STEREOSELECTIVE SYNTHESIS OF BRL 56173, A BICYCLIC ACRYLIC PENICILLIN HIGHLY STABLE TO β-LACTAMASES

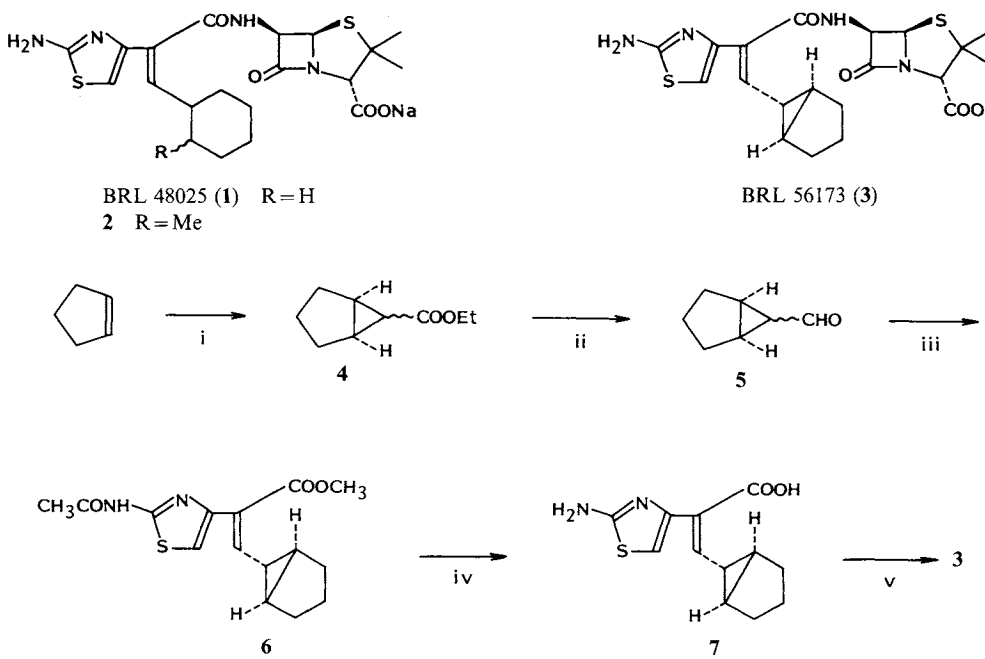
Sir:

Synthesis of the bicyclic acrylic penicillin **3** was initially achieved *via* ethyl diazoacetate addition to cyclopentene and progression of the resulting esters **4**. Problems associated with large-scale reactions of the diazo ester and production of *exo*/*endo* mixtures were avoided by use of an alternative synthesis *via* the 'Meinwald rearrangement' bicyclic aldehyde **8**, which was converted stereoselectively to the desired ester intermediate **6** in three steps. The outstanding biological features of **3**, BRL 56173, were broad-spectrum antibacterial activity coupled with very high stability to a variety of bacterial β-lactamases.

We recently reported[1,2] the synthesis of a series of α-acrylic penicillins typified by **1**, BRL 48025, which combined broad-spectrum activity against a range of Gram-positive and Gram-negative bacteria with good stability to β-lactamases. One of the analogues prepared was the (2-methyl)cyclohexyl compound **2**, which interestingly showed superior stability to β-lactamases (evinced by lower MICs against β-lactamase producing strains of *Haemophilus* and *Staphylococcus*) compared to **1**. However, **2** was produced as a mixture of stereoisomers which were not easily separated and was therefore not promising for further study. Following the theme of 2-substitution, we subsequently discovered a series of bicyclic acrylic penicillins[3] of which the most interesting was **3**, BRL 56173, which could be obtained more readily as the desired single *exo*-isomer shown. Despite the very large volume of research on semisynthetic penicillins and cephalosporins acylated with oximino- or acrylic (2-aminothiazol-4-yl) side-chains, this type of bicyclic [n.1.0] substituent appears to be novel.

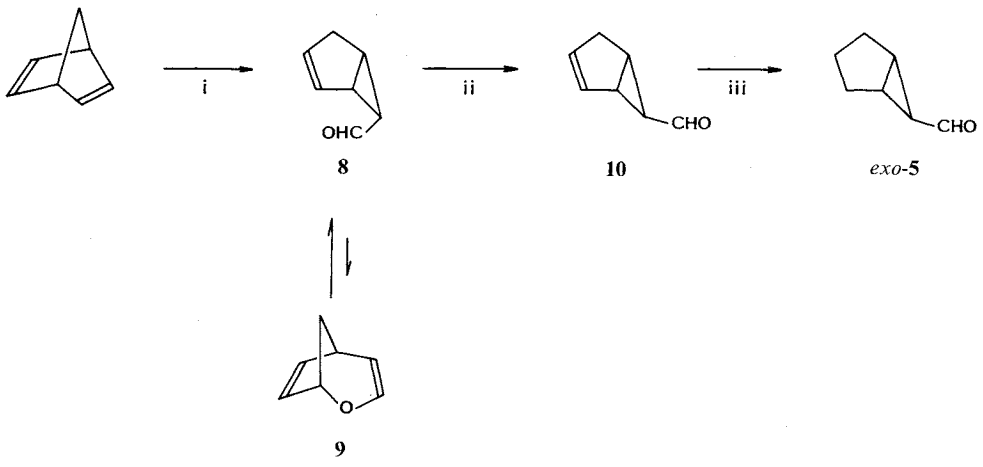
Our original synthesis of **3** is described in Scheme 1. The conversion of cyclopentene to esters **4** was originally performed using a copper catalyst as reported;[4] use of rhodium acetate dimer[5,6] was

Scheme 1. Synthesis of BRL 56173.

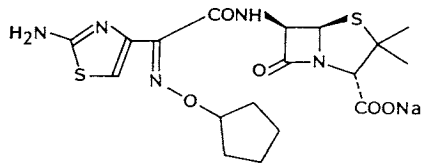


Reagents and conditions: i) EtO_2CCHN_2, $Rh_2(OAc)_4$, 60%; *exo*:*endo* variable, ≥2:1; ii) $LiAlH_4$, Et_2O, then $C_5H_5N^+HClCrO_3^-$, 85% overall; iii) either methyl 2-acetamidothiazol-4-acetate, piperidine, AcOH, PhMe, heat, or $ClCH_2COCH_2CO_2Me$, piperidine, AcOH, benzene, heat, then *N*-acetylthiourea, DMF, 4 Å sieves, 85°C, up to 60%; *Z*:*E ca.* 1:1; iv) separate *Z*,*exo*-isomer, then NaOH, aq dioxan, 90°C, 93%; v) DCC, 1-hydroxybenzotriazole, 6-aminopenicillanic acid, aq DMF, 78%.

Scheme 2. Synthesis of *exo*-**5**.



Reagents and conditions: i) CH_3CO_3H, Na_2CO_3, then SiO_2, 70%; ii) $C_5H_5NH^+I^-$, DMSO, 65%; iii) $(PPh_3)_3RhCl$, H_2, C_6H_6, 64%.



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effective at 1 molar % at below room temperature and gave a much superior yield. However, *exo/endo* mixtures of variable proportions resulted even after considerable experimentation, and the ratio was maintained following routine conversion to the aldehyde **5**.[4] The desired ester **6*** could be prepared using either the one- or two-step procedures shown, in satisfactory yield. By the one-step procedure, a separable mixture of *Z,exo*-**6** and *E,exo*-**6** resulted in about 25% yield, possibly reflecting low stability or reactivity of *endo*-**5** in refluxing toluene. On the other hand, the two-step procedure gave considerably higher yields of **6**, up to 60%, but then we isolated mixtures of *Z,exo*- and *Z,endo*-**6** which required further tedious chromatography or wasteful crystallisation for complete separation. Finally, hydrolysis of *Z,exo*-**6** to acid **7** (single isomer) was achieved in excellent yield, then an active ester coupling to 6-aminopenicillanic acid delivered penicillin **3**.[3]

Table 1. β-Lactamase stabilities of penicillins **1**, **3** and **11**.

Penicillin	Half-life (minutes) (MIC (μg/ml))		
	Staphylococcus aureus MB9	*Haemophilus influenzae* NEMC	*Moraxella catarrhalis* Ravasio
1	63 (0.5)	21 (0.12)	256 (0.25)
3	172 (0.5)	503 (0.12)	238 (0.12)
11	71 (0.5)	82 (0.25)	9.6 (0.5)

A neat solution to our isomer problems, which also obviated the use of the potentially hazardous diazo reagent and expensive rhodium catalyst, was provided by the recognition of the close similarity between **5** and the 'Meinwald rearrangement' bicyclic aldehyde **8**[7] (Scheme 2). After initial

* Spectral data on *Z,exo*-**6**: ν_{max} (KBr) cm^{-1} 1714, 1649, 1610 (sh) and 1559; δ_H (250MHz, $CDCl_3$) 1.19 (1H, ddd, J=13.2, 7.9 and 7.9 Hz, 3β-H), 1.52 (2H, br s, 1α-H and 5α-H), 1.63 (1H, m, J=13.2 Hz+2nd order, 3α-H), 1.77 (2H, dd, J=12.5 and 7.9 Hz, 2α-H and 4α-H), 1.88 (2H, m, J=12.5 Hz+2nd order, 2β-H and 4β-H) 2.13 (1H, ddd, J=11.1, 2.8 and 2.8 Hz, 6-H), 2.19 (3H, s, CH_3CONH), 3.86 (3H, s, CH_3O), 6.22 (1H, d, J=11.1 Hz, olefinic H), 6.97 (1H, s, thiazole 5-H) and 9.67 (1H, br s, D_2O exchange, NH); *m/z* (EI) 306 (M^+) (Found: M, 306.1033. $C_{15}H_{18}N_2O_2S$ requires M, 306.1038).

Table 2. MICs[a] (μg/ml) of 6β-acrylamido penicillins.

Organism	Derivative		
	1	**3**	**11**
Escherichia coli NCTC 10418	1.0	4.0	2.0
E. coli ESS	$\leq$0.03	$\leq$0.03	$\leq$0.03
E. coli 1077	8.0	4.0	32
Proteus mirabilis C977	4.0	4.0	4.0
Haemophilus influenzae Q1	0.06	0.12	0.06
H. influenzae NEMC 1[b]	0.12	0.12	0.25
Moraxella catarrhalis Ravasio[b]	0.25	0.12	0.5
Staphylococcus aureus Oxford	0.25	0.12	0.25
S. aureus Russell[b]	0.5	0.25	0.25
S. aureus MB9	0.5	0.5	0.5
S. aureus V573[c]	4.0	2.0	4.0
S. epidermidis PHLN 20	0.12	0.25	0.5
Streptococcus pneumoniae PU7[c]	1.0	2.0	2.0

[a] MIC values were determined by serial dilution in Blood Agar Base Oxoid against an inoculum of 1×10^6 cfu.
[b] β-Lactamase producing strains.
[c] Intrinsically resistant strains.

problems with polymerisation, exacerbated by attempted distillation of **8**, it was found that flash silica gel chromatography allowed isolation of **8** in 70% yield following peracetic acid oxidation of norbornadiene. The aldehyde **8*** actually exists as a valence tautomer, in equilibrium with bicyclic oxepine **9**[8] *via* oxy-Cope rearrangement: it may be for this reason that hydrogenation of **8** itself was unsuccessful, although this was claimed in an earlier report (no experimental details).[9] However, when **8** was first epimerised to *exo*-isomer **10*** (which cannot undergo the oxy-Cope rearrangement) using a procedure of BROWN's,[10] subsequent hydrogenation of **10** using 2.8 molar % $(PPh_3)_3RhCl$[11] in benzene (1 atm, 35°C) afforded *exo*-**5*** in good purity. Following some optimisation, the condensation of *exo*-**5** to give ester **6** (*Z*, *exo*-) was performed by the one-step procedure (Scheme 1) in up to 50% yield with an improved *Z*:*E* ratio.

The difference in biological properties resulting from introduction of the *exo*-bicyclo[3.1.0]hexyl substituent is demonstrated in Table 1, which shows the antibacterial activities (MIC's) and the stabilities of **1**, **3** and BRL 44154 (**11**[12]) against cell-free preparations of β-lactamases isolated from three different organisms. Apparent discrepancies between MIC's and half-lives in Table 1 are due to the determination of MIC's in whole cells compared with half-lives in cell-free preparations. Table 2 compares the activity of **1**, **3** and **11** against a wider range of organisms. The very high stability of **3** against TEM-1 β-lactamase (*Haemophilus* sp.) is especially noteworthy for a 6α-unsubstituted penicillin, and the improvement of **3** over **1** against penicillinase (*Staphylococcus* sp.) is also impressive. Finally it should be noted that the *exo* bicyclic penicillins of this class[3] showed superior β-lactamase stability over the *endo*-isomers.

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* ^{1}H NMR data for aldehydes **8**, **10** and *exo*-**5**, *inter alia*: **8**: δ_H (270 MHz, $CDCl_3$) 1.68 (1H, dd, J=6.2 and 6.8 Hz, 6-H), 5.85 (2H, br s, 2-H+3-H) and 9.18 (1H, d, J=6.2 Hz, 7-H). Also weak signals owing to oxepin **9**.[8] **10**: δ_H (270 MHz, $CDCl_3$) 1.22~1.31 (1H, m, 6-H), 5.59~5.65, 5.84~6.00 (2H, 2m, 2-H+3-H) and 9.34 (1H, d, J=4 Hz, 7-H). *exo*-**5**: δ_H (270 MHz, $CDCl_3$) 1.07~1.30 (1H, m, 6-H), 1.55~1.72 (2H, m, 1-H+5-H), and 9.11 (1H, d, J=4.7 Hz, 7-H).

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