

CHEMISTRY OF PENICILLIN DIAZOKETONES. PART II¹: FROM BETA-LACTAM TO BETA-LACTONE

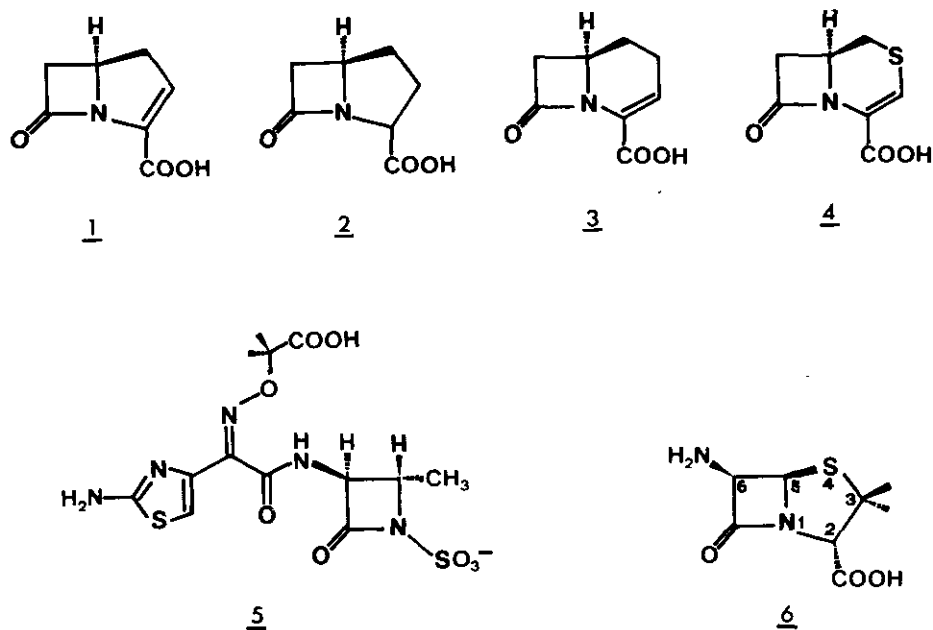
Hans Ludescher, Ching-Pong Mak, Gerhard Schulz, and Hans Fliri

SANDOZ Forschungsinstitut, 1235 Wien, Brunnerstraße 59, Austria

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

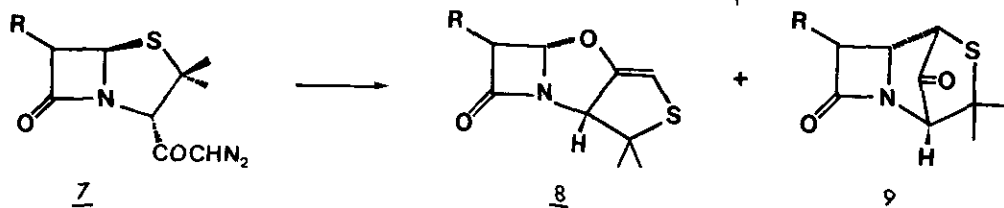
Abstract - Carbenes formed by transition metal catalyzed decomposition of penicillin-derived diazoketones can undergo different reaction pathways, depending on the presence or absence of the gem-dimethyl group. In the presence of the gem-dimethyl group products are formed via a sulfur ylide intermediate. Bis-nor derivatives undergo Wolff-rearrangement into ketenes which react further to give isopenams. If an hydroxyethyl substituent is present at C-6 of the starting material the original β -lactam is converted into a β -lactone.

β -Lactams with carbon substituents in position 4 have attracted considerable attention recently. This structural element is not only present in natural products such as carbapenems (1)² and carbapenams (2)², but also in synthetic antibacterial agents such as carba-cephems (3)³, iso-cephems (4)³ and some monobactams⁴, e.g. azthreonam (5). Of particular interest is the configuration of the methyl substituent in 5 (this stereochemistry renders bicyclic molecules biologically inactive⁵).



6-APA (6) is one of the most readily available natural β -lactams and it is relatively inexpensive. It has three chiral centers and some of the possible diastereoisomers have been described^{5,6}. Thus we began some time ago to investigate intramolecular reactions to replace the C-5/S bond in penicillin derivatives by carbon-carbon bonds in a stereospecific manner. In particular, we concentrated on intramolecular reactions of carbenes generated by photochemical or heavy-metal catalyzed decomposition of diazoketones. As reported previously by us¹ and others⁷, diazoketones (7) derived from penicillanic acid derivatives with natural configuration at C-2 and C-5 afford mixtures of clavams (8) and tricyclic ketones (9), and in both cases the new bonds are formed with inversion of configuration at C-5 (Scheme I). In the present communication we report the synthesis of novel penicillanic acid derivatives with unnatural configuration at C-2 and C-5, and the results obtained upon the decomposition of the corresponding diazoketones.

Scheme 1

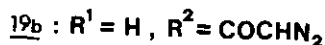
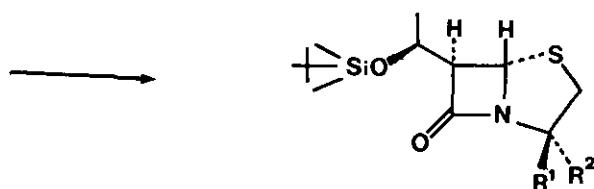
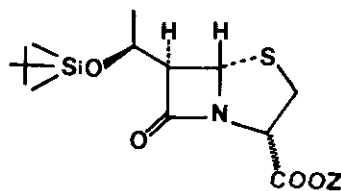
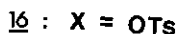
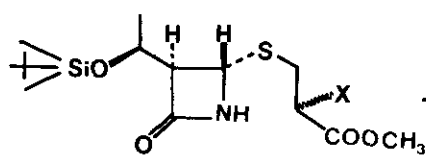
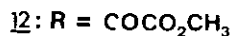
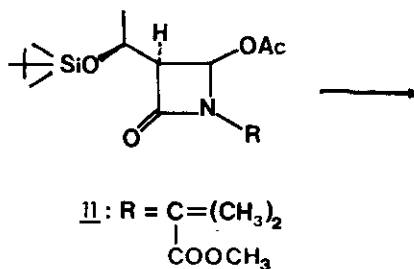
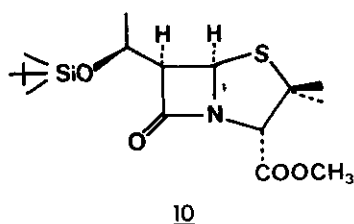


a: R = H

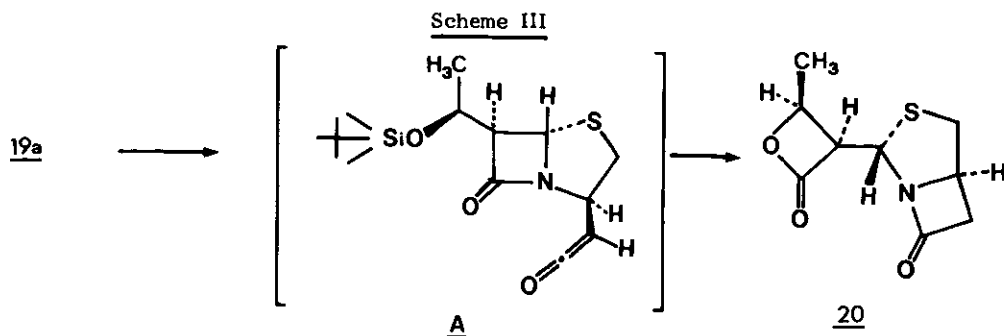
b: R = α -phthalimidoc: R = β -phthalimidod: R = α -1(R)-hydroxyethyl

The synthesis of a penicillanic acid derivative (19a) with unnatural stereochemistry at C-2 and C-5 is outlined in Scheme II. The tert-butyldimethylsilyl ether (TBDMS) of 6(R)-[(1(S)-hydroxy)ethyl]penicillanic acid methyl ester (10)^{8,9} was converted to the monocyclic azetidinone 13⁹ by sequential treatment with mercuric acetate¹⁰, ozone¹¹, and methanol/triethylamine with an overall yield of 82 %. Construction of the second ring was initiated by the displacement of the acetoxy group in 13 with racemic methyl 2-hydroxy-3-mercaptopropionate¹², thus providing 14 as a mixture of diastereomers in 58 % yield, with the expected trans-substitution on the β -lactam ring. Rather than attempting to separate the isomers at this point, we proceeded further with the synthesis. Cyclization of 14 to the bicyclic structures 17 proved to be a major problem, and poor yields of products were consistently obtained¹³. Treatment of 14 with tosyl chloride in the presence of dimethylaminopyridine (DMAP) afforded a mixture of diastereomeric chlorides 15 (12 %) and tosylates 16 (85 %), which were very unstable and decomposed even during storage at -20°C . Immediate exposure of a mixture of 15 and 16 to 2N sodium hydroxide and tetra-n-butylammonium bromide in dichloromethane provided a mixture of the bis-nor-penicillin ester 17 in only 8-10 % yield! Hydrolysis of these esters, activation of the resultant acids via formation of mixed anhydrides, followed by diazomethane treatment under the usual conditions¹⁴ yielded the diazoketones 19. The β -substituted isomer 19a⁹ could be isolated in pure form by column chromatography, but we were unable to obtain 19b completely free from its isomer. The assignment of the configuration at C-2 in 19a was based on spectroscopic evidence: a positive NOE could be observed between the proton signal of the diazomethyl group at 5.76 ppm (singlet) and that of H-5 at 4.90 ppm (doublet, $J = 2$ Hz).

Scheme II



Exposure of 19a to a catalytic amount of rhodium acetate in hot benzene provided one major product which decomposed during attempted purification. The infrared spectrum of the crude product shows, in addition to the 1780 cm^{-1} absorption of the β -lactam carbonyl, a strong band at 1825 cm^{-1} . By performing the experiment in an NMR-tube with deuterobenzene as solvent (60°C), we were able to observe the time-dependent formation of the major product. The β -lactone structure 20⁹ was assigned and could be firmly secured through decoupling experiments (scheme III). In particular, the initial doublet of quartet of the methine proton from the silyloxyethyl group centered at 4.20 ppm underwent a downfield shift by 0.2 ppm.



Since the decomposition reaction of the diazoketone **19a** took an unexpected course, we were interested in clarifying whether it is due to the lack of the gem-dimethyl group, or perhaps due to a different type of substituent at C-6 (until this time, all known reactions of this type were performed on penicillin derivatives either with a nitrogen substituent or no substituent at C-6). Thus, using 6(S)-[(1(R)-hydroxy)ethyl]penicillanic acid methyl ester⁸ as starting material, we prepared using analogous conditions the diazoketone **7d**⁹, which is antipodal to **19a** at all chiral centers, but has additionally the gem-dimethyl group. Treatment of **7d** with a catalytic amount of copper acetylacetonate in hot benzene resulted in smooth conversion into **8d** (31 %) and **9d** (20 %) (Scheme I). Whereas thermal decomposition of **7d** proceeded "normally" via the sulfur ylide to give the observed products, the corresponding bis-nor analog **19d** probably rearranged first to the ketene **A**, which underwent further transformations to give the β -lactone **20** (Scheme III).

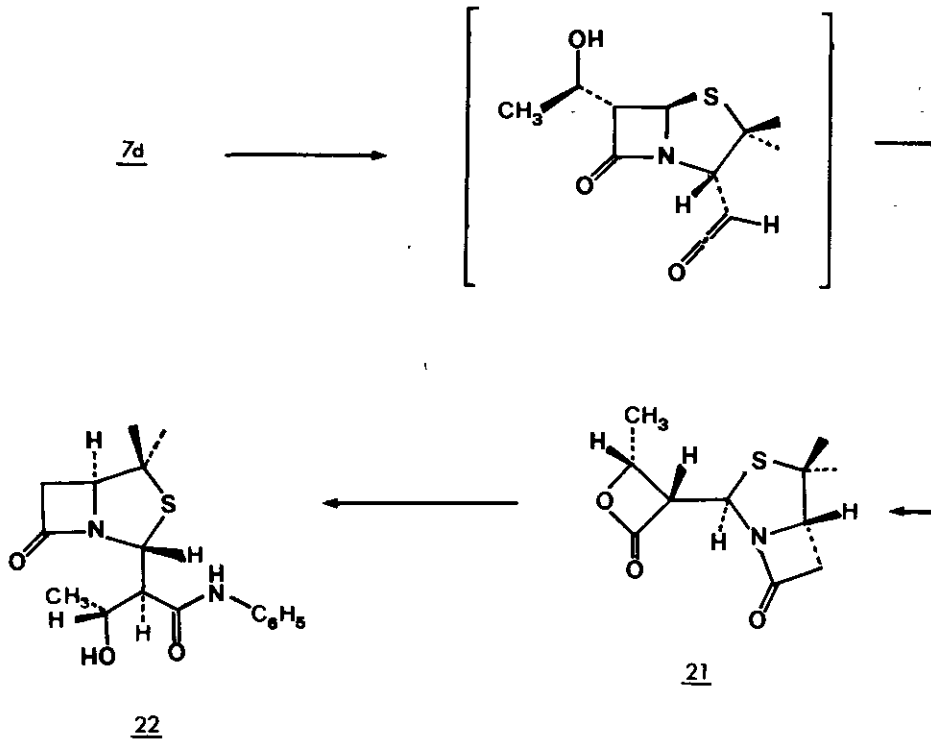
Photochemical Wolff-rearrangement of penicillanoyl diazoketones in aqueous dioxane has been used to convert penicillanic acids into their higher homologs¹⁵. We assumed that irradiation of **7d** in an inert solvent would generate a ketene similar to the intermediate postulated for the formation of lactone **20**. Upon irradiation of **7d** in benzene, a single new product **21** was formed (tlc and nmr), which decomposed during attempted purification by chromatography. The infrared spectrum of the crude product again shows the 1820 cm^{-1} band, which is characteristic of β -lactones, besides the usual carbonyl absorption at 1770 cm^{-1} for the β -lactam. The assigned structure could further be corroborated by the formation of the crystalline anilide **22**⁹ upon treatment of **21** with aniline/ DMAP (Scheme IV).

Scheme V gives a possible mechanistic interpretation of these results.

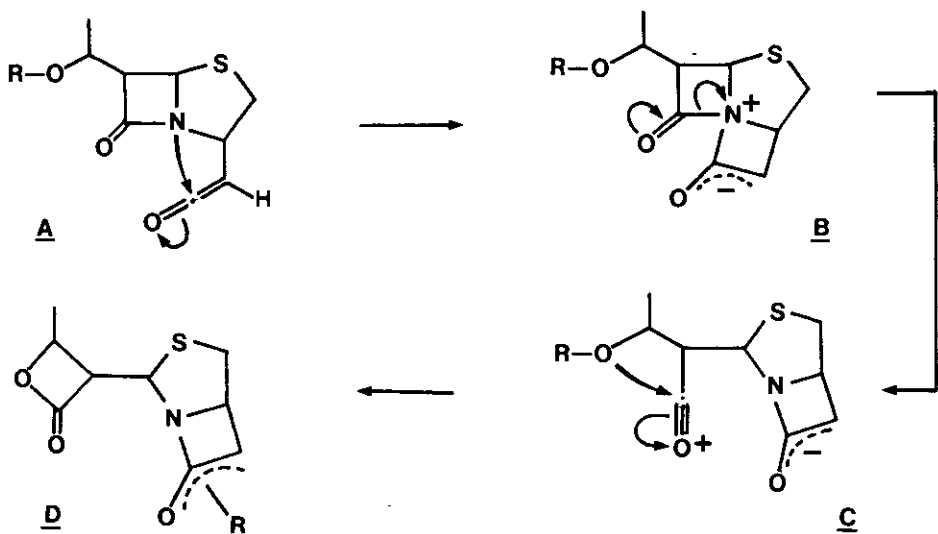
In the absence of external nucleophiles, the penicillanoyl ketenes **A** generated by Wolff-rearrangement of diazoketones **19** and **7d** react intramolecularly with the β -lactam nitrogen to give ylide **B** which can dissociate into ylide **C** thus generating another highly

electrophilic center. Ring closure to the β -lactone with concomitant loss of the silyl protective group generates D and aqueous work-up would give the observed products.

Scheme IV



Scheme V



The question remains: why in the rhodium-catalyzed reaction compounds of type 7 give products derived from sulfur-ylide intermediates, whereas the corresponding bis-nor-penicillins 19 are converted into products via Wolff-rearrangement? There are two nucleophilic centers present in the molecules which are susceptible to intramolecular attack by the rhodium-generated carbene: the β -lactam nitrogen and the sulfur. Obviously in the case of gem-dimethyl compounds 7 the carbene is generated in a conformation where the sulfur is in close proximity to it and ring closure to the sulfur ylide is possible without prior conformational changes. Such facilitating effects of gem-dimethyl group on ring closure reactions are well documented and have been thoroughly investigated¹⁶. In the absence of such a gem-dimethyl effect the carbene may be generated in a different conformation with a larger distance between the carbene and an internal nucleophile. In this case Wolff-rearrangement to a (more stable) ketene occurs faster than conformational changes leading to the required proximity for carbene-derived ylide formation.

Internal capture of penicillin-derived carbenes by the β -lactam nitrogen has also been observed during the preparation of homologous penicillins¹⁵ and in transition metal catalyzed reactions of diazoketones derived from them⁷. A similar ring closure reaction is used on an industrial scale in the synthesis of carbapenem antibiotics¹⁷.

Interesting aspects arise upon a careful stereochemical analysis of the molecules described in this work. Our plan had been to utilize the natural stereochemistry of penicillin for the stereospecific construction of penicillin derivatives with unnatural configuration at C-3/C-5 and then replace the C-S bond by a carbon-carbon bond of natural configuration. Instead, however, the obtained product 20 was an isopenicillin with unnatural configuration at C-5! On the other hand, starting from 7 (with natural configuration) isopenicillin 21 is obtained with natural configuration at C-5. This reaction thus constitutes a rapid method to replace the C-5/S bond of a penicillin derivative stereospecifically by a carbon-carbon bond with retention of configuration.

REFERENCES

- 1) Part I: C.P. Mak, K. Baumann, F. Mayerl, C. Mayerl, and H. Fliri, Heterocycles, 1982, 19, 1647.

- 2) For a comprehensive listing of the structures of natural carbapenems and carbapenams see: Y. Fukagawa, M. Okabe, T. Yoshioka, and T. Ishikura in "Recent Advances in the Chemistry of β -Lactam Antibiotics", Chem. Soc. Spec. Publ. No. 52, p 163, A.G. Brown, and S.M. Roberts, ed., 1985.
- 3) A review of nuclear analogs of Penicillins and Cephalosporins is given in "Chemistry and Biology of β -Lactam Antibiotics", Vol. 2, R.B. Morin, and M. Gorman, ed., Acad. Press, 1982.
- 4) W.H. Koster, C.M. Cimarusti, and R.B. Sykes in "Chemistry and Biology of β -Lactam Antibiotics", Vol. 3, p 339, R.B. Morin, and M. Gorman, ed., Acad. Press, 1982.
- 5) R. Busson, and H. Vanderhaeghe, J. Org. Chem., **41**, 2561 (1976). See also: Topics in Antibiotic Chemistry, Vol. 4, p 155 ff, P.G. Sammes ed., Ellis Horwood LTD, 1980.
- 6) S. Kukolja, J. Am. Chem. Soc., 1971, **93**, 6269.
- 7) a) I. Ernest, Tetrahedron, 1977, **33**, 547.
b) R. Ponsford, Tetrahedron Lett., 1980, **21**, 2451.
- 8) V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto, and R. Rizvi, Tetrahedron Lett., 1981, **22**, 3485.
- 9) Selected physical data:
10: mp 63^o C; IR(KBr) 1775, 1745 cm⁻¹; NMR(CDCl₃) 0.06 (s, 6H); 0.86 (s, 9 H); 1.10 (d, J = 5.8 Hz, 3 H); 1.40 (s, 3H); 1.61 (s, 3 H); 3.52 (dd, J₁ = 5 Hz, J₂ = 9 Hz, 1 H); 3.72 (s, 3 H); 4.20 (dq, J₁ = 5.8 Hz, J₂ = 9 Hz, 1 H); 4.38 (s, 1 H); 5.3 (d, J = 5 Hz, 1 H); MS:m/z = 342 (M⁺-C₄H₉)
13: mp 44-46^o C; [α]_D²⁰ -68.9^o (c = 1.0, CH₂Cl₂); IR(KBr) 1785, 1775, 1745 cm⁻¹; NMR(CDCl₃) 0.08 (s, 6 H); 0.88 (s, 9 H); 1.32 (d, J = 6.8 Hz, 3 H); 2.10 (s, 3 H); 3.22 (dd, J₁ = 1.8 Hz; J₂ = 2.7 Hz, 1 H); 4.28 (dq, J₁ = 2.7 Hz, J₂ = 6.8 Hz, 1 H); 5.69 (d, J = 1.8 Hz, 1 H); 6.44 (br, 1 H).
19a: oil; IR(CHCl₃) 2125, 1780 cm⁻¹; ¹H-NMR(CDCl₃) 0.12 (s, 6 H); 0.94 (s, 9 H); 1.37 (d, J = 6.5 Hz, 3 H); 3.31 (dd, J = 7 Hz, J₂ = 11.5 Hz, 1 H); 3.32 (dd, J₁ = 2 Hz, J₂ = 3.5 Hz, 1 H); 3.73 (dd, J₁ = 3 Hz, J₂ = 11.5 Hz, 1 H); 4.20 (dq, J₁ = 3.5 Hz, J₂ = 6.5 Hz, 1 H); 4.9 (d, J = 2 Hz, 1 H); 5.76 (s, 1 H); NOE: 5.76 (s) and 4.90 (d, 2 Hz); ¹³C-NMR(CDCl₃) -4.82 (q), -4.14 (q), 17.99 (s), 21.56 (q), 25.69 (q), 38.09 (t), 53.73 (d), 62.60 (d), 65.24 (d), 65.53 (d), 68.92 (d), 174.15 (s), 190.24 (s); MS:m/z = 298 (M⁺-C₄H₉).

20: oil; IR(CHCl₃): 1825, 1780 cm⁻¹; NMR (Benzene-d₆): 1.34 (d, J = 5.8 Hz, 3 H); 2.25 (dd, J₁ = 4 Hz, J₂ = 10.5 Hz, 1 H); 2.46 (dd, J₁ = 8.5 Hz, J₂ = 12.5 Hz, 1 H); 2.83 (dd, J₁ = 12.5 Hz, J₂ = 0.7 Hz, 1 H); 3.67 (dd, J₁ = 4 Hz, J₂ = 16 Hz, 1 H); 4.07 (dd, J₁ = 16 Hz, J₂ = 1 Hz, 1 H); 4.41 (dq, J₁ = 4 Hz, J₂ = 5.8 Hz, 1 H); 4.55 (ddd, J₁ = 8.5 Hz, J₂ = 4 Hz, J₃ = 0.7 Hz, 1 H); 4.86 (d, J = 10.5 Hz, 1 H).

7d: oil; IR(CHCl₃): 2120, 1775 cm⁻¹; NMR(CDCl₃): 1.34 (d, J = 7 Hz, 3 H); 1.52 (s, 3 H); 1.70 (s, 3 H); 2.34 (br, 1 H); 3.30 (dd, J₁ = 1.8 Hz, J₂ = 7 Hz, 1 H); 4.20 (s, 1 H); 4.20-4.46 (m, 1 H); 5.21 (d, J = 1.8 Hz, 1 H); 5.8 (s, 1 H); MS:m/z = 169 (M⁺).

8d: oil; IR(CH₂Cl₂): 1790 cm⁻¹; NMR(CDCl₃): 1.28 (d, J = 9 Hz, 3 H); 1.46 (s, 3 H); 1.48 (s, 3 H); 2.03 (br, 1 H); 3.50 (dd, J₁ = 3.6 Hz, J₂ = 9 Hz, 1 H); 4.03-4.38 (m, 1 H); 4.78 (d, J = 2.7 Hz, 1 H); 5.54 (d, J = 2.7 Hz, 1 H); 5.73 (d, J = 3.6 Hz, 1 H); MS:m/z = 241 (M⁺).

9d: oil; IR(CH₂Cl₂): 1780 cm⁻¹; NMR(CDCl₃): 1.36 (d, J = 6.5 Hz, 3 H); 1.48 (s, 3 H); 1.54 (s, 3 H); 1.97 (br, 1 H); 3.61 (dd, J₁ = 5.5 Hz, J₂ = 8.5 Hz, 1 H); 3.74 (s, 1 H); 4.08 (d, J = 5.5 Hz, 1 H); 4.19 (dq, J₁ = 8.5 Hz, J₂ = 6.5 Hz, 1 H); MS:m/z = 241 (M⁺).

22: mp 176-177^o C; [α]_D²⁰ +85^o (C = 1, CH₂Cl₂); IR(KBR): 3450, 1775, 1690 cm⁻¹; NMR(CDCl₃): 1.32 (d, J = 6 Hz, 3 H); 1.46 (s, 3 H); 1.54 (s, 3 H); 2.18 (br, 1 H); 2.48 (dd, J₁ = 3 Hz, J₂ = 15 Hz, 1 H); 2.62 (dd, J₁ = 3 Hz, J₂ = 15 Hz, 1 H); 3.32 (dd, J₁ = 2 Hz, J₂ = 5 Hz, 1 H); 4.12-4.46 (m, 1 H); 4.32 (dd, J₁ = 3 Hz, J₂ = 8 Hz, 1 H); 5.14 (d, J = 2 Hz, 1 H); 7.11 (t, J = 8 Hz, 1 H); 7.31 (t, J = 8 Hz, 2 H); 7.37 (br, 1 H); 7.56 (d, J = 8 Hz, 2 H).

Anal.(calcd) % C 60.99 (61.05), % H 6.63 (6.58), % N 8.37 (8.19), % S 9.59 (10.05)

- 10) R.J. Stoodley and N.R. Whitehouse, J. Chem. Soc., Perkin Trans. I, 1973, 1, 32.
- 11) R.D.G. Cooper and F.L. José, J. Am. Chem. Soc., 1972, 94, 1021.
- 12) D.B. Hope and M. Wälti, J. Chem. Soc. C, 1970, 2475.
- 13) Similar difficulties in the synthesis of bis-nor penicillins have been previously encountered: Beecham, Ger. Pat., 1977, DT 2704-546. See also: J.H. Musser, P.F. von Voightlander, and J. Szmuszkovicz, Heterocycles, 1986, 24, 155.
- 14) K. Prasad, G. Schulz, C.P. Mak, H. Hamberger, and P. Stütz, Heterocycles, 1981, 16, 1305.

- 15) B.G. Ramsay and R.J. Stoodley, J. Chem. Soc. C, 1969, 1319.
- 16) C.K. Ingold, J. Chem. Soc., 1921, 119, 305. For a theoretical analysis see N.L. Allinger, and V. Zalkow, J. Org. Chem., 1960, 25, 701.
- 17) S.H. Pines, IUPAC Symp. Ser., 3rd Symp. Org. Synth., 1981, Madison, Wis., p 327.

Received, 8th December, 1986