Spirocyclic Penicillins

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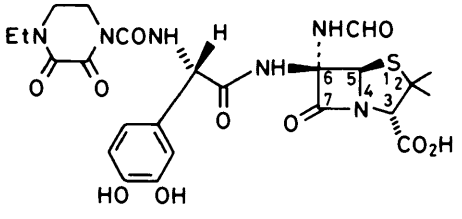
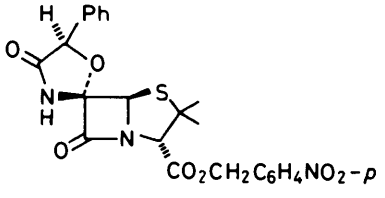
The intramolecular, mercury-mediated cyclisation of (6*S*)-benzyl 6-[(*R*)-and (*S*)-2-amino-2-phenylacetamido]-6-(methylthio)penicillanates, (**8**) and (**9**), has been shown to give spiro[imidazolidine-2,6'-penicillanate] derivatives. Unexpectedly, products (**16**) and (**17**), derived from attack on the more-hindered β-face, were isolated in addition to the predicted products (**10**) and (**11**), formed by attack on the α-face. Formylation and removal of the carboxy protecting group gave spirocyclic penicillins devoid of useful antibacterial activity.

A diverse range of 6(7)-substituted penicillins (cephalosporins) have been described in the literature.[1–8] Although very few substituents have led to compounds with useful antibacterial activity,[9,10] it has recently been shown that the formamido group is of particular utility. Indeed, BRL 36650 (**1**), developed in these laboratories,[11] is a β-lactamase stable semi-synthetic formamidopenicillin with extremely potent Gram-negative activity.[12] In addition, the existence of naturally-occurring 7-formamido cephalosporins has been reported.[13] We now wish to report the preparation of derivatives in which a 6-formamido group is incorporated into a spirocyclic ring.

Although various spirocyclic penicillins have been described,[7,14,15] the disclosure of our own investigation in this area was prompted by a recent report by Sammes.[16] The analogue (**2**) was the sole product when the (*S*)-mandelamide (**3**) was oxidised with lithium methoxide and t-butyl hypochlorite: attack of the internal nucleophile occurring exclusively on the α-face of the putative acylimine intermediate. In the cephalosporin series, the alcohol (**4**) was prepared and the intermediate generated using mercuric chloride and pyridine to provide (**5**) as the only product. These transformations were also performed on the *R*-side-chain analogues with the same results. Our studies involved the synthesis and mercury(II)-mediated cyclisation of both diastereoisomers, (**8**) and (**9**), of (6*S*)-benzyl 6-(2-amino-2-phenylacetamido)-6-(methylthio)penicillanate.



(**1**)



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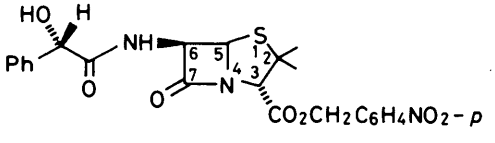

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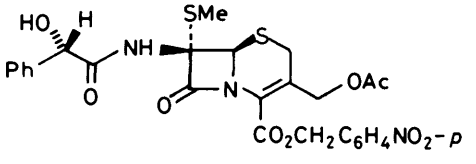
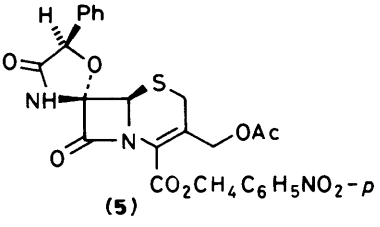
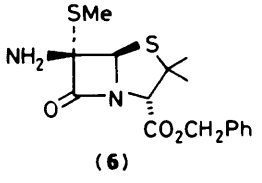


(**4**)



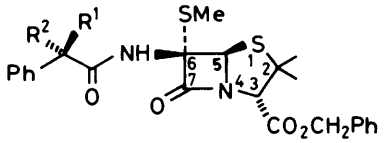
(**5**)



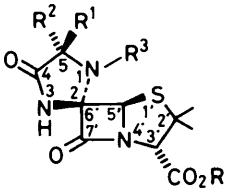
(**6**)

Acylation of (6*S*)-benzyl 6-amino-6-(methylthio)penicillanate (**6**) with (*R*)-2-azido-2-phenylacetyl chloride in the presence of pyridine gave the *R*-side-chain isomer (**7**) as the sole product. Reduction with zinc and ammonium chloride[17] was free from side-chain racemisation and only (**8**) was isolated. However, reduction of (**7**) with triethylamine and hydrogen sulphide[18] caused concomitant racemisation and both diastereoisomers, (**8**) and (**9**), were isolated in 36 and 31% yields respectively. In contrast to the intramolecular cyclisation of the alcohols (**3**) and (**4**), the amines (**8**) and (**9**) each gave a major (30% and 72% yield respectively) and a minor (6% and 14% yields respectively) product on treatment with mercuric acetate[19] in tetrahydrofuran. All four compounds had spectral data consistent with a spiro[imidazolidine-2,6'-penicillanate] structure. Simple side-chain racemisation during the cyclisation was discounted when thin layer and high performance liquid chromatography showed that all four compounds were different. We, therefore, concluded that we had isolated not only the expected products of α-face attack, (**10**) and (**11**), but also the compounds (**16**) and (**17**), derived from attack of the amino group on the β-face of the acylimine intermediate.† On the assumption that the rate of reaction would be faster at the less-hindered α-face, we assigned structures (**10**) and (**11**) to the major products and (**16**) and (**17**) to the minor. Further evidence supporting this assignment was found when the two minor products were shown to be resistant

† One of our referees suggested that the β-face adducts, (**16**) and (**17**), might be formed by equilibration with the α-face products (**10**) and (**11**), during the reaction. We have subjected (**10**) and (**16**) to the appropriate reaction conditions and observed no equilibration.

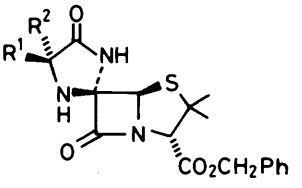


(7) $R^1 = N_3$, $R^2 = H$
(8) $R^1 = NH_2$, $R^2 = H$
(9) $R^1 = H$, $R^2 = NH_2$



(10) $R^1 = R^3 = H$, $R^2 = Ph$, $R = CH_2Ph$
(11) $R^1 = Ph$, $R^2 = R^3 = H$, $R = CH_2Ph$
(12) $R^1 = H$, $R^2 = Ph$, $R^3 = CHO$, $R = CH_2Ph$
(13) $R^1 = Ph$, $R^2 = H$, $R^3 = CHO$, $R = CH_2Ph$
(14) $R^1 = H$, $R^2 = Ph$, $R^3 = CHO$, $R = H$
(15) $R^1 = Ph$, $R^2 = H$, $R^3 = CHO$, $R = H$

to formylation under our normal conditions. This would be expected for a sterically hindered amino group. Molecular models of (**16**) and (**17**) indicate this to be the case. Treatment of (**10**) and (**11**) with acetic formic anhydride and pyridine in



(16) $R^1 = H$, $R^2 = Ph$
(17) $R^1 = Ph$, $R^2 = H$

dichloromethane gave the formyl derivatives (**12**) and (**13**), although (**11**) required 5 h to obtain a satisfactory yield. The two formamido derivatives (**12**) and (**13**) were found to exist as a mixture of rotamers in approximately a 2:1 ratio. A variable temperature ^1H n.m.r. experiment in [$^2H_6$]dimethyl sulphoxide on each isomer (**12**) and (**13**), showed the rotamer peaks coalescing at 130 °C and 170 °C respectively. Hydrogenolysis of (**12**) and (**13**) over 10% palladium-on-carbon gave the free acids (**14**) and (**15**), both of which were biologically inactive.

Experimental

I.r. spectra were recorded for 0.4% w/w KBr discs unless otherwise stated. ^1H N.m.r. spectra at 90 MHz were recorded on a Perkin-Elmer R32 instrument and at 250 MHz on a Bruker WM 250 machine for solutions in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise indicated. Accurate mass measurements were carried out by electron impact on an AEI MS9 instrument. M.p.s. were determined on a Buchi oil-immersion apparatus and are uncorrected. Specific rotations were measured in chloroform on a Perkin-Elmer 141 polarimeter. Ether refers to diethyl ether and reactions were performed at ambient temperature under argon unless otherwise stated. Solutions were routinely dried over anhydrous magnesium sulphate. Chromatographic purifications were performed on silica gel 60, finer than 230 mesh ASTM. All compounds described herein were shown to be homogeneous by t.l.c. on precoated silica gel 60 F_{254} plates and by reverse-phase h.p.l.c., μ-Bondapak C-18 column eluting with 0.05M, pH 4.5, ammonium acetate–methanol mixtures; detection was by u.v. absorption at 240 nm.

(6S)-*Benzyl* 6-[(R)-2-*Azido*-2-*phenylacetamido*]-6-(*methylthio*)*penicillanate* (**7**).—(*R*)-2-Azido-2-phenylacetic acid (1.77 g) in dry dichloromethane (25 ml) was treated with dry DMF (0.01 ml) and oxalyl chloride (1 ml). After 1 h the solvent was removed under reduced pressure and the residue redissolved in THF (15 ml). This solution was added dropwise to a solution of (6*S*)-benzyl 6-amino-6-(methylthio)penicillanate (1.76 g) in THF (10 ml) containing triethylamine (1.4 ml). After 30 min, ethyl acetate and water were added and the phases were separated. The aqueous phase was further extracted with ethyl acetate and the combined organic extracts washed successively with water and brine, dried and evaporated under reduced pressure. Trituration of the residue with ether gave the *azide* (2.39 g, 92%), m.p. 114 °C (ethyl acetate–cyclohexane) (Found: C, 56.4; H, 4.8; N, 13.6; S, 12.6. $C_{24}H_{25}N_5O_4S_2$ requires C, 56.4; H, 4.9; N, 13.7; S, 12.5%); $\nu_{max.}$ 3 390, 2 110, 1 760, and 1 682 cm^{-1}; δ_H (90 MHz) 1.35 (3 H, s, 2-Me), 1.48 (3 H, s, 2-Me), 2.22 (3 H, s, SMe), 4.46 (1 H, s, 3-H), 5.09 (1 H, s, PhC*H*), 5.18 (2 H, s, PhCH_2), 5.55 (1 H, s, 5-H), and 7.30—7.50 (10 H, m, Ph × 2) (Found: M^+, 511.1394. $C_{24}H_{25}N_5O_4S_2$ requires *M*, 511.1347).

(6S)-*Benzyl* 6-[(R)-2-*Amino*-2-*phenylacetamido*]-6-(*methylthio*)*penicillinate* (**8**).—The azide (**7**) (10.22 g) in THF (200 ml) and methanol (400 ml) was treated with ammonium chloride (7.49 g) and zinc powder (4.0 g) with vigorous stirring for 30 min. The insolubles were removed by filtration and the filtrate evaporated to dryness under reduced pressure. Ethyl acetate and water were added to the residue and the organic phase was washed with water and brine, dried, and evaporated to dryness under reduced pressure. Trituration with ether gave the *amine* (5.41 g, 56%), m.p. 121—122 °C (ethyl acetate–cyclohexane), $[\alpha]_D^{20}$ +142.6° (*c*, 0.75) (Found: C, 59.3; H, 5.8; N, 8.5; S, 12.9. $C_{24}H_{27}N_3O_4S_2$ requires C, 59.4; H, 5.6; N, 8.7; S, 13.2%); $\nu_{max.}$ 3 360br, 1 778, 1 740, and 1 685 cm^{-1}; δ_H (90 MHz) 1.32 (3 H, s, 2-Me), 1.40 (3 H, s, 2-Me), 1.60—2.10 (2 H, br, exchangeable, NH_2), 2.17 (3 H, s, SMe), 4.41 (1 H, s, 3-H), 4.53 (1 H, br s, PhC*H*), 5.16 (2 H, s, PhCH_2), 5.52 (1 H, s, 5-H), 7.20—7.50 (10 H, m, Ph × 2), and 7.94 (1 H, br s, exchangeable, CONH) (Found: M^+, 485.1454. $C_{24}H_{27}N_3O_4S_2$ requires *M*, 485.1443).

(6S)-*Benzyl* 6-[(S)-2-*Amino*-2-*phenylacetamido*]-6-(*methylthio*)*penicillinate* (**9**).—The azide (**7**) (2.39 g) and triethylamine (0.77 ml) in dichloromethane (50 ml) were treated with hydrogen sulphide gas for 30 min. The solution was washed with water (× 3) and brine, then dried and evaporated to dryness under reduced pressure. Chromatography (chloroform then 2% methanol in chloroform) gave the *title compound* (0.71 g, 31%), m.p. 147—149 °C (ethyl acetate–cyclohexane), $[\alpha]_D^{20}$ + 143.6° (*c*, 0.65) (Found: C, 59.2; H, 5.7; N, 8.5; S, 13.0. $C_{23}H_{27}N_3O_4S_2$ requires C, 59.4; H, 5.6; N, 8.7; S, 13.2%); $\nu_{max.}$ 3 360, 1 775, 1 700, and 1 690 cm^{-1}; δ_H (90 MHz) 1.28 (3 H, s, 2-Me), 1.41 (3 H, s, 2-Me), 1.87 (2 H, br s, exchangeable, NH_2), 2.21 (3 H, s, SMe), 4.40 (1 H, s, 3-H), 4.54 (1 H, s, PhC*H*), 5.15 (2 H, s, PhCH_2), 5.51 (1 H, s, 5-H), 7.33 (10 H, br s, Ph × 2), and 7.94 (1 H, br s, exchangeable, CONH). Further elution gave the *R*-side-chain diastereoisomer (**8**) (0.81 g, 36%).

(2R,3'S,5R,5'R)-*Benzyl* 2',2'-*Dimethyl*-4-*oxo*-5-*phenylspiro*[*imidazolidine*-2,6'-*penam*]-3'-*carboxylate* (**10**) *and* (2S,3'S,5R,5'R)-*Benzyl* 2',2'-*Dimethyl*-4-*oxo*-5-*phenylspiro*-[*imidazolidine*-2,6'-*penam*]-3'-*carboxylate* (**16**).—The amine (**8**)

(485 mg) in THF (10 ml) was treated at 0—5 °C with mercuric acetate (319 mg). After 15 min, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The filtrate was washed with water (× 2), brine and dried. Evaporation of the solvent under reduced pressure followed by careful chromatography (20% ethyl acetate in cyclohexane) gave the *product* (**10**) (133 mg, 30%), m.p. 167—168 °C (ethyl acetate–cyclohexane) (Found: C, 62.9; H, 5.3; N, 9.4; S, 7.3. $C_{23}H_{23}N_3O_4S$ requires C, 63.2; H, 5.3; N, 9.6; S, 7.3%), $\nu_{max.}$($CHCl_3$) 3 400, 1 785, and 1 740 cm^{-1}; δ_H (250 MHz) 1.42 (3 H, s, 2′-Me), 1.54 (3 H, s, 2′-Me), 3.31 [1 H, d, *J* 7 Hz, exchangeable, N(1)–H], 4.55 (1 H, s, 3′-H), 4.99 (1 H, d, *J* 7 Hz, 5-H), 5.21 (2 H, s, PhCH_2), 5.51 (1 H, s, 5′-H), 6.73 [1 H, s, exchangeable, N(3)–H], 7.26—7.47 (10 H, m, Ph × 2) (Found: M^+, 437.1414. $C_{23}H_{23}N_3O_4S$ requires *M*, 437.1409). Further elution gave the *isomer* (**16**) (28 mg, 6%), $\nu_{max.}$($CHCl_3$) 1 775 and 1 725 cm^{-1}; δ_H (250 MHz) 1.43 (3 H, s, 2′-Me), 1.56 (3 H, s, 2′-Me), 3.55 [1 H, d, *J* 7 Hz, exchangeable, N(1)–H], 4.54 (1 H, s, 3′-H), 4.75 (1 H, d, *J* 7 Hz, 5-H), 5.17—5.21 (2 H, m, PhCH_2), 5.57 (1 H, s, 5′-H), 7.14 [1 H, s, exchangeable, N(3)–H], and 7.26–7.61 (10 H, m, Ph × 2) (Found: M^+, 437.1410. $C_{23}H_{23}N_3O_4S$ requires *M*, 437.1409).

(2R,3′S,5S,5′R)-*Benzyl* 2′,2′-*Dimethyl*-4-*oxo*-5-*phenylspiro*-[*imidazolidine*-2,6′-*penam*]-3′-*carboxylate* (**11**) *and* (2S,3′S,5S,5′R)-*Benzyl* 2′,2′-*Dimethyl*-4-*oxo*-5-*phenylspiro*-[*imidazolidine*-2,6′-*penam*]-3′-*carboxylate* (**17**).—The amine (**9**) (360 mg) was treated with mercuric acetate (240 mg) in THF (10 ml) as described above. The same work-up and purification gave the *title compound* (**11**) (234 mg, 72%), m.p. 148—150 °C (ethyl acetate–cyclohexane) (Found: C, 62.9; H, 5.6; N, 9.5. $C_{23}H_{23}N_3O_4S$ requires C, 63.2; H, 5.3; N, 9.6%), $\nu_{max.}$ 3 340, 3 230br, 1 775, and 1 730br cm^{-1}; δ_H (250 MHz) 1.43 (3 H, s, 2′-Me), 1.54 (3 H, s, 2′-Me), 2.95 [1 H, d, *J* 3 Hz, exchangeable, N(1)–H], 4.56 (1 H, s, 3′-H), 4.65 (1 H, d, *J* 3 Hz, 5-H), 5.20 (2 H, m, PhCH_2), 6.72 [1 H, br s, exchangeable, N(3)–H], and 7.33—7.54 (10 H, m, Ph × 2) (Found: M^+, 437.1401. $C_{23}H_{23}N_3O_4S$ requires *M*, 437.1409). Further elution gave the *isomer* (**17**) (47 mg, 14%), $\nu_{max.}$($CHCl_3$) 1 775 and 1 725 cm^{-1}; δ_H (250 MHz) 1.40 (3 H, s, 2′-Me), 1.55 (3 H, s, 2′-Me), 3.25 [1 H, d, *J* 4 Hz, exchangeable, N(1)–H], 4.50 (1 H, s, 3′-H), 4.79 (1 H, d, *J* 4 Hz, 5-H), 5.18 (2 H, AB system, *J* 12 Hz, PhCH_2), 5.58 (1 H, s, 5′-H), and 7.29—7.54 (10 H, m, Ph × 2) (Found: M^+, 437.1393. $C_{23}H_{23}N_3O_4S$ requires *M*, 437.1409).

(2R,3′S,5R,5′R)-*Benzyl* 1-*Formyl*-2′,2′-*dimethyl*-4-*oxo*-5-*phenylspiro*[*imidazolidine*-2,6′-*penam*]-3′-*carboxylate* (**12**).—The spirocyclic amine (**10**) (177 mg) in dichloromethane (10 ml) was treated with pyridine (320 mg) and acetic formic anhydride (179 mg). After 45 min, further acetic formic anhydride (112 mg) was added and the mixture was stirred for 1 h. The reaction mixture was washed successively with water, saturated aqueous sodium hydrogen carbonate, water, saturated aqueous copper sulphate, water, and brine, and was then dried and the solvent evaporated under reduced pressure. Chromatography (20% ethyl acetate in cyclohexane) gave the *ester* (**12**) (143 mg, 76%), $\nu_{max.}$($CHCl_3$) 1 790, 1 740, and 1 692 cm^{-1}; δ_H (250 MHz) 1.25 (3 H, s, 2′-Me), 1.50 (3 H, s, 2′-Me), 4.60 (1 H, s, 3′-H), 5.22 (2 H, m, PhCH_2), 5.38 (1 H, s, 5-H), 6.03 (1 H, s, 5′-H), 7.06 [1 H, br s, exchangeable, N(3)–H], 7.26—7.44 (10 H, m, Ph × 2), and 8.57 (1 H, s, CHO) (Found: M^+, 465.1347. $C_{24}H_{23}N_3O_5S$ requires *M*, 465.1359). The minor rotamer (ratio *ca.* 2:1) showed δ_H (250 MHz) *inter alia* 1.41 (3 H, s, 2′-Me), 1.62 (3 H, s, 2′-Me), 4.63 (1 H, s, 3′-H), 5.31 (1 H, s, 5-H), 5.70 (1 H, s, 5′-H), and 8.29 (1 H, s, CHO).

(2R,3′S,5S,5′R)-*Benzyl* 1-*Formyl*-2′,2′-*dimethyl*-4-*oxo*-5-*phenylspiro*[*imidazolidine*-2,6′-*penam*]-3′-*carboxylate* (**13**).—The amine (**11**) (234 mg) in dry dichloromethane (10 ml) was treated with pyridine (489 mg) and acetic formic anhydride (235 mg) as described above. A further quantity of acetic formic anhydride (235 mg) was added after 2.5 h and the reaction was worked up as described above after a further 2.5 h to give the *ester* (**13**) (167 mg, 67%), $\nu_{max.}$($CHCl_3$) 1 795, 1 745, and 1 695 cm^{-1}; δ_H [250 MHz; (CD_3)$_2$SO] 1.39 (3 H, s, 2′-Me), 1.55 (3 H, s, 2′-Me), 4.63 (1 H, 2 × s, 3′-H), 5.08—5.24 (2 H, m, PhCH_2), 5.29 (1 H, s, 5-H), 5.90 (1 H, s, 5′-H), 7.32—7.46 (10 H, m, Ph × 2), and 8.52 (1 H, s, CHO) (Found: M^+, 465.1370. $C_{24}H_{23}N_3O_5S$ requires 465.1359). The minor rotamer (ratio *ca.* 2:1) had δ_H (250 MHz) *inter alia* 1.41 (3 H, s, 2′-Me), 1.57 (3 H, s, 2′-Me), 4.77 (1 H, s, 3′-H), 5.08 (1 H, s, 5-H), 5.82 (1 H, s, 5′-H), and 8.30 (1 H, s, CHO).

(2R,3′S,5R,5′R)-1-*Formyl*-2′,2′-*dimethyl*-4-*oxo*-5-*phenylspiro*[*imidazolidine*-2,6′-*penam*]-3′-*carboxylic Acid* (**14**).—The benzyl ester (**12**) (70 mg) in dry THF (10 ml) was hydrogenated over 10% Pd–C (70 mg). The catalyst was removed by filtration through Celite and the solvent was removed under reduced pressure to give the *acid* (**14**) (54 mg, 96%), $\nu_{max.}$(THF) 1 790, 1 745, and 1 698 cm^{-1}; δ_H [250 MHz; (CD_3)$_2$CO] 1.61 (3 H, s, 2′-Me), 1.66 (3 H, s, 2′-Me), 4.53 (1 H, s, 3′-H), 5.59 (1 H, s, 5-H), 6.02 (1 H, s, 5′-H), 7.36—7.50 (5 H, m, Ph), and 8.37 (1 H, s, CHO) (Found: M^+, 375.0900. $C_{17}H_{17}N_3O_5S$ requires *M*, 375.0889). The minor rotamer (ratio *ca.* 2:1) showed δ_H *inter alia* 1.63 (3 H, s, 2′-Me), 1.69 (3 H, s, 2′-Me), 4.65 (1 H, s, 3′-H), 5.39 (1 H, s, 5-H), 6.05 (1 H, s, 5′-H), and 8.66 (1 H, s, CHO).

(2R,3′S,5S,5′R)-1-*Formyl*-2′,2′-*dimethyl*-4-*oxo*-5-*phenylspiro*-[*imidazolidine*-2,6′-*penam*]-3′-*carboxylic Acid* (**15**).—The ester (**13**) (150 mg) was hydrogenated in dry THF (20 ml) over 10% Pd–C as described above. Evaporation of the solvent under reduced pressure gave the *title compound* (**15**) (72 mg, 59%), $\nu_{max.}$(THF) 1 785, 1 745, and 1 695 cm^{-1}; δ_H [250 MHz; (CD_3)$_2$CO] 1.58 (3 H, s, 2′-Me), 1.65 (3 H, s, 2′-Me), 4.53 (1 H, s, 3′-H), 5.34 (1 H, s, 5-H), 6.08 (1 H, s, 5′-H), 7.27—7.56 (5 H, m, Ph), and 8.19 (1 H, s, CHO) (Found: M^+, 375.0900. $C_{17}H_{17}N_3O_5S$ requires *M*, 375.0889). The minor rotamer (ratio of rotamers *ca.* 2:1) showed δ_H *inter alia* 1.60 (3 H, s, 2′-Me), 1.67 (3 H, s, 2′-Me), 4.67 (1 H, s, 3′-H), 5.15 (1 H, s, 5-H), 5.96 (1 H, s, 5′-H), and 8.72 (1 H, s, CHO).

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