CHEMISTRY OF PENICILLIN DIAZOKETONES. PART III¹,²:
TRANSFORMATION OF TRICYCLIC BETA–LACTAMS

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Dedicated to Professor George Büchi on the occasion of his 65th birthday.

Abstract - The transformation of tricyclic beta–lactams 1a–c, which are obtained from the corresponding penicillin diazoketones, into carbapenams 7–11 are described. Whereas reduction of 1c with tetra-n-butylammonium borohydride gave cleanly the hydroxy-lactam 3c, the isomeric ketone 1b yielded 3c, together with two tricyclic lactones 5a/5b. Azido-lactones 5c/5d were obtained similarly when we reacted 1b with aluminium chloride/sodium azide. The structural assignment of these novel compounds was based mainly on spectroscopic analysis and comparison with the corresponding tricyclic lactam 3c.

INTRODUCTION

Penicillin³ is a readily available and inexpensive natural antibiotic. Its usefulness has been demonstrated not only as a drug, but also as starting material for the syntheses of other beta-lactam antibiotics⁴ (cephalosporins, in particular), as well as for many fascinating transformations leading to other structures⁵.

Our group has also been involved in the use of penicillin as precursor for the construction of carbapenem, which possesses many structural elements uncommon to the other types of beta-lactam antibiotics⁶. In particular, the heteroatom (sulfur) on the bicyclic ring has been replaced by carbon. This has presented the synthetic chemists with new challenges, and considerable efforts have been made in this direction⁷. In previous papers, we have reported the metal-catalysed decomposition of penicillin diazoketones of the general type 8, which gave either the tricycles 9 and 9c, or, depending upon the nature of the substituents (R'), yielded isopenam¹ of structure 9. The former transformation proceeded in a stereospecific manner, irrespective of the substituents on C-6 (R¹) of the penicillin nucleus⁸, to give a moderate to excellent yield of the insertion product with the formation of a new carbon–carbon bond (C-7/C-8) in 9c.
Unfortunately, starting from "natural" penicillins (3R,5R configuration), it produced always the "undesired" S-configuration at C-7 (C-5 of the corresponding carbapenem). However, we felt that the application of this process might be important because with proper manipulation of the functional groups on penicillin, it could lead to the correct stereochemistry at C-5. Synthetic studies for the transformation of compounds of the structural type into potential carbapenem intermediates were therefore carried out and herein we report our results.

SCHEME I

RESULTS AND DISCUSSION

Conceptually, we envision that bicyclic ketone \( E \), which has been used by many as key intermediate for the preparation of carbapenem derivatives could be derived from tricyclic ketone \( \sim \): (i) Cleavage of the C-2/S bond, to be followed by oxidation of C-2 to a carboxylic function after removal of the extra carbon atoms; (ii) removal of the sulfur appendage from C-8; however, it might also be interesting to study the influence of sulfur substituents at this carbon on the biological properties \( \sim \) of the corresponding carbapenems.
Raney-Nickel desulfurization on 1a gave in low yield, an inseparable mixture of the bicyclic ketone 2a and its unsaturated isomers 2b; the latter could be completely converted into the conjugated isopropylidene ketone by treatment with triethylamine13, and allowed separation from 2a by chromatography. Nevertheless, we quickly abandoned this approach due to the limited possibilities for further transformation, as well as the poor yield of the process.

It occurred to us that we should be able to cleave the C-21S bond by thermolysis of the sulf oxide, in analogy to the Morin reaction14, which has found numerous synthetic applications. Attempted direct oxidation of 1a with a variety of mild oxidants (m-chloroperbenzoic acid, periodate, ozone etc.) were met with limited success: complex mixtures of products usually resulted. Since competing reactions of the ketone carbonyl group (IR absorption: 1160 cm⁻¹) might complicate the desired oxidation we decided to protect this carbonyl group by reduction to the diol.

Whereas reduction of the unsubstituted beta-lactam 1a (R¹ = R² = H) proceeded smoothly with sodium borohydride to afford the alcohol 3a as a single diastereoisomer (see below for structural proof), the reduction of the phthalimido-substituted derivatives 1b and 1c gave complex mixtures of products whose ¹H NMR spectra revealed that reduction of the phthalimido carbonyl groups had also taken place.

In order to suppress the concomitant reduction of the other carbonyl function, we chose to use tetra-n-butylammonium borohydride16, which can be used in methylene chloride and at low temperature. Exposure of ketone 1c in methylene chloride to an equimolar amount of the hydride at -78°C gave cleanly the alcohol 3c (60 %), whose structure could further be confirmed spectroscopically via the acetate 4c (positive NOE between H-5 and H-7); however reduction of the
7a isomer 1b required higher temperature (0-20°C) and the major product was found to be 3c (50%), together with two isomeric (mircronanalysis, NMR) compounds 5a/5b (7% and 14% respectively). Alcohol 2b was never observed.

Based on the following spectroscopic evidence (see also Table I), these novel tricyclic structures could be assigned as drawn: (i) H-5 has been shifted 0.8 ppm down-field in the proton NMR spectrum (as compared to 3c) indicating an ester function and not an alcohol; (ii) no OH coupling could be observed; (iii) C-8 (lactone) appears about 10 ppm towards higher field than the corresponding lactam in the \(^{13}\)C NMR spectrum; (iv) Protons α and β to the nitrogen are greatly influenced by the addition of trifluoroacetetic acid and with a down-field shift (presence of basic nitrogen); (v) in 5a, positive NOE could be observed between H-1 and H-7, which are probably oriented in a 1,3-diaxial relationship; (vi) the signals (167.1/168.5 ppm) from the carbonyls of the phthalimido group in 5a are much broader than the corresponding ones (only appear as one peak) in 5b. This phenomenon could be explained by assuming hindered rotation of the phthalimido group, possibly due to a hydrogen bridge with the neighboring NH function. This correlates also with the measurement of a distinct coupling (5 Hz) between H-4 and NH in 5a whereas only line-broadening of the corresponding signals could be detected in 5b.

To account for the formation of the observed product, we assume that due to steric hindrance from both sides of the ketone function, reduction does not take place in 1b at low temperature. At higher temperature, epimerization of the phthalimido group to 1c proceeds hydride attack
### TABLE I

$^1$H and $^{13}$C NMR Chemical Shifts (Multiplicities and Coupling Constants) of Tricyclic Lactones $^5a$-$^d$ and Lactam $^5c$

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<th>NMR</th>
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from the "re" face to give $3_c$, while direct attack from the "si" face would yield initially the diastereomeric alkoxide, which because of close proximity to the beta-lactam carbonyl would also lead to lactone formation\textsuperscript{17}. The ease of formation of such bicyclic structure could further be demonstrated when we heated $1_b$ in tetrahydrofuran, in the presence of aluminium chloride/sodium azide\textsuperscript{18}. A quantitative yield of a 1:1 mixture of the azido-lactone $5_c/5_d$ was isolated.

Our attention was then directed to further transformation of these tricyclic alcohols. Indeed, treatment of either $3_a$ or $3_c$ with excess sodium metaperiodate produced a mixture of sulfoxides ($6_a/6_a'$ and $6_b/6_b'$ respectively) in excellent yield. As depicted in Scheme II, these sulfoxides underwent smooth conversion into carbapenam structures $7-11$ as planned, under a variety of conditions analogous to the Morin reaction\textsuperscript{14}. Interestingly the product with structure $12$, which corresponds to the penicillin-cephalosporin transformation route, could not be found.
Direct functionalization of the isopropylidene group (7, 9, and 11) and its transformation into the carboxylic acid moiety (with the loss of two carbons) was not successful. However, upon ozonolysis, 7b was converted in 80 % yield to the methyl ketone 13. Unfortunately, further attempts on 13 or its acetate 14 to remove oxidatively the last extra carbon were failed. 

CONCLUSION

Despite the fact that this sequence of transformation could not provide an entry into the carbapenem structure with the proper functional groups at this time, we believe that the readily available penicillin diazoketones, together with the demonstrated ease of transformation into other tricyclic systems, could be important for the stereoselective synthesis of other heterocyclic natural products.

EXPERIMENTAL

General methods and materials. Melting points were determined on a Reichert hotstage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 421 spectrometer and are reported in cm⁻¹. Proton and carbon-13 magnetic resonance (¹H and ¹³C NMR) were obtained either on a Varian HA 100 or a Bruker WH-90 DS spectrometer in CDCl₃ with tetramethylsilane as an internal standard, unless otherwise stated, and chemical shifts are given in parts per million (δ). Mass spectra were recorded with a Varian Mat CH-7 spectrometer. Microanalyses were performed by the Mikroanalytisches Labor of the Inst. für Physikalische Chemie, University of Vienna, Austria. Chromatography was performed on silica gel (Kieselgel 60, E. Merck), using ethyl acetate/dichloromethane mixtures as eluents.

Desulfurization of 1a. The tricyclic ketone 1a (325 mg) was treated with Raney nickel, and then followed by triethylamine, under similar conditions as reported by Ernst. The ketones 2a (40 mg, 15 %) and 2b (70 mg, 25 %) were isolated after chromatography. 2a: waxy solid; ¹H NMR: δ 0.84 (d, 3, J = 7 Hz), 1.04 (d, 3, J = 7 Hz), 2.04-2.34 (m, 1), 2.44 (dd, 1, J = 18.8 Hz), 2.72 (dd, 1, J = 18, 7 Hz), 2.98 (dd, 1, J = 17, 2.5 Hz), 3.58 (dd, 1, J = 17, 5 Hz), 3.75-4.06 (m, 2). 2b: mp 80-80° C, ¹H NMR: δ 2.11 (s, 3), 2.20 (s, 3), 2.53 (dd, 1, J = 18, 8 Hz), 2.83 (dd, 1, J = 18, 7 Hz), 2.95 (dd, 1, J = 16, 2.5 Hz), 3.52 (dd, 1, J = 16.5 Hz), 3.98 (dddd, 1, J = 8, 7, 5, 2.5 Hz).

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Tricyclic alcohol 3a. To a cooled (ice-bath) suspension of the tricyclic ketone 1a (4.05 g) in 250 ml of MeOH was added portionwise 1 g of sodium borohydride. After the addition was completed, the mixture was stirred at 0°C for another 20 min, and then to this mixture was added excess brine. The resulting mixture was extracted thoroughly with dichloromethane (CH₂Cl₂) and the combined organic layers were dried (MgSO₄) and concentrated. Chromatography of the crude residue gave 2.62 g (64%) of 2, mp 125-127°C; [α]D +216 (c 1.0, CHCl₃); IR (CHCl₃) 3335, 1761; ¹H NMR: δ 1.52 (s, 3H), 1.56 (s, 3H), 2.98 (dd, 1, J = 17, 3.5 Hz), 3.37 (dd, 1, J = 17, 5.3 Hz), 3.57 (d, 1, J = 2.3 Hz), 3.78 (d, 1, J = 2.3 Hz), 3.82 (dd, 1, J = 5.3, 3.5 Hz), 4.56 (t, 1, J = 2.3 Hz). Anal. Calcd for C₉H₁₃N₂O₂S: C, 54.24; H, 6.57; N, 7.03; S, 16.08. Found: C, 54.33; H, 6.58; N, 6.96; S, 16.16.

Tricyclic alcohol 3c. A solution of the ketone 1b (3 g) and 2.5 ml of triethylamine in CH₂Cl₂ (10 ml) was stirred at room temperature for 30 min. The mixture was concentrated in vacuo, and excess triethylamine was removed by repeated addition and evaporation of toluene. The resultant foam was re-dissolved in 50 ml of CH₂Cl₂, and cooled to -78°C. To this stirred solution was added, in one portion, 0.55 g of tetra-n-butylammonium borohydride. The mixture was stirred further at this temperature, until complete disappearance of starting material. It was then quenched with one equivalent of acetic acid and poured into water. After separation of the layers, the aqueous phase was extracted once with CH₂Cl₂. The combined organic layers were dried and concentrated to give an oil, which was chromatographed to give 1.8 g (60%) of the alcohol 3c, mp 207-210°C; IR (KBr) 3425, 1780, 1760, 1720, 1390; [α]D -80 (c 0.011, CHCl₃); NMR (see Table I). Anal. Calcd for C₁₇H₁₆N₂O₄S: C, 59.29; H, 4.68; N, 8.13. Found: C, 58.94; H, 4.72; N, 8.04.

Reduction of ketone 1b: Reaction of 5.05 g of the tricyclic ketone 1b with 0.925 g of tetra-n-butylammonium borohydride in 100 ml of CH₂Cl₂ at 0°C, under analogous condition as described above, yielded after chromatography, 360 mg (7%) of 5a, 700 mg (14%) of 5b, and 2.5 g (50%) of 3c.

5a: amorphous powder; [α]D +50 (c 0.01, CHCl₃); IR (KBr) 3350, 1770, 1740, 1710, 1390; mass spectrum (70 eV), m/z (rel intensity) 345 (M⁺ + 1, 5), 344 (M⁺, 27), 311 (46), 91 (100); NMR (see Table I). Anal. Calcd for C₁₇H₁₆N₂O₄S: C, 59.29; H, 4.68; N, 8.13. Found: C, 58.96; H, 4.67; N, 8.17.

5b: mp 198-203°C; IR (KBr) 3360, 1745, 1729, 1390; [α]D +184 (c 0.04, CHCl₃); NMR (see Table I). Anal. Calcd for C₁₇H₁₆N₂O₄S: C, 59.29; H, 4.68; N, 8.13. Found: C, 58.98; H, 4.67; N, 8.17.
Acetate A. This compound was prepared from the corresponding alcohol 3c by the reaction with excess dimethylaminopyridine (DMAP) and acetic anhydride: foam; \( ^1H \) NMR: \( \delta \) 1.57 (s, 3), 1.61 (s, 3), 2.17 (s, 3), 3.95 (d, 1, \( J = 2 \) Hz); 4.09 (d, 1, \( J = 2 \) Hz), 4.17 (d, 1, \( J = 3 \) Hz), 5.11 (t, 1, \( J = 2 \) Hz), 5.30 (d, 1, \( J = 3 \) Hz), 7.68-7.94 (m, 4).

Azido-lactones 5c and 5d. Tricyclic ketone 1c (100 mg, obtained by triethylamine epimerization of 1b as before) was dissolved in 2 ml of tetrahydrofuran (THF). To this was added a solution of aluminium chloride (40 mg) and sodium azide (80 mg) in 5 ml of THF. The mixture was refluxed for 2 h, cooled, and then concentrated in vacuo. The residue was chromatographed on silica gel to give 5c (50 mg, 45%) and 5d (50 mg, 45%). mp 176-180\(^\circ\) C; \([\alpha]_D^20\) -4.9\(^\circ\) (c 0.12, CHCl\(_3\)). NMR (see Table I).

Anal. Calcd for C\(_{11}\)H\(_{15}\)N\(_5\)O\(_4\)S: C, 52.98; H, 3.92; N, 18.11. Found: C, 52.27; H, 4.00; N, 11.76.

5d: mp 164-161\(^\circ\) C; \([\alpha]_D^20\) +91\(^\circ\) (c 0.145, CHCl\(_3\)). NMR (see Table I).

Sulfoxides 6a/6a'. A suspension of sodium metaperiodate (4.36 g) in 10 ml of water and 30 ml of isopropanol was added in one portion to a stirred solution of the alcohol 2 (2.03 g) in 50 ml of THF. The mixture was stirred for 20 h at room temperature, during which a heavy precipitate was formed. It was then diluted with water and CH\(_2\)Cl\(_2\), and after separation of the layers, the aqueous layer was extracted thoroughly with CH\(_2\)Cl\(_2\). The combined organic layers were washed once with brine and dried (MgSO\(_4\)). Removal of solvent yielded 1.1 g of the desired sulfoxides 6a/6a' (80%), which could be used without further purification.

Sulfoxides 6b/6b'. Analogously, the sulfoxides 6b/6b' were prepared from 3c in 85% yield. An analytical sample of the \( \alpha \)-sulfoxide (6b') was obtained after chromatography as a foam. 6b': \([\alpha]_D^20\) -35.5\(^\circ\) (c 1.05, CHCl\(_3\)); IR (KBr) 3300, 1700, 1720, 1390, 1280, 1190, 1120; \( ^1H \) NMR: \( \delta \) 1.57 (s, 3), 1.65 (s, 3), 3.44 (d, 1, \( J = 1.8 \) Hz), 3.91 (d, 1, \( J = 2.2 \) Hz), 4.96 (dt, 1, \( J = 9 \) Hz, 2 Hz), 5.35 (d, 1, \( J = 3 \) Hz), 5.55 (d, 1, \( J = 9 \) Hz), 7.68-7.90 (m, 4). Anal. Calcd for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_5\)S: C, 56.65; H, 4.48; N, 7.77; S, 8.90. Found: C, 56.59; H, 4.73; N, 7.30; S, 8.34. \( \delta ^1H \) NMR: \( \delta \) 1.30 (s, 3), 1.62 (s, 3), 4.07 (d, 1, \( J = 2.3 \) Hz), 4.12 (d, 1, \( J = 2.7 \) Hz), 4.38 (d, 1, \( J = 3.3 \) Hz), 4.64 (br t, 1, \( J = 2.7 \) Hz), 5.39 (d, 1, \( J = 3.3 \) Hz), 7.68-7.90 (m, 4).

Hydroxy-carbapenam 7a. A mixture of the sulfoxides 6a/6a' (150 mg) and mercaptobenzthiazole (127 mg) was heated at 100\(^\circ\) C for 1.5 h. After cooling, the solvent was removed in vacuo, and
the residue was taken up in CH₂Cl₂. The organic solution was washed successively with 0.1 N NaOH and brine, and dried (MgSO₄). Evaporation of solvent gave 160 mg (60 %) of the product 78, which could be used without further purification. An analytical sample was obtained after chromatography: mp 150-152°C; [α]²⁰D -440° (c 0.1, CHCl₃), ¹H NMR: 8.1.78 (br s, 3), 2.84 (dd, 1, J = 15.5, 2.5 Hz), 3.20-3.50 (m, 2), 3.92 (ddd, 1, J = 10, 5.2 Hz), 4.34 (br, 1), 4.58-4.76 (m, 1), 5.00-5.24 (m, 3), 7.35-7.50 (m, 2), 7.76-8.00 (m, 6); ¹³C NMR: 20.3 (C-8), 41.4 (C-5), 54.7 (C-3), 63.2/67.2 (C-4/C-1), 78.2 (C-2), 113 (C-9), 140.4 (C-7), 169.3 (C-6), 121.6/122.3/125.6/127.0/136.4/153.2/176.1 (aromatic carbons). Anal. Calcd for C₁₆H₁₆N₂O₅S₃: C, 52.72; H, 4.42; N, 7.69; S, 26.39. Found: C, 52.72; H, 4.38; N, 7.61; S, 26.74.

Hydroxy-carbapenam 7b. This was prepared similarly according to the procedure described for the preparation of 7a. Thus, 1.06 g of 6b/6b' afforded 0.7 g (47 %) of 7b, together with 0.1 g of recovered starting material, after column chromatography: mp 198-204°C; [α]²⁰D -133° (c 1.28, CHCl₃), ¹H NMR (in part) H-1: 4.56 (d, J = 4.5 Hz) and 4.48 (d, J = 3.5 Hz); H-2: 4.98 (t, J = 4.5 Hz) and 5.10 (t, J = 3.5 Hz); H-3: 3.80 (dd, J = 9.5, 3.7 Hz), 4.20 (dd, J = 9.5, 2 Hz), 4.55 (br d, J = 2 Hz), 5.23 (d, J = 2 Hz); mass spectrum (FAB): 459 (M⁺ + 1).

Vinyl sulfoxides 8. A mixture of the sulfoxides 6b/6b' (120 mg) and ethyl propiolate (1 ml) in 10 ml of toluene was heated at 110°C for 4 h, under an atmosphere of argon. The mixture was cooled, concentrated in vacuo, and excess ethyl propiolate was removed by repeated addition and evaporation of toluene. The resultant solid was triturated with CH₂Cl₂ and diisopropyl ether to yield 70 mg of the product 8 as a 1/1 diastereomeric mixture: IR (KBr) 3430, 1771, 1725, 3196, 1390; ¹H NMR (in part) H-1: 4.56 (d, J = 4.5 Hz) and 4.48 (d, J = 3.5 Hz); H-2: 4.98 (t, J = 4.5 Hz) and 5.10 (t, J = 3.5 Hz); H-3: 3.33 (dd, J = 9, 4.5 Hz) and 3.35 (dd, J = 9.5, 3.5 Hz); H-5: 4.79 (dd, J = 9, 2.2 Hz) and 4.40 (dd, J = 9.5, 2.2 Hz); H-6: 5.15 (d, J = 2 Hz) and 5.23 (d, J = 2 Hz); mass spectrum (FAB): 459 (M⁺ + 1).

3-Acetyltiicarbapenam 9. To the hot (110°C) solution of sulfoxides 6b/6b' (80 mg) and acetic anhydride (114 mg) in toluene (10 ml) was added triphenylphosphine (64 mg). The reaction mixture was heated for 20 min, then cooled and concentrated. After chromatography of the residue, 54 mg (62 %) of the carbapenam 9 was obtained as an oil: IR(CHCl₃) 3551, 1771, 1725, 1665, 1390; ¹H NMR: 8.1.83 (br s, 3), 2.38 (s, 3), 3.80 (dd, 1, J = 9.5, 3.7 Hz), 4.20 (dd, 1, J = 9.5, 2 Hz), 4.55 (br d, 1, J = 3.7 Hz), 4.64 (t, 1, J = 3.7 Hz), 5.42 (d, 1, J = 2 Hz),
5.22-4.46 (m, 2), 7.68-7.98 (m, 4); mass spectrum (70 eV), m/z (rel intensity) 344 (0.5), 326(26), 218(78).

Symmetrical disulfide 10. To the cooled (-10°C) suspension of the hydroxy-carbapenam 7b (150 mg) and acetic acid (17.6 mg) in 10 ml of CH₂Cl₂ was added a solution of triphenylphosphine (77 mg in 2 ml of CH₂Cl₂). The reaction mixture became homogeneous immediately and after stirring for another 5 min, it was concentrated and the residue was chromatographed to give 60 mg (60 %) of the disulfide 2, mp 242-245°C; [α]D²⁰ -88° (c 0.05, DMSO); IR(KBr) 3450, 1780, 1720, 1390; H NMR: 6 1.83 (br s, 3), 2.46 (d, 1, J = 4.5), 3.52 (dd, 1, J = 9, 4 Hz), 4.20 (dd, 1, J = 9, 2 Hz), 4.45-4.60 (m, 1), 4.71 (br quint, 1, J = 4.5 Hz), 5.12-5.28 (m, 1), 5.35 (d, 1, J = 2 Hz), 5.40-5.52 (m, 1), 7.65-8.00 (m, 4); FD-MS: 687 (M⁺ + 1).

Acetate 11. Acetylation of hydroxy-carbapenam 7b with excess pyridine and acetic anhydride gave the acetate 11 in quantitative yield as a foam. ¹H NMR: 6 1.75 (br s, 3), 2.14 (s, 3), 3.68 (dd, 1, J = 9, 4.5 Hz), 4.56 (br d, 1, J = 4.5 Hz), 4.70 (dd, 1, J = 9, 2 Hz), 5.04-5.36 (m, 2), 6.08 (t, 1, J = 4.5 Hz), 7.06-7.24 (m, 2), 7.48-7.72 (m, 6); mass spectrum (FAB): 552 (M⁺ + 1).

Methyl ketone 13. A solution of the hydroxy-carbapenam 7b (100 mg) in 10 ml of THF and 15 ml of CH₂Cl₂ was cooled to -78°C, and ozone was passed into this solution until a blue color persisted. After excess ozone was driven off with nitrogen, excess dimethyl sulfide (2 ml) was added and the mixture was allowed to come to room temperature. Solvent was then removed in vacuo and the residue was chromatographed to give 50 mg (50 %) of ketone 13 as an amorphous solid: [α]D²⁰ +117° (c 1.0, DMSO); IR (KBr) 3480, 3320, 1780, 1720, 1390; ¹H NMR (CDCl₃/DMSO-d₆) 6 2.43 (s, 3), 3.55 (dd, 1, J = 9, 4 Hz), 4.43 (d, 1, J = 4 Hz), 4.78 (dd, 1, J = 9, 2 Hz), 5.04 (br q, 1, J = 4 Hz), 5.26 (d, 1, J = 2 Hz), 6.14 (br d, 1, J = 5.5 Hz), 7.14-8.00 (m, 8); mass spectrum (FAB) 512 (M⁺ + 1).

Acetate 14. Acetylation of methyl ketone with acetic anhydride (1.2 equivalent) and DMAP (1.1 equivalent) gave the desired product in quantitative yield as an amorphous solid: [α]D²⁰ -30° (c 0.1, DMSO); IR(KBr) 1780, 1755, 1720, 1390; ¹H NMR: 6 2.12 (s, 3), 2.40 (s, 3), 3.68 (dd, 1, J = 9, 4.5 Hz), 4.59 (d, 1, J = 4.5 Hz), 4.80 (dd, 1, J = 9, 2 Hz), 5.32 (d, 1, J = 2 Hz), 6.31 (t, 1, J = 4.5 Hz), 7.10-8.00 (m, 8); mass spectrum (FAB) 554 (M⁺ + 1).
ACKNOWLEDGEMENT

The expert technical assistance of K. Baumann, Ch. Mayerl, and K. Wagner is gratefully acknowledged.

NOTES AND REFERENCES

1. Part II, see preceding accompanied paper.
2. Part of this work has been reported in the 12th Northeast Regional meeting of the American Chemical Society held in the University of Vermont, June 27-30, 1982.
3. Penicillins are being referred to those which are obtainable directly by fermentation.
8. Examples of this reaction were first reported by I. Ernest, Tetrahedron, 1977, 33, 547. The clavam \( C \) was subsequently observed by R.J. Ponsford, Tetrahedron Lett., 1980, 21, 2451, and also by us; see ref. 9.
10. In principle, the diazoketone derived from the optical antipode of any natural penicillin will yield the correct carbon-carbon bond:

\[
\begin{align*}
H & \quad \text{R} \quad \text{S} \quad \text{O} \quad \text{N} \quad \text{CHN}_2 \\
\text{O} & \quad \text{N} \quad \text{=O} \quad \text{S} \quad \text{CHN}_2 \\
\end{align*}
\]
13. Similar results have also been obtained by I. Ernest on the 6-acylamino series; see reference 8.
19. We have tried, for example, the following sequence of reaction: i) LDA/-78°C; ii) TMSCl; iii) ozonolysis.
20. The carboxyl function can be replaced by other groups, such as the tetrazoyl moiety, and still retains significant antibacterial activities; see A. Andrus, J.V. Heck, B.G. Christensen, and B. Partridge, J. Am. Chem. Soc., 1984, 106, 1808.

Received, 8th December, 1986