, 770 cm^{-1}.

3-Dimethylthexylsilyloxypropanal 13d. To a vigorously stirred mixture of pyridinium chlorochromate (11.1 g, 51 mmol) and neutral alumina (50 g) in 100 mL of methylene chloride was added a solution of 7.5 g (34.4 mmol) of **12d** in 50 mL of methylene chloride. Within 10 to 15 min the mixture turned dark brown. The mixture was stirred at room temperature for 8 h and then diluted with 100 mL of diethyl ether. The mixture was filtered through a small column of Florisil. The eluent was evaporated to give a dark brown residue which was diluted with ethyl acetate and filtered through a short column of silica gel eluting with 25% ethyl acetate in hexanes to separate the product from the chromium salts. The filtrate was concentrated and the residue was distilled using a Kugelrohr apparatus (100°C at 20 mm) to produce 4.6 g (62%) of the desired liquid aldehyde. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.0 (s, 6H), 0.73 (s, 6H), 0.75 (d, 6H, J = 6.9 HZ), 1.50 (m, 1H), 2.48 (dt, 2H, J = 6Hz, 4Hz), 3.86 (t, 2H, J = 6Hz), 9.7 (t, 1H, J = 4Hz); IR (neat film) 2720, 1725 cm^{-1}.

Aldol product 17d. To a solution of 3.2 g (12.9 mmol) of butyryl thiazolidinethione **16**[7] in 50 mL of methylene chloride under argon at 0°C (internal temperature) was added 3.84 mL of freshly prepared di-n-butylboron triflate.[7] After 5 min at 0°C, 2.8 mL of diisopropylethylamine was added dropwise. After stirring for another 30 min, the resulting light orange solution was cooled to -78°C and 2.94 g (13.6 mmol) of neat aldehyde **13d** was added with a syringe. The reaction mixture was stirred at -78°C for 2 h and then allowed to warm to -50 to -20°C over 0.5 h. The reaction was then quenched by addition of excess pH 7 phosphate buffer precooled to 0°C while the reaction mixture was stirred vigorously. The organic layer was separated and dried over $MgSO_4$. Filtration, followed by evaporation of the solvent, gave a residual oil which was redissolved in ethyl acetate and filtered through a small plug of silica gel. The eluent was concentrated and purified by flash chromatography on silica gel eluting with ethyl acetate - hexanes to afford 3.5 g (58%) of a single diastereomer of the aldol product (**17d**) as an oil. (Repetition of the experiment with less careful attention given to the temperature control gave mixtures of diastereomers ranging from 10-13 : 1.) ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 6H), 0.81 (s, 6H), 0.84 (d, 6H, J = 6.9 Hz), 0.97 (t, 3H, J = 7.2 Hz), 1.5 - 1.9 (m, 5H), 3.34 (dd, 1H, J = 10.3, 1.9 Hz), 3.59 (dd, 1H, J = 10.3, 7.3 Hz), 3.80 (s, 3H), 3.75 - 3.85 (m, 2H), 4.08 (m, 1H), 4.88 (m, 1H), 5.66 (dd, 1H, J = 7.3, 1.9 Hz); ^{13}C NMR δ -3.8, 11.2, 18.2, 20.1, 24.8, 30.4, 33.8, 35.5, 49.9, 52.9, 61.8, 67.411, 71.96, 168.6, 175.7, 200.5; IR (neat film) 3495, 2960, 2875, 1755, 1700, 1170, 835, 780 cm^{-1}; mass spec (CI with isobutane) m/e 464 (M + 1).

p-Nitrobenzyl aminodimethylphosphonoacetate 18. This compound was prepared by the general procedure described by Steglich.[11] It was isolated and temporarily stored as the oxalic acid salt. The free amine was liberated just before use by treatment with aqueous dipotassium hydrogen phosphate buffer (pH ~8) extraction with ethyl acetate and concentration *in vacuo* gave an oil. The resulting free amine was used directly in the next reaction. ^1H NMR ($CDCl_3$, 200 MHz,

of the free amine) δ 1.90 (br s, 2H); 3.78 (d, 3H, J_{PH} = 11 Hz); 3.84 (d, 3H, J_{PH} = 11 Hz), 4.09 (d, 1H, J_{PH} = 22 Hz), 5.35 (dd, 2H, J = 14 Hz), 7.59 (d, 2H, J = 8 Hz), 8.23 (d, 2H, J = 8 Hz).

ß-Hydroxyamide 19d. A mixture of aldol adduct **17** (1.58 g, 3.44 mmol), N-hydroxybenzotriazole (0.59g, 4.35 mmol) and pyridine (279 µL, 3.54 mmol) in 25 mL of acetonitrile was stirred at room temperature for 1 h. Aminophosphonoacetate **18** (1.39 g, 4.35 mmol) in acetonitrile containing a catalytic amount of N,N-dimethylaminopyridine (DMAP) was added to the reaction mixture. After 84 h at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 60 mL each of saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 2.73 g of an oil which was purified by chromatography on silica gel eluting with a linear gradient from 3:1 to 1:1 hexanes - ethyl acetate. Evaporation of the product containing fractions afforded 0.46 g (77%) of the recovered chiral auxiliary and 0.875 g (42.5 %) of the desired ß-hydroxy amide **19d** as an oily mixture of diastereomers epimeric at the methine carbon of the aminophosphonoacetate. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.0 (s, 6H), 0.73 (s, 6H), 0.76 (d, 6H, J = 6.8 Hz), 0.83 (t, 3H, J = 7.5 Hz), 1.4 - 1.7 (m, 5H), 2.23 (m, 1H), 3.65 (d, 6H, d, J_{PH} = 11 Hz), 3.70 (m, 2H), 3.9 (m, 1H), 5.15 - 5.40 (m, 3H), 7.5 (d, 2H, J = 8.5 Hz), 8.2 (d, 2H, J = 8.5 Hz); ^{13}C NMR (Since the spectrum appears quite complex due to the doubling of peaks from the diastereomeric mixture and coupling to phosphorous, only the carbonyl carbons, the aromatic carbons and the dimethylsilyl carbons are given.) δ -3.6 ($SiMe_2$), 100.6, 123.7, 128.3, 142.2 (aromatic carbons), 166.5, 173.9 (carbonyl carbons); IR (neat film) 3440, 3250, 2950, 1745, 1670, 1600, 1540, 1455, 1360, 1244, 1050, 850 cm^{-1}; mass spec (CI with isobutane) 605 (M+1).

ß-Lactam 20. To a solution of amide **19d** (280 mg, 0.463 mmol) in 5 mL of THF was added 180 mg (0.68 mmol) of triphenylphosphine and 0.16 g (0.68 mmol) of di-t-butylazodicarboxylate. The solution was stirred at room temperature for 24 h with periodic monitoring until the infrared peak at 1670 cm^{-1} disappeared. The reaction mixture was concentrated and purified by flash column chromatography eluting with a step gradient from 2:1 ethyl acetate - hexanes to ethyl acetate. The product containing fractions were evaporated to give 0.18 g (66%) of ß-lactam **20** as an oil (diastereomeric at the methine of the aminophosphonate). Attempts to recrystalize **20** failed. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s, 6H), 0.78 (s, 6H), 0.83 (d, 6H, J = 6.9 Hz), 1.00 (t, 3H, J = 7.5 Hz), 1.5 - 1.8 (m, 5H), 2.9 (m, 1H), 3.6 (m, 2H), 3.8 (m, 7H), 5.1 (d, 1H, J_{PH} = 24 Hz), 5.25 (d, 1H, J = 13 Hz), 5.34 (d, 1H, J = 13 Hz), 7.55 (d, 2H, J = 8 Hz), 8.22 (2H, J = 8 Hz); IR (neat film) 2950, 1745, 1520, 1380, 1245, 1050, 850 cm^{-1}; mass spec (CI with isobutane) 587 (M + 1).

ß-Lactam 21 by desilylation of 20. To a solution of ß-lactam **20** (0.107 g, 0.182 mmol) in 4 mL of THF was added n-tetrabutylammonium fluoride (1.8 mL of 1.0 M solution in THF) at room temperature under argon to give a purple solution. After stirring at room temperature for 16 h, 0.5 mL of water was added with vigorous stirring. The stirring was continued for 30 min during which time the purple solution turned to a yellow green. The mixture was concentrated and diluted with 15 mL of ethyl acetate. The ethyl acetate was washed with water and then dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by flash chromatography on silica gel

with 1:1 ethyl acetate - hexanes to give 50 mg (62% yield) of ß-lactam **21** (diastereomeric at the methine position of the aminophosphonate group) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, J = 7.3 Hz), 1.65 (ddt, 1H, J = 14.7, 7.3, 7.3 Hz), 1.79 (ddt, 1H, J = 14.7, 7.3, 7.3 Hz), 1.85 (m, 1H), 2.00 (m, 1H), 2.90 (dt, 1H, J = 7.3, 2.1 Hz), 3.60 (m, 2H), 3.77 (d, 3H, J_{PH} = 11.2 Hz), 3.81 (d, 3H, J_{PH} = 11.2 Hz), 3.8 (m, 1H), 5.13 (d, 1H, J_{PH} = 24 Hz), 5.25 (d, 1H, J = 13 Hz), 5.31 (d, 1H, J = 13 Hz), 7.55 (d, 2H, J= 8 Hz), 8.22 (d, 2H, J = 8 Hz). Irradiation at δ 3.8 resulted in collapse of the the δ 2.9 dt to a triplet. Irradiation at 3.6 resulted in collapse of the δ 1.85 and 2.00 peaks from multiplets to double doublets with J = 6.1, 14.3 Hz and 4.6, 14.3 Hz, respectively; ^{13}C NMR ($CDCl_3$) δ 11.34, 21.23, 36.69, 53.35 (d, J_{CP} = 135 Hz), 53.32, (d, J_{CP} = 6.8Hz), 54.67 (d, J_{CP} = 6.8 Hz), 58.05, 59.46, 59.93, 66.51, 123.87, 128.66, 128.76, 141.66, 165.59, 170.92; IR (neat film) 3420, 1742, 1520, 1345, 1250, 1030, 840 cm^{-1}; mass spec (CI with isobutane) 445 (M + 1).

ß-Lactam aldehyde 22. To a vigorously stirred mixture of pyridinium chlorochromate (0.1 g, 0.45 mmol) and alumina (0.32 g) in 5 mL of methylene chloride in an ice bath was added ß-lactam **21** (0.1 g, 0.225 mmol) in 1 mL of methylene chloride. The resulting dark orange mixture was allowed to warm to room temperature and stirred for 6 h. Diethyl ether (5 mL) was added and the mixture was stirred another 10 min. The mixture was then filtered through a plug of florisil and the eluent was purified by flash chromatography on silica gel eluting with a step gradient from ethyl acetate to ethyl acetate - methanol (2:1) to give 0.05 g of aldehyde **22** as an oil in 50% yield. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, J = 7.2 Hz), 1.76 (m, 2H), 2.85 (m, 1H), 3.2 (dd, 1H, J = 18.5, 5.3 Hz), 3.3 (dd, 1H, J = 18.5, 5.3 Hz), 3.77 (d, 3H, J_{PH} = 11.2), 3.81 (d, 3H, J_{PH} = 11.2 Hz), 4.02 (dt, 1H, J = 5.3, 2.9 Hz), 5.10 (d, 1H, J_{PH} = 25 Hz), 5.24 (d, 1H, J = 13 Hz), 5.36 (d, 1H, J = 13 Hz), 7.55 (d, 2H, J = 8.6 Hz), 8.22 (d, 2H, J = 8.6 Hz), 9.76 (bt, 1H); IR ($CDCl_3$) 1750, 1720 cm^{-1}; mass spec (CI with isobutane) 443 (M + 1).

Carbapenem 23. To a suspension of 2 mg of sodium hydride (washed with hexanes) in 1 mL of THF at -20°C (carbontetrachloride / dry ice bath) was added 38 mg (0.086 mmol) of aldehyde **22** in 5 mL of THF. After 30 min at -20°C, the reaction mixture was allowed to warm to room temperature. The reaction was monitored periodically by silica gel TLC until the starting material was completely consumed (1.5 h). The reaction mixture was filtered and evaporated to give 37 mg of a residual oil. A 30 mg portion of the crude residue was purified by flash chromatography eluting with 1:1 ethyl acetate - hexanes to give 9 mg (41%) of the unstable carbapenem **23**. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.05 (t, 3H, J = 7 Hz), 1.80 (ddq, 1H, J = 14.4, 7.8, 7.2 Hz), 1.86 (ddq, 1H, J = 14.4, 7.8, 7.2 Hz), 2.77 (ddd, 1H, J = 19.7, 8.0, 2.7 Hz), 2.95 (ddd, 1H, J = 19.7, 9.9, 2.7 Hz), 3.14 (dt, 1H, J = 7.8, 2.9 Hz); 4.01 (ddd, 1H, J = 8.0, 9.9, 2.9 Hz), 5.20 (d, 1H, J = 13.7 Hz), 5.40 (d, 1H, J = 13.7 Hz), 6.53 (t, 1H, J = 2.7 Hz), 7.55 (d, 2H, J = 8.6 Hz), 8.22 (d, 2H, J = 8.6 Hz); IR ($CDCl_3$) 1777, 1725 cm^{-1}; UV (CH_2Cl_2) λ_{max} = 263 nm; $[\alpha]_D$ = +72° (c = 0.3, $CHCl_3$); mass spec calcd for $C_{16}H_{16}N_2O_5$ 316.1059: found 316.1055.

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