

SYNTHESIS OF OPTICALLY ACTIVE (5R, 3S)-1-DEOXA-1-THIA ANALOGUES OF CLAVULANIC ACID FROM
PENICILLANIC ACID DERIVATIVES

Maurizio Foglio, Giovanni Franceschi*, Guido Serra-Errante, Marzia Ballabio and Federico Arcamone

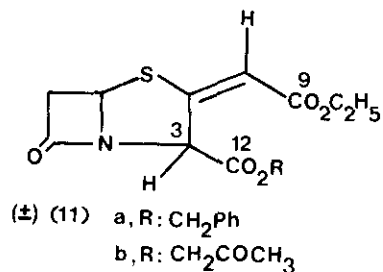
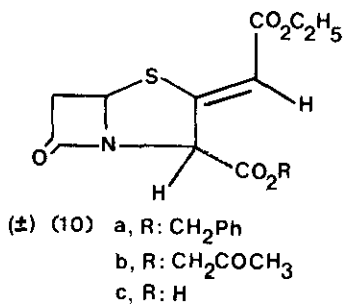
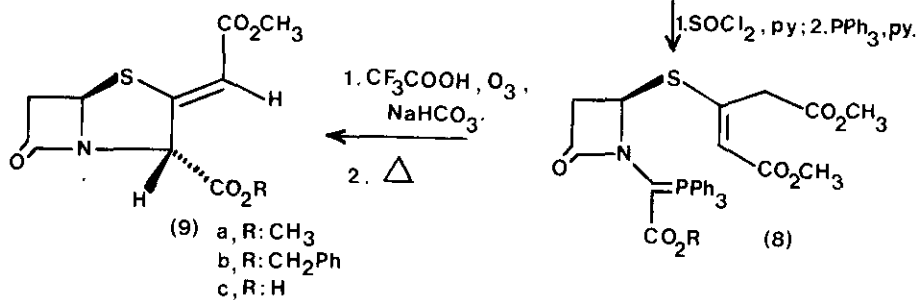
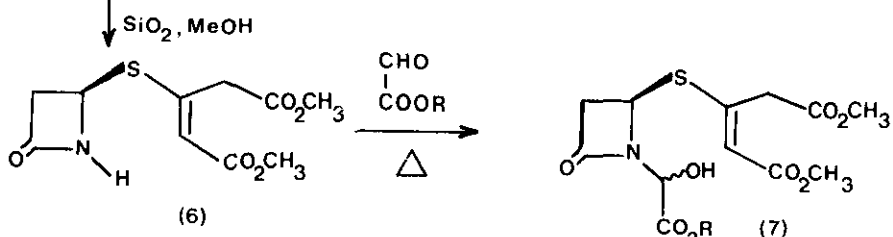
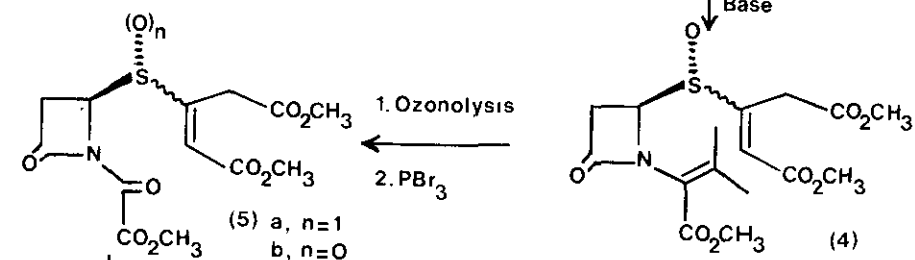
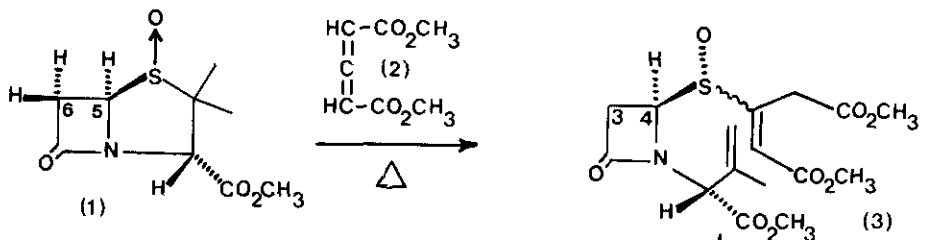
Farmitalia Carlo Erba S.p.A. - Ricerca & Sviluppo Chimico - Via dei Gracchi, 35
20146 Milan, Italy

Abstract — A novel synthesis of the chiral 1-thiaclavulanic skeleton consisting in the trapping reaction of penicillinate-S-oxide and glutinic acid dimethylester followed by demolition of the N-appendage and rebuilding of the thiazolidine ring is reported. Stereochemical assignments of the products are also discussed.

Over the past few years a big effort has been directed toward the preparation of nuclear analogues of penicillins and cephalosporins containing an oxygen atom in the place of sulphur, lately with gratifying success.¹ Following the isolation of naturally occurring clavulanic acid,² we have been engaged³ in the opposite challenge, i.e. the synthesis of sulphur analogous skeleton (9) potentially useful as β -lactamase inhibitor. We wish to report here the first synthesis of the new chiral (5R, 3S)-1-deoxa-1-thia-clavulanic analogues (9a, b, c) (2-alkylidene penam) starting from penicillins.

The new ring system was built up by trapping⁴ the sulphenic acid derived by thermal rearrangement of penicillinate-S-oxide (1) with an allene. Methyl penicillinate-S-oxide (1) was allowed to react with the allene (2) (refluxing toluene, 12 hours) giving an inseparable mixture (3:1) of diastereoisomeric sulphoxides (3) [^1H NMR: major: 2.93 (dd, $J=5.0, 14.0$ Hz, H-3 α); 3.40 (dd, $J=2.0, 14.0$ Hz, H-3 β); 3.5-4.0 (m, CH_2COO); 5.24 (bm, N-CH, H-4 α); 6.60 (s, =CH). Minor: 6.40 (s, =CH)] derived from a regiospecific cis-addition of sulphenic acid to the allene system.⁵

^{13}C NMR spectrum of the diastereoisomers (4) [$\text{triethylamine, CH}_2\text{Cl}_2$, rt, 100%]; ^1H NMR: major: 3.00 (dd, $J=4.5, 15.0$ Hz, H-3 α); 3.40 (dd, $J=2.5, 15.0$ Hz, H-3 β); 5.12 (dd, $J=2.5, 4.5$ Hz, H-4 α); 6.60 (s, =CH). Minor: 4.63 (m, H-4 α); 6.45 (s, =CH)] derived from isomerization of (3), showed differences in chemical shifts at C-4 ($\Delta\delta = 3.54$ ppm), C-3 ($\Delta\delta = 0.40$ ppm), C-6 ($\Delta\delta = 0.96$ ppm), C-7 ($\Delta\delta = 1.60$ ppm) and C-10 ($\Delta\delta = 0.35$ ppm), which could not be justified by a geometrical isomerism in the appendage, but only by a change involving all the nuclear shielding factors in the molecule, i.e. the different stereochemistry at the sulphur,⁶ with related conformational differences. This attribution was confirmed by the observation that when the mixture of oxamide sulphoxides (5a) was reduced to the oxamide sulphide (5b), only one product was detected by ^1H and ^{13}C NMR. In open chain sulphoxides (3), (4) and (5a) H-3 α was always more upfield than H-3 β , both keeping their characteristic values of the coupling constants, thus suggesting a syn orientation of the S=O bond and the H-4 α as the preferred conformation of the said compounds in solution.^{7,8}



Compound (4) was subsequently selectively ozonized (-78°C , CH_2Cl_2 , 80%) in the isopropylidene moiety, the vinylogous double bond being protected⁹ by the sulphoxide, giving (5a) $\int^1\text{H NMR}$: major: 3.23 (dd, $J = 6.0, 17.0$ Hz, H-3 α); 3.60 (dd, $J = 4.0, 17.0$ Hz, H-3 β); 3.8 (m, CH_2COO); 5.33 (dd, $J = 4.0, 6.0$ Hz, H-4 α); 6.65 (s, =CH). Minor: 6.42 (s, =CH). Reduction of the sulphoxide (5a) to (5b) (PBr_3 , DMF, -20°C , 60%) and hydrolysis (MeOH, silica gel) of the oxamide afforded (6) which was condensed with benzyl glyoxylate (refluxing benzene, 2 hours) to give (7), purified by silica gel column chromatography (CH_2Cl_2 -AcOEt 8:2). The carbinolamide (7), as a mixture of epimers, was transformed into the corresponding chloroderivative (SOCl_2 , py, 0°C) and then into the phosphorane (8) (PPh_3 , 60°C).

Protection of the phosphorane function through the formation of its phosphonium salt (CF_3COOH) allowed selective cleavage of the double bond attached to sulphur giving the corresponding thioester. Restoration of the phosphorane function with NaHCO_3 , followed by simple heating of the phosphorane thioester, afforded (9b) (60%) $\int^1\text{H NMR}$: 3.27 (dd, $J = 2.0, 16.0$ Hz, H-6 β); 3.78 (dd, $J = 4.0, 16.0$ Hz, H-6 α); 3.79, 3.80 (two s, COOCH_3 , $=\text{COOCH}_3$); 5.30 (dd, $J = 2.0, 4.0$ Hz, H-5 α); 5.52 (d, $J = 1.2$ Hz, H-3 β); 6.18 (d, $J = 1.2$ Hz, =CH). Following the same procedure, the corresponding methylester (9a) was also synthesized. The product showed the natural configuration at C-3, as deduced from the H-3 chemical shift (5.52 δ) which was in the normal range for natural penicillins and clavulanic acid derivatives. Surprisingly, no traces of the corresponding "penem" were found. Well beyond our hopes, the presence of an electron withdrawing group completely drives the isomerization of the double bond from the endo to the exo position. Hydrogenolysis of (9b) (Pd/C 10%, AcOEt) afforded the free acid (9c)^{10a} in poor yields^{10b} characterized through its methylester which was identical to the sample previously obtained.

In order to assign the geometry of the double bond of compound (9b), (10a) was prepared in a shorter way by total synthesis.³ Photochemical isomerization of (10a) (benzene, Hanovia lamp, rt, N_2) afforded an inseparable mixture of (10a) and (11a) in 4:6 ratio. Having now both isomers in hand, the geometry of the double bond was safely assigned. The allylic coupling constant J^{all} between H-3 and the vinylic hydrogen turned out to have different values, i.e. 1.2 Hz in (10a) and 1.6 Hz in (11a). Although reported examples for geometrical isomers of clavulanic derivatives^{11a} and for sulphur heterocycles with exo double bond¹² gave no difference between cisoid and transoid allylic coupling, in other structures it is generally well known¹³ that $|J_{\text{trans}}^{\text{all}}| > |J_{\text{cis}}^{\text{all}}|$. The different J^{all} values, together with the large shielding difference for H-3 ($\int^1\text{H NMR}$ 5.44 δ in (10a), 5.97 δ in (11a))^{11b} were decisive in establishing the geometry of thioclavulanic esters: (10a) has cisoid allylic coupling, whereas (11a), the photoisomerization product, has transoid allylic coupling and shows a large downfield shift of H-3 in analogy with the E isomer in clavulanic esters.^{11b}

¹³C NMR supported the said assignments. Product (11a) showed upfield compression shifts at C-3 ($\Delta\delta_3 = -5.0$ ppm) and at carboxylic carbons ($\Delta\delta_{12} = -0.8$ ppm; $\Delta\delta_9 = -2.5$ ppm). The ethylester moiety, which in ¹H NMR showed a noticeable difference between isomers ($\Delta\delta_{\text{CH}_3} = -0.09$ ppm; $\Delta\delta_{\text{CH}_2} = 0.12$ ppm) exhibited in ¹³C NMR the same shielding for both isomers, pointing to anisotropic effects from vicinal groups in proton shielding. In order to obtain another pair of geometrical isomers, (10b) was also synthesized and photoisomerized in the same conditions as (10a) to an inseparable mixture

of (10b) and (11b). The free acid (10c) was subsequently obtained by mild alkaline hydrolysis of the acetyl moiety.¹⁴

TABLE 1

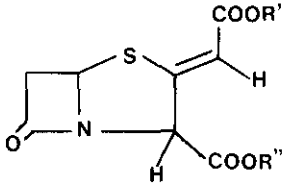
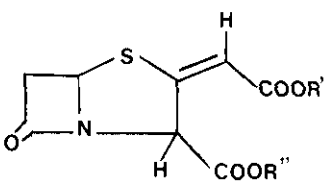


			 Z			 E		
	R ^I	R ^{II}	Compound	J = 1.2 Hz		Compound	J = 1.6 Hz	
				H-3			H-3	
5R, 3S	CH ₃	CH ₃	9a	5.52	6.18		-	-
5R, 3S	CH ₃	CH ₂ Ph	9b	5.51	6.13		-	-
±	CH ₂ CH ₃	CH ₂ Ph	10a	5.44	6.04	11a	5.97	6.17
±	CH ₂ CH ₃	CH ₂ COCH ₃	10b	5.60	6.20	11b	6.08	6.30
±	CH ₂ CH ₃	H	10c	5.50	6.20		-	-

Table 1 collects ¹H NMR relevant chemical shifts for all thiaclavulanic derivatives. ¹H NMR behaviour similar to (10a) and (11a) was found for (10b) and (11b). It is clear that ¹H-chemical shift for vinyl hydrogen is not a very good indication of geometry; so in a preceding paper,³ (10a) was assigned the wrong geometry and we are now able to correct the previous assignment. Proton at C-3 is instead a very good probe of E and Z configurations because of its large downfield shift when in the deshielding cone of the conjugated carboxylic group in the E form. The free acid (10c) showed chemical shifts and coupling constant similar to those of (10b). Since H-3 and the vinylic hydrogen chemical shifts were not sensitive to substitutions at the carboxy group in position 3, the following chemical shift ranges can be considered as characteristic of the Z isomers: H-3, 5.4-5.6 ppm; vinyl H, 6.0-6.2 ppm. The Z geometry can now be safely assigned to the optically active thiaclavulanic esters (9a) and (9b), because of the correspondence of their chemical shifts with (10a-c) for which the geometry was established as discussed above.

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6. The same trapping reaction on 6 β -acylamidopenicillins afforded also two isomeric sulphoxides, but in this case the S-O bond was assigned the β -position because of a strong H bonding between oxygen and the amide hydrogen. See reference (5).
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10. a) Product (9c) was tested and showed no significant activity as both β -lactamase inhibitor and antibacterial agent. Reduction of the ester function in position (9) in order to obtain 1-deoxa-1-thia-clavulanic acid is now currently being investigated in our laboratory.
b) It is reported that in the same conditions benzyl clavulanate gave the corresponding acid in good yields. A.G. Brown, J. Goodacre, J.B. Hardbridge, T.T. Howarth, R.J. Pondsford, and I. Stirling; 1977. In "Recent Advances in the Chemistry of β -lactam Antibiotics" (295-298) (Ed. J. Elks) London: The Chemical Society S.P. 28.
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15. ir, ms, ^1H NMR (60 MHz, CDCl_3) and ^{13}C NMR (20 MHz, acetone- d_6) were in agreement with the assigned structures.

Received, 26th August, 1980