Alkene metathesis in the synthesis of novel β-lactams

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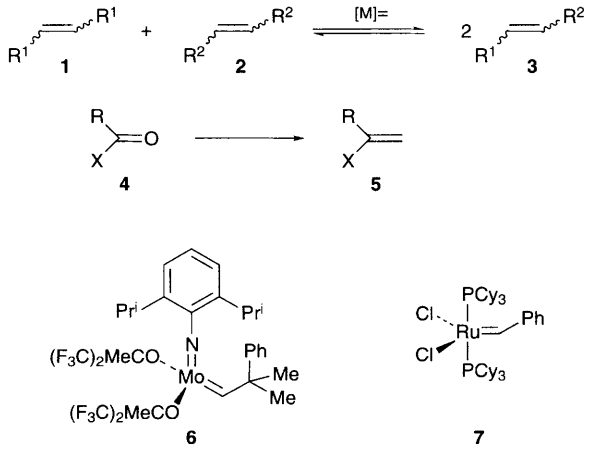
Both monocyclic and bicyclic β-lactams systems are prepared *via* alkene metathesis reactions using Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$Pr$^i_2$-2,6)[OCMe(CF$_3$)$_2$]$_2$ or Ru(=HPh)Cl$_2$(PCy$_3$)$_2$.

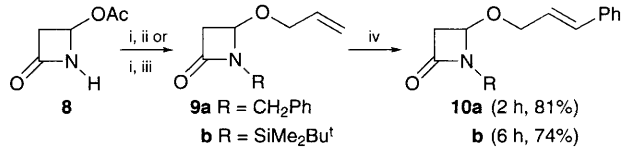
The elaboration of carbon skeletons *via* the construction of carbon–carbon bonds represents one of the most important endeavours in synthetic organic chemistry. Transition metal catalysed processes are especially valuable particularly for the selective transformation of polyfunctional precursors into products of enhanced complexity. Alkene metathesis and related transition metal mediated alkylidenylation reactions are of considerable potential in synthesis and these transformations are illustrated by the equilibration of alkenes **1**, **2** and **3** and the preparation of alkene **5**. Both processes are effected using metal carbene complexes. The development of isolable, well defined catalysts for alkene metathesis of types **6**[1] and **7**[2] and their use in ring-opening metathesis polymerisation (ROMP)[3] are especially noteworthy. In addition, cross-metathesis reactions,[4,5] and ring-closing metathesis (RCM)[6,7,8] using these well-defined catalyst systems have been recently reported. The power of alkene metathesis in closing a 12-membered ring was highlighted by Hoveyda in the total synthesis of fluvirucin B$_1$ aglycon.[6] A recent publication by Schneider and Blechert on crossed alkene metathesis included a single β-lactam example[9] and this publication prompts us to report the use of catalysts **6** and **7** in the elaboration of both monocyclic and bicyclic β-lactam ring systems.

The readily accessible 4-acetoxyazetidin-2-one **8**[10,11] was derivatised to produce a number of potential substrates for alkene metathesis studies. Sequential reaction of β-lactam **8** with allyl alcohol and benzyl bromide or *tert*-butyldimethylchlorosilane gave the adducts **9a** (69%) and **9b** (76%).† Treatment of **9a** with excess styrene (4 equiv.) in the presence of carbene **7** (1 mol%) gave the β-lactam cinnamyl ether **10a**‡ (81%). In the same way, metathetic exchange of **9b** with excess styrene gave the β-lactam **10b**‡ (74%) (Scheme 1).

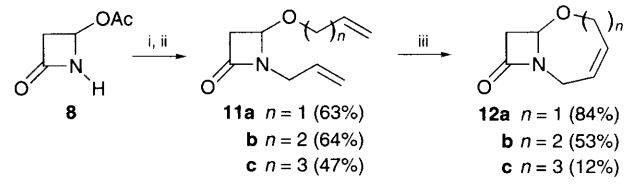


The substrates necessary for ring-closing metathetic reactions, dienes **11a–c**, were readily synthesised in two steps from 4-acetoxyazetidin-2-one **8**. Condensation of **8** with allyl alcohol, but-3-en-1-ol and pent-4-en-1-ol followed by *N*-allylation gave the β-lactam dienes **11a** (63%), **11b** (64%) and **11c** (47%). The reaction of diene **11a** with the molybdenum catalyst **6** proceeded smoothly in dichloromethane to provide the homo-oxacephem system **12a** in excellent yield (84%). Cyclisation *via* the alkene metathesis manifold was also useful in the conversion of the homologous β-lactam dienes **11b–c** into the corresponding bicyclic β-lactams although the efficiency of reaction decreased in the series [**12b** (53%), **12c** (12%)]. A dimer **13** was formed in significant quantities (17%) in the elaboration of **12c** (Scheme 2) and such dimerisation in the elaboration of strained medium ring dienes is precedented in simple systems.[8] Finally, during the synthesis of **9a**, a minor side product **14** resulting from cleavage of the azetidinone ring was isolated. Reaction of diene **14** with the ruthenium carbene **7** (5 mol%) afforded the dioxepine **15** (83%) (Scheme 3).

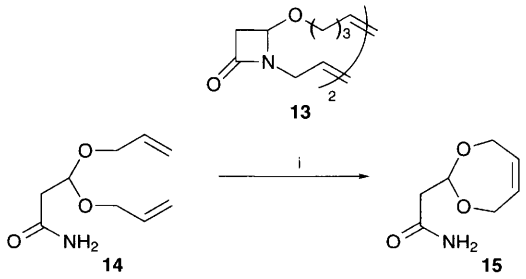
These results clearly show that alkene metathesis is an effective process for the functionalisation of monocyclic



Scheme 1 *Reagents and conditions*: i, $HOCH_2CH{=}CH_2$, $Zn(OAc)_2$, PhH, heat, 4 h, 83%; ii, $BrCH_2Ph$, NaH, 0 °C, 83%; iii, $ClSiMe_2Bu^t$, NEt_3, CH_2Cl_2, 0 °C, 92%; iv, 1 mol% **6**, $PhCH{=}CH_2$, CH_2Cl_2, 25 °C‡



Scheme 2 *Reagents and conditions*: i, $HO(CH_2)_nCH{=}CH_2$, n = 1–3, $Zn(OAc)_2$, PhH, heat, 4 h; ii, $BrCH_2CH{=}CH_2$, NaH, DMF, 0 °C; iii, 5 mol% **6**, CH_2Cl_2, 25 °C



Scheme 3 *Reagents and conditions*: i, 5 mol% **7**, CH_2Cl_2, 1 h, 25 °C, 83%

β-lactams and for the preparation of bicyclic β-lactams from the ring closure of monocyclic diene precursors. The method should be especially valuable for the elaboration of common bicyclic β-lactam ring systems although yields of β-lactams fused to medium ring alkenes are lower. The method is therefore relevant to the synthesis of antibiotics. The ruthenium catalysed closure of the diene **14** underscores the tolerance of the catalyst **7** to the polar primary amide functionality. Further aspects of this chemistry will be reported in due course.

We thank Glaxo Wellcome Research Ltd for the most generous endowment (to A. G. M. B.) and for a CASE grant (to S. P. D. B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College, and the Engineering and Physical Science Research Council for a CASE grant (to S. P. D. B.).

Footnotes

† All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

‡ Only the *trans* isomer was detected by ^{1}H NMR.

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Received, 9th July 1996; Com. 6/04805F