

## A Short Formal Synthesis of the Carbapenem Antibiotic ( $\pm$ )-PS-5

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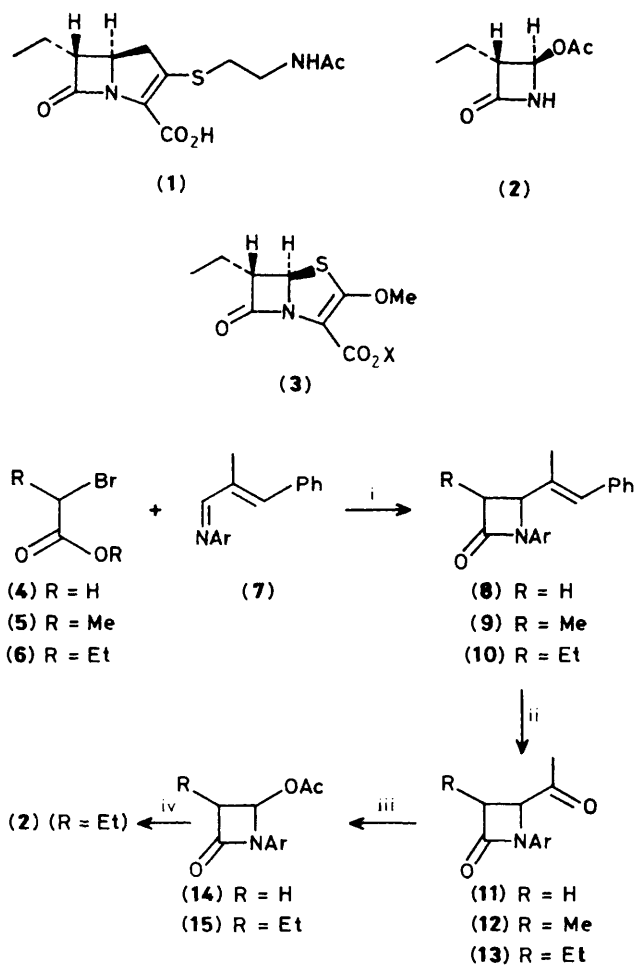
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A practical stereoselective synthesis of 4-acetoxy-3-ethylazetididin-2-one *via* Reformatsky reaction between methyl- $\alpha$ -bromobutyrate and *N*-4-methoxyphenyl- $\alpha$ -methylcinnamylideneamine is described.

The carbapenem family of antibiotics is often characterized by the presence of alkyl side chains adjacent to the  $\beta$ -lactam carbonyl.<sup>1</sup> Most of the reported syntheses of these compounds involve as the key step the formation of the corresponding 3-alkyl-4-acetoxyazetididin-2-one.<sup>2</sup> The carbapenem ( $\pm$ )-PS-5 (**1**) is such an antibiotic which is active against Gram-positive and Gram-negative bacteria including  $\beta$ -lactamase-producing organisms.<sup>3</sup> Kametami *et al.*<sup>4</sup> reported a synthesis of ( $\pm$ )-PS-5 starting from 4-acetoxy-3-ethylazetididin-2-one (**2**). Also Wasserman and Han<sup>5</sup> have employed such an intermediate in the synthesis of penems like (**3**). Of the most suitable methods for the synthesis of substituted  $\beta$ -lactams with alkyl side chains, the Reformatsky type reaction of Gilman and Speeter<sup>6</sup> 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.<sup>7</sup> The recent paper of Hart and Ha<sup>8</sup> has prompted us to report our initial efforts to apply the Reformatsky reaction to the synthesis of building blocks of  $\beta$ -lactam antibiotics.

Our strategy (Scheme 1) involved the synthesis of the precursors (**8**)–(**10**) with a 4-alkenyl substituent as the latent carbonyl functionality, then an ozonolysis–Baeyer–Villiger sequence to generate the required 4-acetoxy group.<sup>9</sup> The synthesis of the racemic form of (**2**) starting from  $\alpha$ -bromobutyrate (**6**) and the imine (**7**) was examined first.<sup>†</sup> Thus, treatment of (**7**) with a slight excess of methyl  $\alpha$ -bromobutyrate (**6**) under Gilman and Speeter's conditions<sup>6</sup> for 6 h in refluxing benzene gave a 1 : 2 mixture of *cis* and *trans* isomers of (**10**) (60% yield).<sup>‡</sup> 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<sup>7</sup> such as *t*-butyl, menthyl, isopropyl, and *t*-butyldimethylsilyl  $\alpha$ -bromobutyrate failed and only the last two were successful for  $\beta$ -lactam formation. Ozonolysis of (**10**) in methylene chloride at  $-70^\circ\text{C}$  followed by dimethylsulphide work-up<sup>11</sup> gave a mixture of the corresponding *cis* and *trans* isomers of (**13**) in 70% yield, from which the *cis* isomer [ $\delta$  3.28–3.50 (m, H-3), 4.55 (d, *J* 6 Hz, H-4)] was separated by crystallization from  $\text{CHCl}_3$ –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 [ $\delta$  3.0 (br. t, *J* 7 Hz, H-3), 5.95 (br. s, H-4)]. Oxidative



**Scheme 1.** Reagents and conditions: i, Zn,  $\text{HgCl}_2$ , Ar = *p*- $\text{MeOC}_6\text{H}_4$ , toluene, reflux 8 h; ii,  $\text{O}_3$ ,  $-78^\circ\text{C}$ ,  $\text{CH}_2\text{Cl}_2$ , then  $\text{Me}_2\text{S}$ ; iii, MCPBA, benzene, reflux; iv, CAN,  $\text{MeCN-H}_2\text{O}$ , 25–30 min.

**Table 1.** Functionalized  $\beta$ -lactams prepared.

Compound <sup>a</sup>	% Yield	M.p./ $^\circ\text{C}^b$
(8) <sup>c</sup>	53	138–139
(9) <sup>d</sup>	50 <sup>e</sup>	114–115 <sup>f</sup>
(10) <sup>d</sup>	12	93–94 <sup>g</sup>
(11)	65	99–100 <sup>f</sup>
(13)	60	oil <sup>g</sup>
(13)	10	oil <sup>g</sup>
(14)	10	119–120 <sup>f,h</sup>
(14)	50	oil <sup>g</sup>
(15)	65	oil <sup>g</sup>
(15)	55	99–100
(15)	55	71–72 <sup>g</sup>

<sup>a</sup> Products were racemic mixtures and gave satisfactory spectral and analytical data. <sup>b</sup> Recrystallized from EtOH. <sup>c</sup> Prepared from the corresponding ethyl ester. <sup>d</sup> Prepared from the corresponding methyl ester. <sup>e</sup> Isolated as 1 : 1 mixture of *cis* and *trans* isomers. <sup>f</sup> *cis* Isomer. <sup>g</sup> *trans* Isomer. <sup>h</sup> Recrystallized from  $\text{CHCl}_3$ –hexane.

<sup>†</sup> The acid chloride–imine method or equivalent was ineffective for the preparation of the starting  $\beta$ -lactam (**10**).<sup>10</sup>

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

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

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

This work was supported by Comisión Asesora de Investigación Científica y Técnica (project 994/84). A grant from Ministerio de Educación y Ciencia (to J. M. O.) is gratefully acknowledged.

Received, 18th December 1987; Com. 1816

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