Highly functionalised monocyclic and bicyclic β-lactams *via* alkene metathesis

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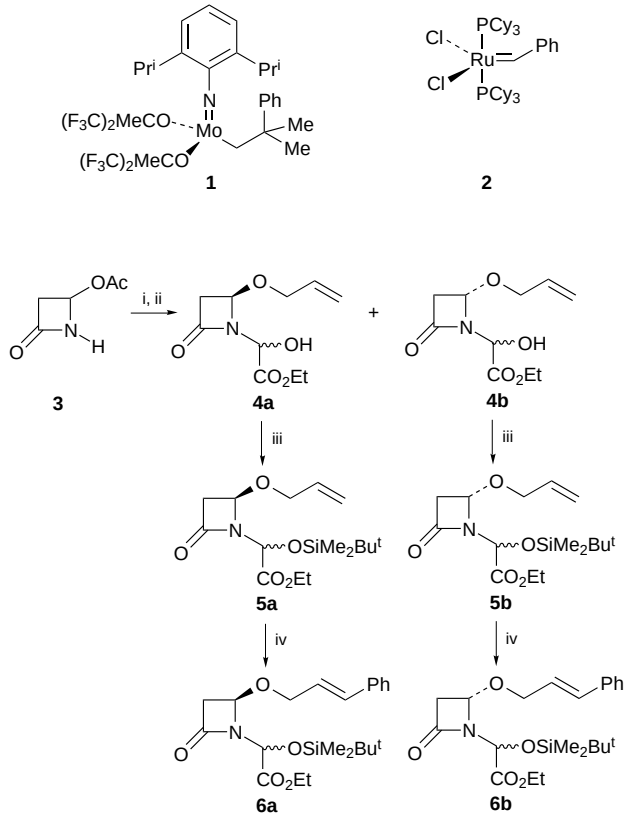
Both monocyclic and bicyclic β-lactam systems are prepared *via* alkene metathesis reactions using Mo(=CHCPhMe$_2$)(=NC$_6$H$_3$Pr$^i_2$)[(OCMe(CF$_3$)$_2$]$_2$ or Ru(=CHPh)Cl$_2$(PCy$_3$)$_2$.

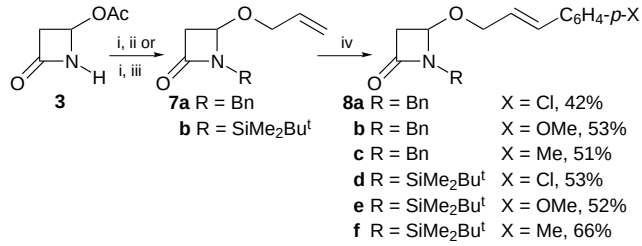
The elaboration of carbon skeletons *via* the construction of carbon–carbon bonds represents one of the most important endeavours in synthetic organic chemistry. Transition metal catalysed processes are especially valuable, particularly for the selective transformation of polyfunctional precursors into products of enhanced complexity. The pioneering work of Grubbs has shown that a wide variety of compounds may be synthesised *via* ring-closing metathesis (RCM) procedures[1] using molybdenum **1**[2] and ruthenium **2**[3] based catalysts. Other workers have extended this methodology which is now finding increasing use in synthesis.[4–8] Our group has recently shown that a number of previously unexplored systems are amenable to alkene metathesis.[9,10] In particular we have shown that β-lactams are well tolerated under metathesis conditions furnishing both mono- and bi-cyclic systems alike in good to excellent yields. Herein we report the extension of this work to the synthesis of more highly functionalised β-lactams.

Sequential reaction of the commercially available 4-acetoxyazetidin-2-one **3** with allyl alcohol and ethyl glyoxylate produced the diastereomeric alkenes **4a,b** (Scheme 1) which were separable by chromatography. Protection of **4a** and **4b** with *tert*-butyldimethylchlorosilane gave the metathesis substrates **5a,b**† in quantitative yield. In a similar manner treatment of 4-acetoxyazetidin-2-one **3** with allyl alcohol followed by benzyl bromide or *tert*-butyldimethylchlorosilane gave alkenes **7a** (69%) and **7b** (76%) respectively. Reaction of **5a** with excess styrene (4 equiv.) and a catalytic amount of carbene **1** (1 mol%) in dichloromethane at room temperature for 2 h produced the desired alkene **6a** (79%) (Scheme 1). Similarly epimer **5b** gave **6b** under the same conditions in comparable yield (67%). In all the cross metathesis processes reported herein only the *trans* double bond isomers were observed. We then explored a series of electronically diverse styrenes (*p*-Cl, *p*-OMe, *p*-Me) as the cross metathetic partners of protected β-lactams **7a** and **7b**. The reactions proceeded smoothly in the presence of **1** (1 mol%) to furnish *trans* alkenes **8a**–**f** (42–66%) (Scheme 2).

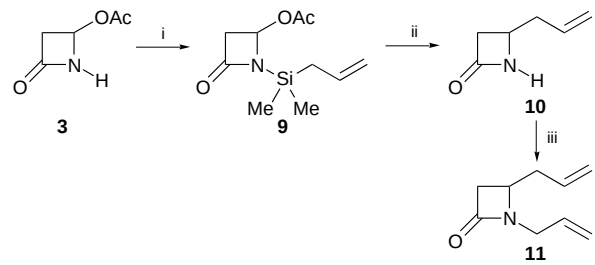
The synthesis of novel heteroatom-containing β-lactam substrates suitable for RCM were examined next. Following the procedure of Uyeo[11] a modified Sakurai-type reaction was utilised to synthesise 4-allylazetidin-2-one **10** (Scheme 3). Treatment of 4-acetoxyazetidin-2-one **3** with allylchlorodimethylsilane in the presence of an amine base followed by



Scheme 1 *Reagents and conditions*: i, $HOCH_2CH{=}CH_2$, $Zn(OAc)_2$, PhH, heat, 4 h, 83%; ii, $H(O)CCO_2Et$, PhMe, heat 15 h, 79%; iii, Bu^{t}Me$_2$SiCl, DMAP, CH_2Cl_2, 25 °C, 2 d, 100%; iv, **1** (1 mol%), $PhCH{=}CH_2$, CH_2Cl_2, 25 °C

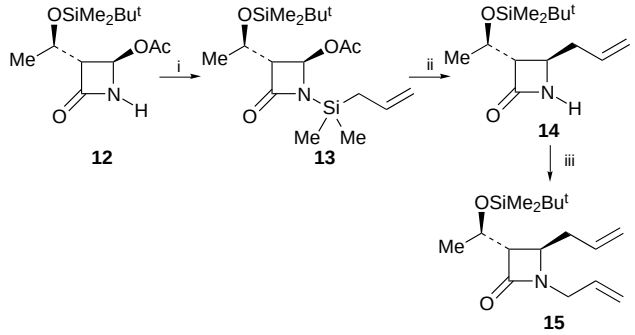


Scheme 2 *Reagents and conditions*: i, $HOCH_2CH{=}CH_2$, $Zn(OAc)_2$, PhH, heat, 4 h, 83%; ii, $BrCH_2Ph$, NaH, DMF, 0 °C, 83%; iii, Bu^{t}Me$_2$SiCl, NEt_3, CH_2Cl_2, 0 °C, 92%; iv, **1** (1 mol%), *p*-X-$C_6H_4CH{=}CH_2$, CH_2Cl_2, 25 °C

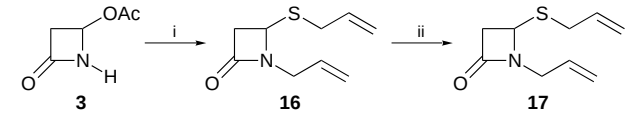


Scheme 3 *Reagents and conditions*: i, $ClSiMe_2CH_2CH{=}CH_2$, NEt_3, CH_2Cl_2, 25 °C, 15 h, 85%; ii, Me_3SiOTf, CH_2Cl_2, 0 °C, 2 h, 71%; iii, $BrCH_2CH{=}CH_2$, KOH, 18-crown-6, PhH, 25 °C, 2 h, 77%

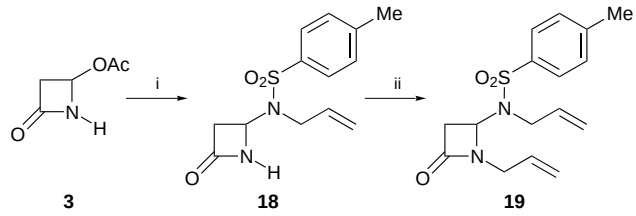
reaction with a catalytic quantity of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) gave 4-allylazetidin-2-one **10** (59% over 2 steps). This proved to be rather unstable and was treated immediately with allyl bromide and potassium hydroxide to give the diene **11** (77%). In an analogous manner substrate **15** was synthesised, starting from commercially available (3*R*,4*R*)-3-[(*R*)-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one **12** (Scheme 4, 46% over 3 steps). In this reaction sequence the Me_3SiOTf mediated allyl transfer to produce **14** from **13** was a stereoselective process furnishing a single



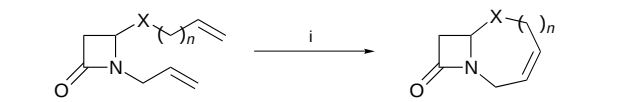
Scheme 4 *Reagents and conditions*: i, $ClSiMe_2CH_2CH{=}CH_2$, NEt_3, CH_2Cl_2, 25 °C, 15 h, quant.; ii, Me_3SiOTf, CH_2Cl_2, 0 °C, 2 h, 91%; iii, $BrCH_2CH{=}CH_2$, KOH, 18-crown-6, PhH, 25 °C, 2 h, 92%



Scheme 5 *Reagents and conditions*: i, $HSCH_2CH{=}CH_2$, NaOMe, MeOH, 25 °C, 90 min, 69%; ii, $BrCH_2CH{=}CH_2$, NaH, DMF, 0 °C, 1 h, 81%



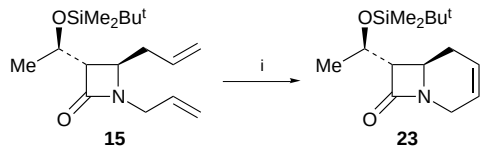
Scheme 6 *Reagents and conditions*: i, *p*-$MeC_6H_4SO_2NHCH_2CH{=}CH_2$, KOBu^t, 18-crown-6, MeCN, 25 °C, 30 min, 67%; ii, $BrCH_2CH{=}CH_2$, NaH, DMF, 0 °C, 1 h, 89%



11 X = CH_2, *n* = 0
17 X = S, *n* = 1
19 X = *p*-$MeC_6H_4SO_2N$, *n* = 1

20 X = CH_2, *n* = 0
21 X = S, *n* = 1
22 X = *p*-$MeC_6H_4SO_2N$, *n* = 1

Scheme 7 *Reagents and conditions*: i, X = CH_2, *n* = 0, **2** (5 mol%), CH_2Cl_2, 25 °C, 6 h, 81%; i, X = S, *n* = 1, **1** (5 mol%), CH_2Cl_2, 25 °C, 2 h, 78%: i, X = *p*-$MeC_6H_4SO_2N$, *n* = 1, **1** (5 mol%), CH_2Cl_2, 25 °C, 2 h, 91%



Scheme 8 *Reagents and conditions*: i, **2** (5 mol%), CH_2Cl_2, 25 °C, 6 h, 78%

diastereomer. The novel diene **17** was obtained by sequential treatment of 4-acetoxyazetidin-2-one **3** with prop-2-enethiol and allyl bromide (Scheme 5, 56% over 2 steps). Alkene **19** was synthesised by reaction of 4-acetoxyazetidin-2-one **3** with *N*-tosylallylamine (67%) according to the procedure of Campbell and Connarty[12] followed by *N*-allylation of the resulting β-lactam **18** with allyl bromide (89%).

With the RCM substrates in hand, diene **11** was exposed to a catalytic quantity of ruthenium carbene **2** (5 mol%) in dichloromethane at room temperature. Diene **11** was rapidly converted into the bicyclic [2.4.0]carbacephem **20** in excellent yield (81%) (Scheme 7). In this and the other RCM processes (*vide infra*), only a single product component was evident by TLC analysis. In a similar manner diene **15** was converted into carbacephem **23** in high yield (Scheme 8, 78%). RCM of dienes **17** and **19** proceeded only slowly with ruthenium catalyst **2** (5 mol%) giving bicyclic lactams **21** and **22** in low isolated yield (22 and 36% respectively). However, replacement of the ruthenium catalyst **2** with the molybdenum catalyst **1** (5 mol%) resulted in rapid reactions leading to the isolation of homocephem **21** (78%) and homo-azacephem **22** in excellent yield (91%) (Scheme 7).

In conclusion we have shown that alkene metathesis is an extremely useful synthetic tool for the synthesis of highly functionalised monocyclic β-lactams and a variety of bicyclic β-lactams. The range of heteroatoms tolerated in the ring-closing metathesis reaction (C, O, N and S) suggests that this methodology should be of enormous use for the synthesis of a great range of antibiotics and their derivatives. The azacephem system is of particular interest as this is a relatively unexplored area. Recent work on azapenems has been published by Hegedus[13,14] and our work provides an alternative metal-mediated route to such systems.

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Footnote

† All new compounds were fully characterised spectroscopically and further by microanalysis and/or HRMS.

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