Pergamon

Tetrahedron Vol. 50, No. 22, pp. 6643-6652, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0273-V

Stereoselectivity in the Peterson Reaction - Application to the Synthesis of BRL 49467.

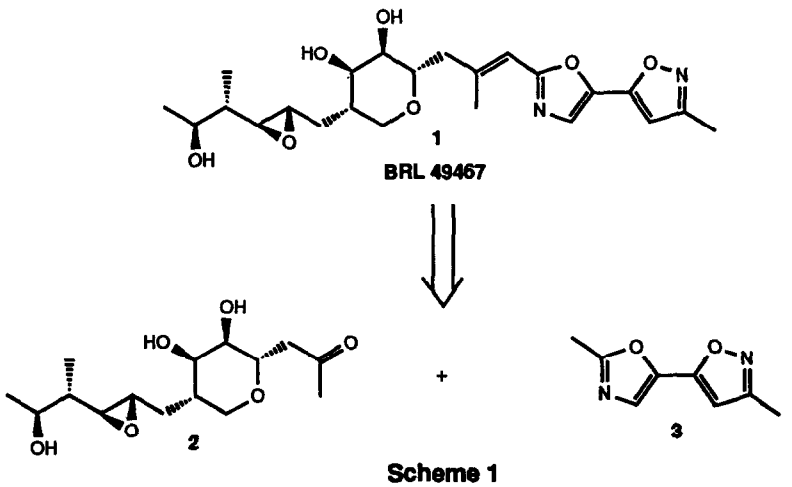
David Bell, Eleanor A. Crowe, Nicholas J. Dixon, Graham R. Geen*, Inderjit S. Mann and Mark R. Shipton

SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex, CM19 5AD, U.K.

Abstract.- The *E:Z* selectivity in the introduction of the tri-substituted double bond in BRL 49467 could be controlled by the choice of base and silyl group used in a Peterson olefination reaction. The method allowing optimum *E*-selectivity was developed such that it could be scaled up to 100mmol.

The Peterson reaction allows the stereospecific generation of an olefin from an aldehyde or ketone and an α-silyl carbanion *via* separation and elimination of the intermediate alcohols. However, when the α-silyl carbanion is stabilised by an electron withdrawing or aryl group *in situ* elimination occurs, and more subtle means are required for generating any desired stereoselectivity[1]. Predicting the stereochemical outcome of such reactions is difficult, and empirical methods are usually employed. We report here the stereoselective introduction in high yield of a tri-substituted *E*-olefin through the use of this reaction.

BRL 49467 **1** is a novel anti-bacterial compound, based on the topical antibiotic mupirocin **4** (Bactroban)[2-4], and shows activity against upper and lower respiratory tract infections as well as methicillin-resistant *Staphylococcus aureus* (MRSA). Previous preparations of BRL 49467[5], although suitable for small to medium scale work, were expensive and lacked convergence, and a short, efficient synthesis was required in order to fund toxicological and clinical studies. This paper describes our efforts in this direction.

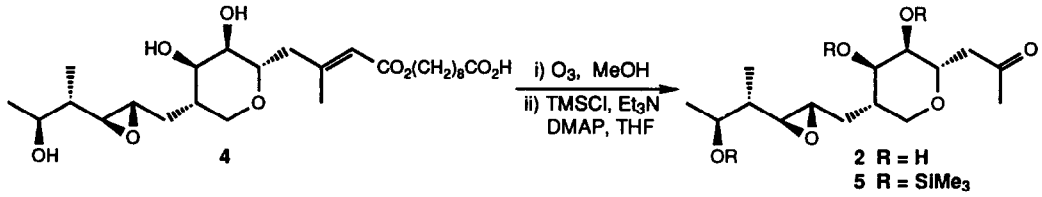


Scheme 1

Earlier work on compounds related to BRL 49467 had shown that a variety of 2-methyl oxazole derivatives could be coupled in a Peterson or Wittig reaction with the tris-trimethylsilyl ether protected methyl ketone **5**[6,7]. The Wittig reactions gave yields up to 43% and *E:Z* selectivities from 3:1 to 8:1, and the Peterson reactions gave yields up to 60% and *E:Z* selectivities from 1:1 to 13:1, (BRL 49467 has the *E*-stereochemistry). Although the yields were moderate to poor, the *E:Z* selectivities were encouraging, which suggested to us that it would be worth exploring this area in greater depth. The Peterson approach seemed the more promising both in terms of yield and selectivity, and we also felt that it would be easier to prepare the requisite silyl bis-heterocycle rather than a phosphine or phosphonate derived from **3**, (Scheme 1).

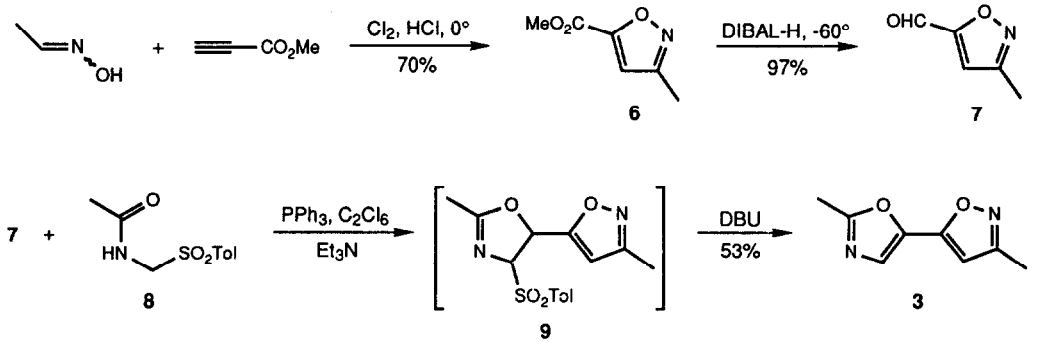
Synthesis of the reactants for the Peterson olefination

The ketone **2** was readily prepared by ozonolysis of pseudomonic acid A (mupirocin) **4**[4], and protected to give the tris-trimethylsilyl ketone **5** in 64% overall yield[7]. This material was used without further purification in olefination studies, (Scheme 2).



Scheme 2

Dipolar cycloaddition of the nitrile oxide derived from acetaldoxime with methyl propiolate followed by DIBAL-H reduction of the resulting isoxazole ester **6** afforded the aldehyde **7** having the desired regiochemistry. The bis-heterocycle **3** was then prepared in a single step from the isoxazole aldehyde **7**, and p-toluenesulphonylmethyl acetamide **8**[8]. Cyclisation to the p-toluenesulphonyl oxazoline **9** was achieved with triethylamine, triphenylphosphine and hexachloroethane in acetonitrile solution. The reaction products were extracted into ethyl acetate, and the solvent evaporated to give a dark semi-solid. It was found unnecessary to isolate **9**, but the crude mixture was dissolved in acetonitrile, and the elimination effected with DBU at ambient temperature. The pure bis-heterocycle **3** was isolated as pale yellow crystals by ethyl acetate extraction followed by silica chromatography, (Scheme 3).



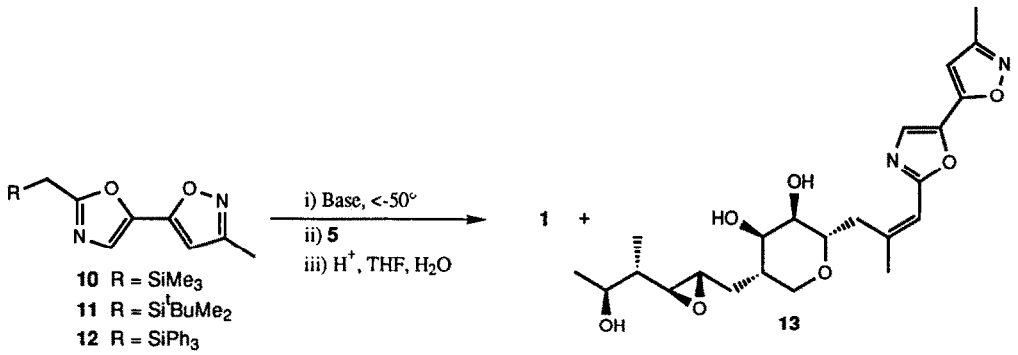
Scheme 3

Preliminary deuteration studies confirmed that the sole sites of n-butyllithium mediated deprotonation of **3** and the derived **10** were as desired at the oxazole methyl (**3**) or methylene (**10**).

Isolation of the trimethylsilyl bis-heterocycle **10** was complicated by its hydrolytic instability. Addition of chlorotrimethylsilane to the anion of **3** at -78°C resulted in decolorisation. Thin-layer chromatography indicated complete formation of product, but on work-up protodesilylation occurred, and only starting material was recovered. Further study confirmed that the silylated bis-heterocycle **10** could be efficiently formed at -78°C in 15 minutes and it was routinely used *in situ* without further treatment.

Standard procedure for Peterson olefination

A tetrahydrofuran solution of the bis-heterocycle **3** was deprotonated using n-butyllithium and the resulting deep red anion quenched with the appropriate chlorosilane or silyl triflate. After deprotonation of the silyl bis-heterocycle **10**, **11** or **12**, the red solution was added to a solution of the protected ketone **5**, the temperature being kept below -50°C to prevent competitive enolisation of **5**. After one hour the reaction was quenched with ammonium chloride solution, extracted with hexane, and freed of polar impurities by flash filtration through silica. Deprotection was effected by dissolution in 4:1 tetrahydrofuran / 0.4M hydrochloric acid for fifteen minutes, to give a mixture of the desired *E*-olefin **1** and the *Z*-isomer **13**, (Scheme 4). The geometric isomers were distinguished by nOe difference experiments, and the *E*:*Z* product ratio was measured from the ^{1}H NMR olefin proton integrations, or by hplc.



10 R = $SiMe_3$
11 R = Si^tBuMe_2
12 R = $SiPh_3$

Scheme 4

RESULTS

a) Change of silyl group

Initial studies followed the example of Crimmin *et al.* by generating the α-silyl anion with n-butyllithium[6,7]. It was anticipated that altering the nature of the bis-heterocycle silyl group would lead to changes in stereoselectivity[9]. Although this was found to be the case (see Table of Results, entries 1-3), the most stereoselective reaction was that using *tert*-butyldimethylsilyl **11** which gave a 7:1 selectivity in favour of the unwanted *Z*-isomer.

b) Change of Base

A marked change in selectivity was observed on varying the nature of the base employed in the deprotonation of the silyl bis-heterocycle, (see Table of Results). The use of amide bases resulted in the *E*-isomer being the major product, (entries 4-6). When using one equivalent of the anion generated from **10**, the *E*:*Z* product ratio improved from 1:1.5 with n-butyllithium to 7:1 with potassium bis(trimethylsilyl)amide. Greater *E*-selectivity was also observed when generating anions from **11** or **12**. The yield of products was still moderate, with unreacted ketone **5** remaining.

The presence of unreacted ketone **5** suggested that not all of the anion generated from **10** was reacting in the desired fashion. In order to drive the reaction to completion a two-fold excess of the α-silyl anion was needed, (entries 7-11). An attempt to recover the unreacted **3** resulted in only 11% of the excess being obtained, which suggested that significant degradation of **10** was occurring. Not only did the use of two equivalents of anion prove very successful in achieving complete reaction of **5**, but an added benefit was a further improvement in selectivity from 7:1 to 13:1 using the most *E*-selective base (potassium bis(trimethylsilyl)amide). (This could be further improved to 16:1 if the reaction was run at -100°C). The 90% yield of isolated products **1** + **13** was twice that obtained when using one equivalent of anion, (the use of 1.5 equivalents giving a yield of 72%).

Table of Results

Entry	Silyl bisheterocycle	Base	Equivs. silyl anion	Yield *E*+*Z* (**1**+**13**)%	*E*:*Z* (**1**:**13**)
1	**10**	n-BuLi	1	25	1 : 1.5
2	**11**	n-BuLi	1	29	1 : 7
3	**12**	n-BuLi	1	43	2 : 1
4	**10**	$KN(SiMe_3)_2$	1	45	7 : 1
5	**11**	$KN(SiMe_3)_2$	1	19	3 : 1
6	**12**	$KN(SiMe_3)_2$	1	28	4 : 1
7	**10**	$KN(SiMe_3)_2$	2	90	13 : 1
8	**10**	$NaN(SiMe_3)_2$	2	45	10 : 1
9	**10**	$LiN(SiMe_3)_2$	2	80	9.2 : 1
10	**10**	LiNTMP	2	c	6.4 : 1
11	**10**	LDA	2	c	4 : 1

c. Reaction proceeded to completion by hplc.

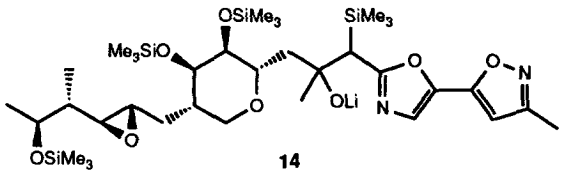
In early studies the *E*- and *Z*-isomers **1** and **13** were separated by column chromatography; latterly however, it was found that the desired *E*-isomer could be crystallized from acetone and hexane in high purity. The reaction between the tris-trimethylsilyl ketone **5** and the trimethylsilyl bis-heterocycle **10** was successfully scaled-up to 100mmol, giving BRL 49467 of suitable quality for the planned studies.

DISCUSSION

Evidence for chelation control

The generally accepted mechanism for the Peterson reaction of stabilised α-silyl carbanions with ketones involves the addition step to form an intermediate β-hydroxy silane which undergoes *syn* elimination to the olefin[10].

When the olefination reaction between **5** and **10** was carried out in the presence of an excess of 12-crown-4 ether to sequester the lithium present, no reaction ensued. Additionally, if suitable care was taken, the intermediate silyl bis-heterocycle **10** could be isolated by flash filtration through silica under nitrogen. Subsequent deprotonation of this with potassium bis(trimethylsilyl)amide followed by addition of the ketone **5** again failed to afford any product. This evidently points to the reaction being under chelation control, and any examination of the factors for stereocontrol must take this into account.



14

The reactive species in these reactions is the α-silyl carbanion derived from **10**, **11** or **12** which can exist in two enolate like forms **15a** and **15b**, and it appears that the relative proportions of these two forms is dependent on the base used to deprotonate, i.e. by analogy with deprotonation of carbonyl and oxazoline systems where *E*- or *Z*-enolate formation can be dictated by the nature of the base employed[11] (Figure 1, see also reference 7).

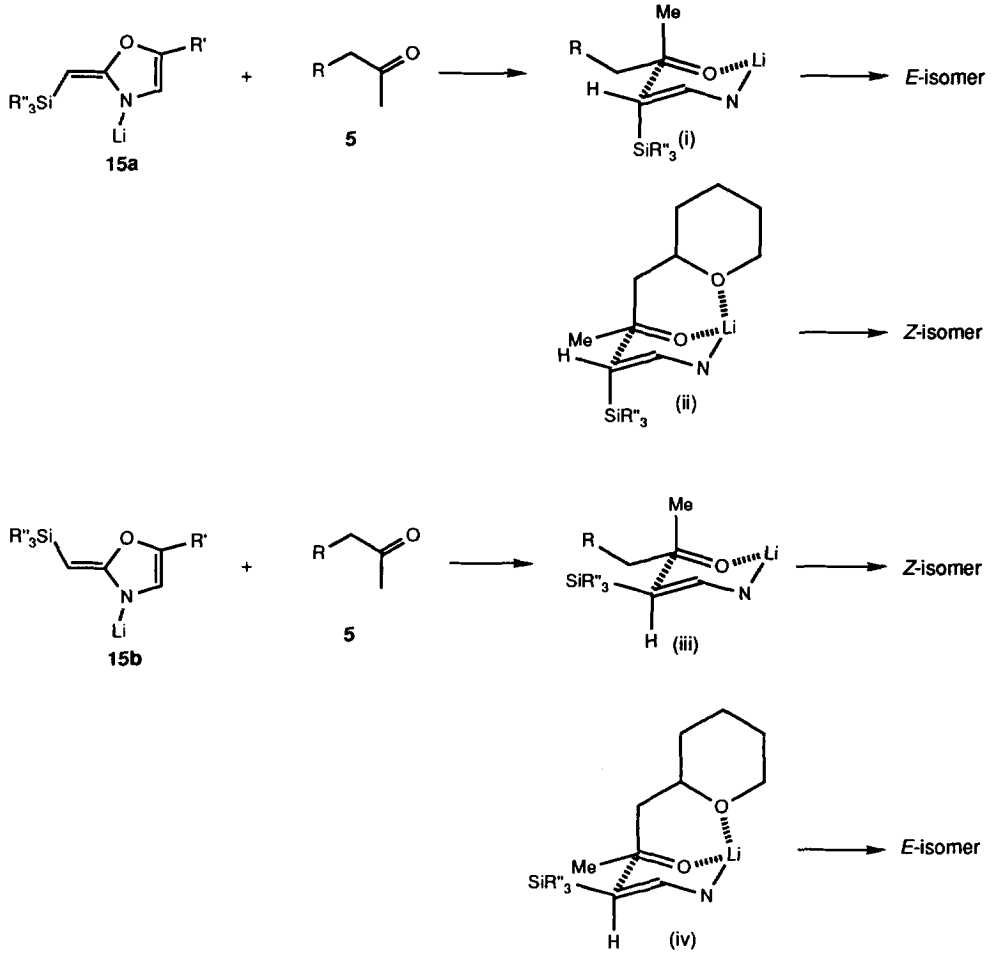


Figure 1

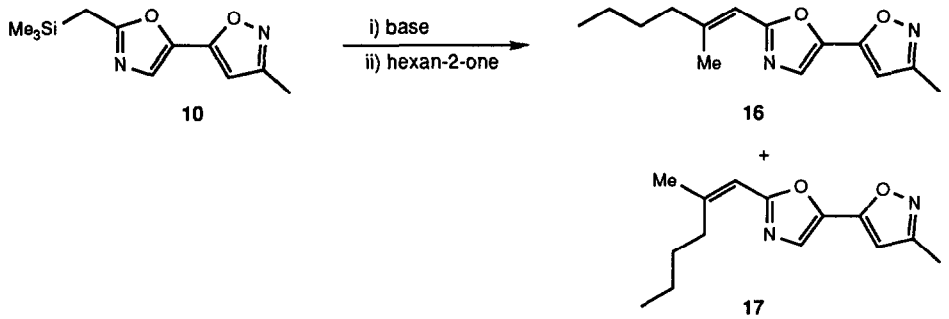
Since chelation control is involved this leads to a consideration of four possible chair-like transition states leading to the β-oxysilane **14**. Under normal circumstances transition state (iii) would be most favoured

where both the silyl group and the bulky ketone substituent are both lying equatorial, but because of the extra coordination possible via the pyran ring oxygen, transition state (iv) is most favoured leading to the *E*-isomer.

When n-butyllithium is used to deprotonate the silyl bis-heterocycle a mixture of the geometrical isomers **15a** and **15b** results, and if the rate of the addition step between the anion and the ketone is faster than the anion interconversion this would lead to preferential formation of *Z*-isomer from **15a**, and *E*-isomer from **15b**, resulting in an overall lack of selectivity.

Changing to amide bases presumably favours the form **15b** on the basis of steric repulsion between the trimethylsilyl group of **10** and the sterically-demanding base, hence leading to preference for the *E*-isomer[12]. The effect of using excess bis-heterocycle would also be to give a greater concentration of **15b** relative to the ketone leading to the improved selectivity as observed, from 7:1 to 13:1.

The significance of coordination of the pyran ring oxygen in the transition state was exemplified when a simple ketone was substituted for **5** in the Peterson reaction with **10**. Use of hexan-2-one would have been expected to favour transition state (iii) (R = n-propyl) *via* **15b**, and transition state (i) *via* **15a**, and we have observed a slight preference for the *Z*-isomer **17** over the *E*-isomer **16** when using n-butyllithium (*E*:*Z*, 1:1.2) and potassium bis(trimethylsilyl)amide (*E*:*Z*, 1:2), which is consistent with the transition states postulated, (Scheme 5).



10 **16** + **17**

Scheme 5

Deprotonation of the *tert*-butyldimethylsilyl bis-heterocycle **11** with n-butyllithium and subsequent reaction with **5** gives an *E*:*Z* ratio of 1:7, whereas the analogous reaction with potassium bis(trimethylsilyl)amide gives an *E*:*Z* of 3:1. This result is not so readily explained, but would suggest that deprotonation with n-butyllithium favours form **15a** and that the reaction proceeds primarily through transition state (ii), consistent with the Bassindale-Taylor model[13] of steric approach control, thus leading to the *Z*-isomer. Form **15b** (R" = *tert*-butyldimethylsilyl) is favoured when potassium bis(trimethylsilyl)amide is used, leading to preference for the *E*-isomer.

In conclusion, we would recommend that attention is paid to the nature of the silyl group, the base employed and the stoichiometry when designing a Peterson reaction involving a stabilised α-silyl carbanion, and when a specific product stereochemistry is desired.

ACKNOWLEDGEMENTS

We acknowledge the experimental assistance of G.T. Borrett and E.A. Twamley.

EXPERIMENTAL

^{1}H NMR spectra were recorded either on a Bruker AMX 400 spectrometer at 400MHz, or on a Jeol GX 270 spectrometer at 270MHz. Signals are quoted as δppm downfield from internal tetramethylsilane. ^{13}C NMR spectra were recorded on the same instruments at 100MHz (Bruker), or 67.5MHz (Jeol), chemical shifts were referenced to the deuterated solvent signals. Mass spectra were obtained on a Fisons VG Biotic Trio 2 spectrometer. Analytical hplc was performed using a Spherisorb S5 ODS2 15cm x 4.6mm column, eluting with solutions of acetonitrile / 0.05M potassium dihydrogen phosphate buffered to pH 7.0 with triethylamine; U.V. detection was employed at 300nm.

5-Carboxymethyl-3-methylisoxazole (6).

Acetaldoxime (156.8g, 2.66mol) was dissolved in 1.5M hydrochloric acid (630mL) and the solution cooled to -10°C. Chlorine gas (189.3g, 2.66mol) was bubbled in at such a rate that the temperature did not exceed -5°C. After the addition was complete, the mixture was extracted with dichloromethane (4x400mL) and the combined organic extracts were added without delay to a solution of methyl propiolate (240g, 2.84mol) in dichloromethane (12.4L) containing a suspension of potassium hydrogen carbonate (693g) and water (27mL). The initial blue green colour faded to a pale straw after 75 minutes. Water (2L) was added and the mixture stirred vigorously to dissolve the potassium hydrogen carbonate. The organic phase was separated and passed through a pad of anhydrous sodium sulphate, and the resulting dichloromethane solution evaporated to give a mass of oily crystals which by ^{1}H NMR contained the title compound **6** along with its 3,4-isomer in a ratio of 5:1 and combined yield of 275.4g, 75%. The mass of crystals was taken up in boiling dichloromethane (500mL), hexane (500mL) was added and the mixture evaporated until 400mL of solvent had been removed. The mixture was then allowed to cool in the refrigerator overnight. The resultant crystalline product was filtered off to give the title compound **6** as a colourless granular crystalline solid, (176.9g, 47%) m.p. 107°C; (lit. m.p. 108°C)[14].

^{1}H NMR ($CDCl_3$): 2.53 (3H,s,C-3 methyl), 4.00 (3H,s,CO_2Me), 6.55 (1H,s,H-4).

3-Methylisoxazole-5-carboxaldehyde (7).

5-Carboxymethyl-3-methylisoxazole **6** (112.0g, 0.784mol) was dissolved in dichloromethane and cooled to -65°C whilst the solution was thoroughly purged with dry nitrogen. Diisobutylaluminium hydride (1 molar solution in hexanes, 800mL, 0.8mol) was added dropwise over 90 minutes so as to maintain the temperature below -62°C. The solution was stirred at -65°C for a further 2 hours, and then 250mL of water was added slowly with vigorous stirring. The temperature was allowed to rise to 0°C, and the suspension was treated with 5 molar hydrochloric acid (625mL) to dissolve all the aluminium salts, causing the temperature to rise to 25°C. The organic phase was separated and the aqueous extracted with dichloromethane (3x500mL). The combined organic extracts were passed through a pad of anhydrous sodium sulphate and the resultant solution evaporated to dryness to yield the title compound **7** as a colourless solid, (88.1g, 100%), contaminated with 2% starting material. Recrystallisation from hexane afforded an analytically pure sample as colourless crystals m.p. 48°C; (lit. m.p. 47-48°C)[15].

^{1}H NMR ($CDCl_3$): 2.41 (3H,s,CH_3), 6.91 (1H,s,H-4), 9.93 (1H,s,CHO).

3-Methyl-5-(2-methyloxazol-5-yl)isoxazole (3).

p-Toluenesulphonylmethyl acetamide **8**[8] (28.4g, 0.125mol) and 3-methylisoxazole-5-carboxaldehyde **7** (18.0g, 0.162mol, 1.3eq) were dissolved in dry acetonitrile (345mL) under nitrogen at 25°C. Triphenylphosphine (49.1g, 0.188mol, 1.5eq) and triethylamine (45.4g, 0.25mol, 3.6eq) were added and the pale yellow solution was cooled to 5°C. Hexachloroethane (44.5g, 0.188mol, 1.5eq) was then added in two portions, the solution darkened rapidly and the temperature rose to 48°C. When the exothermicity had subsided, the cooling bath was removed and the reaction stirred overnight at ambient temperature. The

reaction mixture was diluted with ethyl acetate (800mL), washed with water (800mL) and the aqueous back extracted with ethyl acetate (600mL). The organic phases were combined, dried ($MgSO_4$) and the solvent evaporated to give a dark semi-solid. This was dissolved in dry acetonitrile (500mL), DBU (32mL) was added and the solution stirred at ambient temperature overnight. The solution was diluted with ethyl acetate (800mL), washed with water (750mL), dried ($MgSO_4$) and the solvent evaporated. Silica column chromatography of the dark solid eluting with 1:1 ether:hexane yielded the title compound (10.9g, 53%) as a yellow solid. Recrystallisation from hexane afforded pale yellow crystals m.p. 105-107°C.
^1H NMR ($CDCl_3$): 2.35 (s,3H,3-CH_3), 2.54 (s,3H,2'-CH_3), 6.30 (s,1H,H-4), 7.39 (s,1H,H-4'). ^{13}C NMR ($CDCl_3$): 11.26 (isoxazole CH_3), 13.94 (oxazole CH_3), 100.98 (C-4), 126.48 (C-4'), 140.66 (C-3), 158.84 (C-5 or C-5'), 159.97 (C-5 or C-5'), 162.64 (C-2').
EI-MS. m/e: 164 (M^+), 82 (M^+-C_4H_4NO).
Found; C:58.64, H:4.92, N:16.99. $C_8H_8N_2O_2$ requires; C:58.53, H:4.91, N:17.06%.

Purification of the dark semi-solid resulting from the cyclisation by silica column chromatography, eluting with dichloromethane resulted in the isolation of 3-methyl-5-[2-methyl-4-(toluene-4-sulphonyl)-4,5-dihydro-oxazol-5-yl]isoxazole **9** as a colourless crystalline solid, m.p. 106-107°C, (diethyl ether/hexane).
^1H NMR ($CDCl_3$): 2.10 (d,3H,2'-CH_3), 2.31 (s,3H,3-CH_3), 2.46 (s,3H,PhCH_3), 5.28 (dq,1H,H-5'), 6.03 (d,1H,H-4'), 6.23 (s,1H,H-4), 7.39 (d,2H,Ph), 7.84 (d,2H,Ph). ^{13}C NMR ($CDCl_3$): 11.37 (isoxazole CH_3), 14.01 (oxazoline CH_3), 21.76 (PhCH_3), 72.10 (C-4'), 90.48 (C-5'), 104.48 (C-4), 129.51 (Ph), 129.97 (Ph), 132.91 (Ph), 145.86 (Ph), 160.14 (C-3), 166.30 (C-5), 170.26 (C-2').
CI-MS. m/e: 321 (MH^+), 296 (MH^+-CH_3).
Found; C:56.40, H:5.04, N:8.74. $C_{15}H_{16}N_2O_4S$ requires; C:56.24, H:5.03, N:8.74%.

3-Methyl-5-(2-trimethylsilylmethyloxazol-5-yl)isoxazole (10).

To a solution of 3-methyl-5-(2-methyloxazol-5-yl)isoxazole **3** (0.246g, 1.5mmol) in dry tetrahydrofuran (15mL) under an atmosphere of dry nitrogen at -78°C was added n-butyllithium (1.6 molar solution in hexane, 0.94mL, 1.5mmol), and the reaction stirred at that temperature for 15 minutes. Chlorotrimethylsilane (0.18g, 1.65mmol) was then added, and the solution stirred at the same temperature for a further 40 minutes before being allowed to warm to ambient temperature overnight. The solvent was then evaporated under reduced pressure, and the residue purified by flash column chromatography on silica under nitrogen. Elution with 30% diethyl ether in hexane afforded 3-methyl-5-(2-trimethylsilylmethyloxazol-5-yl)isoxazole (0.124g, 35%) **10** as a pale yellow solid which deteriorated quickly on storage.
^1H NMR (DMSO-d_6, shifts referenced to residual DMSO-d_5 at 2.50 ppm): 0.08 (s,9H,Si[CH_3]$_3$), 2.28 (s,3H,3-CH_3), 2.39 (s,2H,CH_2), 6.65 (s,1H,H-4), 7.63 (s,1H,H-4').

Typical Peterson Procedure.

To a solution of 3-methyl-5-(2-methyloxazol-5-yl)isoxazole **3** (0.164g, 1.0mmol) in dry tetrahydrofuran (10mL) under an atmosphere of dry nitrogen at -78°C was added n-butyl lithium (1.6 molar solution in hexane, 0.66mL, 1.05mmol) and the deep red reaction stirred for 15 minutes. The chlorosilane (or triflate in the case of *tert*-butyldimethyl) (1.05mmol) was then added, and the reaction stirred for a further 20 minutes, during which time the red colour was largely discharged. The desired base (1.0mmol) was added, and the reaction mixture stirred at -78°C for 30 minutes, a deep red colour once again persisting. A solution of the ketone **5**[7] in dry tetrahydrofuran was then added, the reaction mixture stirred for a further 60 minutes, and then allowed to warm to ambient temperature overnight. The reaction was quenched by addition of ammonium chloride solution (35mL), and extracted with ethyl acetate (3x35mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated to afford the crude product mixture as an orange oil. Deprotection was effected by dissolving the oil in tetrahydrofuran (40mL) and water (10mL), adding conc. hydrochloric acid (5 drops), and stirring the solution at ambient temperature for 5 minutes. Saturated sodium bicarbonate solution was then added, and the mixture extracted with ethyl acetate (3x35mL). The combined

organic extracts were dried ($MgSO_4$) and the solvent evaporated to afford an oil which was purified by column chromatography on silica. Elution with 2% methanol in dichloromethane afforded firstly the Z-isomer **13**, then the *E*-isomer **1** as pale glasses.

Z-isomer (13).

^1H NMR (CD_2Cl_2): 0.92 (d,3H,CH_3-17), 1.16 (d,3H,CH_3-14), 1.28 (m,1H,CH-12), 1.59 (m,1H,CH_2-9), 1.74 (m,1H,CH_2-9), 1.99 (m,1H,CH-8), 2.13 (d,3H,CH_3-15), 2.33 (s,3H,isoxazole CH_3), 2.34 (d,1H,OH), 2.64 (dd,1H,CH-11), 2.76 (ddd,1H,CH-10), 2.86 (brs,1H,OH), 2.96 (ABM-multiplet,2H,CH_2-4), 3.49 (ddd,1H,CH-6), 3.60 (dd,1H,CH_2-16), 3.76 (m,2H,CH-5,13), 3.87 (dd,1H,CH_2-16), 3.92 (m,1H,CH-7), 6.02 (d,1H,OH), 6.29 (m,1H,CH-2), 6.38 (s,1H,isoxazole CH), 7.49 (s,1H,oxazole CH).

^{13}C NMR (CD_2Cl_2): 10.8 (isoxazole CH_3), 12.2 (CH_3-17), 20.2 (CH_3-14), 27.1 (CH_3-15), 31.4 (CH_2-9), 36.0 (CH_2-4), 38.8 (CH-8), 42.8 (CH-12), 55.6 (CH-10), 60.9 (CH-11), 65.2 (CH_2-16), 66.9 (CH-6), 69.9 (CH-7), 71.0 (CH-13), 76.8 (CH-5), 101.4 (isoxazole C-4), 111.4 (CH-2), 125.9 (oxazole C-4), 139.2 (oxazole C-5), 153.0 (C-3), 158.2 (isoxazole C-5), 160.0 (isoxazole C-3), 161.9 (oxazole C-2).

EI-MS. m/e: 449 (MH^+), 420 (M^+-H_2O), 233 ($C_{12}H_{13}N_2O_3^+$), 204 ($C_{11}H_{12}N_2O_2^+$).

Found; C:61.51, H:7.00, N:6.30. $C_{23}H_{32}N_2O_7$ requires; C:61.59, H:7.19, N:6.25%.

***E*-isomer (1).**

^1H NMR (CD_2Cl_2): 0.92 (d,3H,CH_3-17), 1.18 (d,3H,CH_3-14), 1.31 (m,1H,CH-12), 1.71 (m,2H,CH_2-9), 1.99 (m,1H,CH-8), 2.30 (d,$^4J_{15\text{-}2}$=1.3Hz,3H,CH_3-15), 2.32 (s,3H,isoxazole CH_3), 2.39 (dd,1H,CH_2-4), 2.52 (brs,1H,OH), 2.69 (dd,1H,CH-11), 2.71 (dd,1H,CH_2-4), 2.79 (ddd,1H,CH-10), 2.88 (brd,1H,OH), 3.00 (brs,1H,OH), 3.48 (m,1H,CH-6), 3.56 (dd,1H,CH_2-16), 3.78 (m,2H,CH-5,13), 3.89 (dd,1H,CH_2-16), 3.92 (m,1H,CH-7), 6.25 (m,1H,CH-2), 6.35 (s,1H,isoxazole CH), 7.50 (s,1H,oxazole CH).

^{13}C NMR (CD_2Cl_2): 10.8 (isoxazole CH_3), 12.2 (CH_3-17), 19.1 (CH_3-15), 20.3 (CH_3-14), 31.3 (CH_2-9), 39.6 (CH-8), 42.68 (CH-12), 42.74 (CH_2-4), 55.3 (CH-10), 60.8 (CH-11), 65.0 (CH_2-16), 68.8 (CH-6), 70.3 (CH-7), 71.0 (CH-13), 74.8 (CH-5), 100.9 (isoxazole C-4), 112.1 (CH-2), 127.0 (oxazole C-4), 138.9 (oxazole C-5), 149.5 (C-3), 158.7 (isoxazole C-5), 160.0 (isoxazole C-3), 162.1 (oxazole C-2).

EI-MS. m/e: 449 (MH^+), 448 (M^+), 233 ($C_{12}H_{13}N_2O_3^+$), 216 ($C_{12}H_{12}N_2O_2^+$), 204 ($C_{11}H_{12}N_2O_2^+$).

Found; C:61.84, H:7.12, N:6.41. $C_{23}H_{32}N_2O_7$ requires; C:61.59, H:7.19, N:6.25%.

Large Scale Preparation of BRL 49467 (1).

To a solution of 3-methyl-5-(2-methyloxazol-5-yl)isoxazole **3** (32.8g, 0.20mol) in dry tetrahydrofuran (2.0L) under an atmosphere of dry nitrogen at -70°C was added n-butyllithium (1.5 molar solution in hexane, 140mL, 0.21mol) over a period of ten minutes. Twenty minutes after completion of the addition, chlorotrimethylsilane (23.1g, 0.21mol) was added, (tlc indicated complete formation of **10** in 25 minutes). Potassium bis(trimethylsilyl)amide (0.5 molar solution in toluene, 400mL, 0.20mol) was then added over a period of twenty minutes, and the reaction mixture stirred for a further 75 minutes at -65 to -70°C. A solution of the ketone **5** (51.8g, 0.10mol) in dry tetrahydrofuran (200mL) was then added over a period of 20 minutes, and the reaction mixture stirred for a further 60 minutes at the same temperature. The reaction was quenched by addition of ammonium chloride (1.0 molar solution in water, 1.5L), and allowed to warm to ambient temperature before being extracted with hexane (1x2L, 1x1L). The organic extracts were dried ($MgSO_4$) and the solvent evaporated to afford the crude product mixture as an orange oil.

This was redissolved in a little hexane and filtered through a silica pad (800g), eluting with 25% diethyl ether in hexane (6L). Reduced-pressure evaporation of solvent from the filtrate afforded an oil which was dissolved in tetrahydrofuran (1L). To this was added aqueous hydrochloric acid (0.15 molar, 223mL) and the solution stirred at ambient temperature for 8 minutes, before adding saturated sodium bicarbonate solution (40mL) and water (50mL). The mixture was extracted with ethyl acetate (1x700mL, 1x500mL), and the combined organic extracts washed with brine (500mL), dried ($MgSO_4$) and evaporated under reduced pressure. The dark orange oil was redissolved in ethyl acetate (150mL), and diisopropyl ether (1.5L) added slowly, precipitating an off-white solid. After stirring overnight under an atmosphere of nitrogen, the precipitate was filtered off, washed with diisopropyl ether and vacuum dried to give 30.0g, 67% off-white solid. This was dissolved in acetone (270mL) and hexane (330mL) added. The solution was seeded and

stirred under nitrogen at ambient temperature for 2 hours. Further hexane (100mL) was then added, and the mixture stirred for 1 hour before filtering off the product. This was then washed with a little 25% acetone in hexane, and dried under vacuum to afford **BRL 49467** (**1**) (24.1g, 54%) as colourless crystals m.p. 105-107°C. Refrigerating the mother liquors allowed isolation of a second crop of crystals (2.8g, 6%).

Reactions of 3 with hexan-2-one.

The experimental methods followed the typical Peterson procedure described above. Deprotonation of the intermediate **10** was conducted with n-butyllithium and potassium bis(trimethylsilyl)amide. The reactions were run at a 2.0mmol scale, and the hexan-2-one added as a neat liquid. Deprotection was of course unnecessary, and the product mixtures were purified by silica column chromatography. Elution with 10% diethyl ether in hexane afforded mixtures of *E*- and *Z*-isomers as colourless oils. Integration of the characteristic ^{1}H NMR signals at δ1.86 and 2.60 (*Z*-isomer), and δ2.12 and 2.14 (*E*-isomer) for the methyl and methylene groups adjacent to the olefinic centre suggested a product ratio of *E*:*Z* of 1:1.2 for the n-butyl lithium mediated reaction, and 1:2 for that using potassium bis(trimethylsilyl)amide. The products **16** and **17** were not separated.

REFERENCES AND NOTES

1. Ager, D.J. *Synthesis*, **1984**, 384-398; *Org. Reactions*, **1990**, *38*, 1-223; and references cited therein. Larcheveque, M.; Debal, A. *J. Chem. Soc., Chem. Commun.*, **1981**, 877-878. Larson, G.L.; de Kaifer, C.F.; Seda, R.; Torres, L.E.; Ramirez, J.R. *J. Org. Chem.*, **1984**, *49*, 3385-3386. Inoue, S.; Sato, Y. *J. Org. Chem.*, **1991**, *56*, 347-352. Barrett, A.G.M.; Flygare, J.A. *J. Org. Chem.*, **1991**, *56*, 638-642.
2. Bactroban is a trade mark of SmithKline Beecham.
3. Chain, E.B.; Mellows, G. *J. Chem. Soc., Perkin Trans. I*, **1977**, 294-309.
4. Alexander, R.G.; Clayton, J.P.; Luk, K.; Rogers, N.H. *J. Chem. Soc., Perkin Trans. I*, **1978**, 561-565.
5. O'Hanlon, P.J.; Walker, G. *European Patent Application*, 0 399 645 A.
6. Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H. *J. Chem. Soc., Perkin Trans I*, **1985**, 541-547.
7. Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H.; Walker, G. *J. Chem. Soc., Perkin Trans I*, **1989**, 2047-2057.
8. Olijnsma, T.; Engberts, J.B.F.N.; Strating, J. *Rec. Trav. Chim.*, **1967**, *86*, 463-473.
9. Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H.J. *J. Am. Chem. Soc.*, **1981**, *103*, 5568-5570. Larson, G.L.; Quiroz, F.; Suarez, J. *Synthetic Commun.*, **1983**, *13*, 833-844. Bassindale, A.R.; Ellis, R.J.; Taylor, P.G. *Tetrahedron Lett.*, **1984**, *25*, 2705-2708.
10. Peterson, D.J. *J. Org. Chem.*, **1968**, *33*, 780-784. Hudrlik, P.F.; Peterson, D. *J. Am. Chem. Soc.*, **1975**, *97*, 1464-1468.
11. Evans, D.A. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1. Meyers, A.I.; Snyder, E.S.; Ackerman, J.J.H. *J. Am. Chem. Soc.*, **1978**, *100*, 8186-8189. Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. *J. Am. Chem. Soc.*, **1978**, *100*, 8182-8185.
12. Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.*, **1976**, *98*, 2868-2877.
13. Bassindale, A.R.; Ellis, R.J.; Lau, J.C-Y.; Taylor, P.G. *J. Chem. Soc., Chem. Comm.*, **1986**, 98-100. Bassindale, A.R.; Ellis, R.J.; Lau, J.C-Y.; Taylor, P.G. *J. Chem. Soc., Perkin Trans II*, **1986**, 593-597.
14. Barco, A.; Benetti, S.; Pollini, G.P.; Baraldi, G.P. *Synthesis*, **1977**, 837.
15. Quilico, A.; Panizzi, L.; Epifani, C. *Gazz. Chim. Ital.*, **1939**, *69*, 536-546.

(*Received in UK* 14 *March* 1994; *accepted* 25 *March* 1994)