A Short Formal Synthesis of the Carbapenem Antibiotic (±)-PS-5

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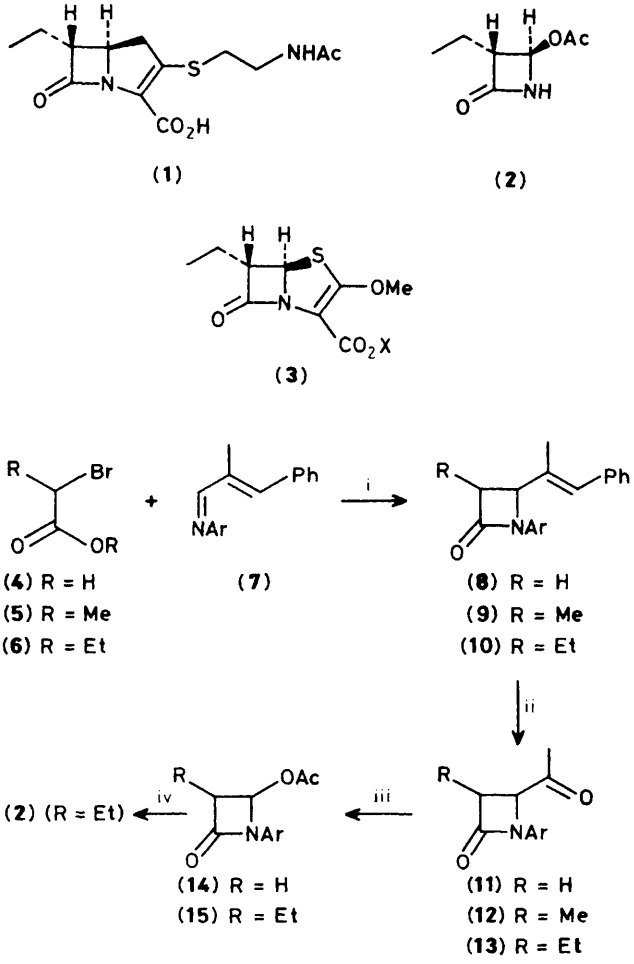
A practical stereoselective synthesis of 4-acetoxy-3-ethylazetidin-2-one *via* Reformatsky reaction between methyl-α-bromobutyrate and *N*-4-methoxyphenyl-α-methylcinnamylideneamine is described.

The carbapenem family of antibiotics is often characterized by the presence of alkyl side chains adjacent to the β-lactam carbonyl.[1] Most of the reported syntheses of these compounds involve as the key step the formation of the corresponding 3-alkyl-4-acetoxyazetidin-2-one.[2] The carbapenem (±)-PS-5 (**1**) is such an antibiotic which is active against Gram-positive and Gram-negative bacteria including β-lactamase-producing organisms.[3] Kametami *et al.*[4] reported a synthesis of (±)-PS-5 starting from 4-acetoxy-3-ethylazetidin-2-one (**2**). Also Wasserman and Han[5] have employed such an intermediate in the synthesis of penems like (**3**). Of the most suitable methods for the synthesis of substituted β-lactams with alkyl side chains, the Reformatsky type reaction of Gilman and Speeter[6] is of considerable interest, not only because of the ready availability of starting materials but also the possibility of controlling the stereoselectivity of the reaction.[7] The recent paper of Hart and Ha[8] has prompted us to report our initial efforts to apply the Reformatsky reaction to the synthesis of building blocks of β-lactam antibiotics.



Scheme 1. *Reagents and conditions*: i, Zn, $HgCl_2$, Ar = *p*-$MeOC_6H_4$, toluene, reflux 8 h; ii, O_3, −78 °C, CH_2Cl_2, then Me_2S; iii, MCPBA, benzene, reflux; iv, CAN, MeCN–H_2O, 25–30 min.

Our strategy (Scheme 1) involved the synthesis of the precursors (**8**)—(**10**) with a 4-alkenyl substitutent as the latent carbonyl functionality, then an ozonolysis–Baeyer–Villiger sequence to generate the required 4-acetoxy group.[9] The synthesis of the racemic form of (**2**) starting from α-bromobutyrates (**6**) and the imine (**7**) was examined first.† Thus, treatment of (**7**) with a slight excess of methyl α-bromobutyrate (**6**) under Gilmann and Speeter's conditions[6] for 6 h in refluxing benzene gave a 1 : 2 mixture of *cis* and *trans* isomers of (**10**) (60% yield).‡ When the reaction was carried out in boiling toluene a 1 : 4 (*cis* : *trans*) mixture of (**10**) was obtained in 80% yield. All attempts to improve the stereoselectivity of the reaction starting from bulky esters[7] such as t-butyl, menthyl, isopropyl, and t-butyldimethylsilyl α-bromobutyrates failed and only the last two were successful for β-lactam formation. Ozonolysis of (**10**) in methylene chloride at −70 °C followed by dimethylsulphide work-up[11] gave a mixture of the corresponding *cis* and *trans* isomers of (**13**) in 70% yield, from which the *cis* isomer [δ 3.28—3.50 (m, H-3), 4.55 (d, *J* 6 Hz, H-4)] was separated by crystallization from $CHCl_3$–hexane. Subsequent Baeyer–Villiger oxidation of the *trans* isomer of (**13**) with *m*-chloroperbenzoic acid (MCPBA) (molar ratio 1 : 3) in boiling benzene for 2.5 h gave an equimolar mixture of (**15**) and the starting product (**13**). Further oxidation of this mixture under the same conditions as above, yielded the corresponding *trans* isomer of (**15**) as only reaction product [δ 3.0 (br. t, *J* 7 Hz, H-3), 5.95 (br. s, H-4)]. Oxidative

Table 1. Functionalized β-lactams prepared.

Compound[a]	% Yield	M.p./°C[b]
(**8**)[c]	53	138—139
(**9**)[d]	50[e]	114—115[f]
		93—94[g]
(**10**)[d]	12	99—100[f]
	65	oil[g]
(**11**)	60	oil
(**13**)	10	119—120[f,h]
	50	oil[g]
(**14**)	65	99—100
(**15**)	55	71—72[g]

[a] Products were racemic mixtures and gave satisfactory spectral and analytical data. [b] Recrystallized from EtOH. [c] Prepared from the corresponding ethyl ester. [d] Prepared from the corresponding methyl ester. [e] Isolated as 1 : 1 mixture of *cis* and *trans* isomers. [f] *cis* Isomer. [g] *trans* Isomer. [h] Recrystallized from $CHCl_3$–hexane.

† The acid chloride–imine method or equivalent was ineffective for the preparation of the starting β-lactam (**10**).[10]

‡ The *cis* isomer could be isolated by crystallization from EtOH, see Table 1.

removal of the *N*-aryl substituent[12] by means of cerium(IV) ammonium nitrate (CAN) afforded *trans*-(**2**) in 90% yield as an oil.[13]

Following the above methodology, further functionalized β-lactams were prepared and the results are listed in Table 1. Since formation of β-lactam (**8**) could be improved using the method recently reported by Bose *et al.*,[14] our procedure should be also valuable for the synthesis of 3-unsubstituted-4-acetoxy-β-lactams. Our approach thus provides an application of the Reformatsky reaction to the synthesis of building blocks of β-lactam antibiotics, and uses readily available, inexpensive starting materials, and a wide variety of 4-acetoxy-β-lactams with 3-alkyl side chains should be easily accessible.

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