A one pot, metathesis–hydrogenation sequence for the selective formation of carbon–carbon bonds†

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A combination of homogeneous hydrogenation and metathesis reactions allows highly efficient, stepwise chemo- and stereoselective formation of three separate 2,7-diaminosuberic acid derivatives in a single pot without isolation of intermediates.

The selective formation of C–C bonds in complex molecules is one of the major challenges in organic chemistry. Olefin metathesis provides an efficient methodology for C–C bond synthesis[1] and in this communication we demonstrate the application of this technology for the formation of three identical dicarba bridges by selective and successive formation of three diaminosuberic acid derivatives.

Towards this end, a metathesis triplet **1**, **2**, **3** has been developed to facilitate the controlled formation of the three dicarba bridges (Table 1). The method involves cross-metathesis of reactive olefins to form a new olefin followed by hydrogenation to form the saturated bridge. The differing olefin substitution in the molecules provides tuneable reactivity towards homogeneous metathesis and hydrogenation catalysts. Three different *N*-acyl protecting groups were employed to facilitate unambiguous assessment of cross-metathesis selectivity and did not affect the mechanistic course of the reaction sequence. An equimolar mixture of olefins **1**, **2** and **3** was subjected to the catalytic sequence outlined below and in Table 1. Olefin **1**, a derivative of allylglycine, readily underwent homodimerisation with first (20 mol%) and second generation Grubbs' catalysts[2] (5 mol%) to form an unsaturated dicarba bridge **4**. Under these reaction conditions, the more sterically hindered olefin **2** and the electronically compromised olefin **3** were unreactive. The resultant alkene **4** was then hydrogenated in the presence of $Rh(I)(PPh_3)_3Cl$ (Wilkinson's catalyst)[3] to afford the saturated dicarba bridge **5**. Again, olefins **2** and **3** were unreactive under these conditions. Both the metathesis and hydrogenation reactions proceeded under mild experimental conditions with quantitative, unambiguous conversion to give the *first* suberic acid derivative **5** as shown by NMR and MS analysis (Scheme 1).

The next reaction in the sequence involved the activation of the dormant prenyl olefin **2** *via* cross-metathesis with 2-butene (butenolysis) to generate a more reactive crotylglycine derivative **6** (Scheme 1). The mixture of **2**, **3** and **5** was exposed to an atmosphere of 2-butene (15 psi) in the presence of 5 mol% second generation Grubbs' catalyst to afford the expected crotylglycine derivative **6** with quantitative conversion. Interestingly, exposure of **2** to 20 mol% of second generation Grubbs' catalyst under an atmosphere of ethylene (15 psi) resulted in only poor conversions to the allylglycine analogue of **6** (<32%). We postulated that this result may be due to the unstable nature of the *in situ* generated ruthenium–methylidene intermediate at elevated temperature[4] or

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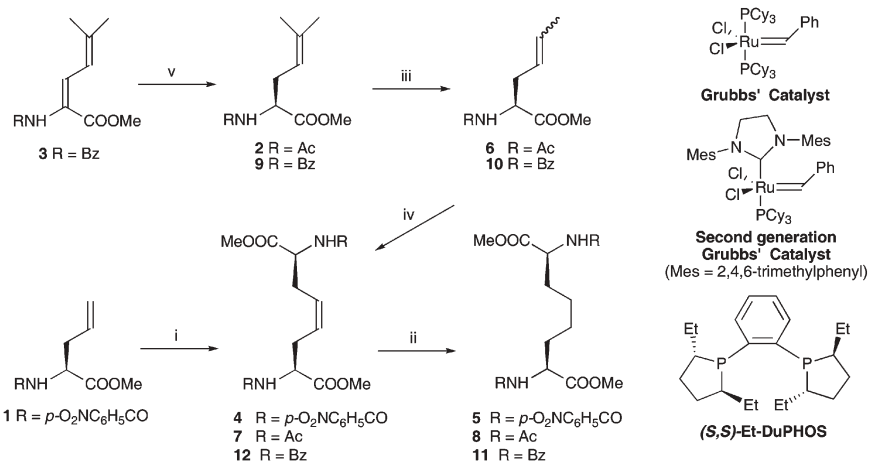

Scheme 1 Reagents and conditions: (i) 20 mol% first generation Grubbs' catalyst, DCM, 50 °C, 18 h; (ii) $Rh(I)(PPh_3)_3Cl$, 15 psi H_2, RT, THF:^{t}BuOH (1:1), 14 h; (iii) 5 mol% second generation Grubbs' catalyst, 15 psi C_4H_8, DCM, 50 °C, 17 h; (iv) 5 mol% second generation Grubbs' catalyst, DCM, 50 °C, 17 h; (v) [(COD)Rh(I)(*S*,*S*)-Et-DuPHOS]OTf, 75 psi H_2, RT, MeOH, 2 h, >99% ee.

Table 1 Reaction sequence for the construction of three dicarba bridges[a]

Monomers	CM–H: 1st or 2nd generation Grubbs' catalyst		Wilkinson's hydrogenation	CM: 2nd generation Grubbs' catalyst	CM–H: 2nd generation Grubbs' catalyst		Wilkinson's hydrogenation	Rh(I)DuPHOS hydrogenation	CM: 2nd generation Grubbs' catalyst	CM–H: 2nd generation Grubbs' catalyst	Wilkinson's hydrogenation	Summary of activity
	C=C	C–C		Act	C=C	C–C		Act	Act	C=C	C–C	
1	√	√		—	—	—		—	—	—	—	*Terminal allylic olefin.* No activation required.
2	X	X		√	√	√		—	—	—	—	*Trisubstituted olefin.* Activated *via* CM with ethylene/2-butene.
3	X	X		X	X	X		√	√	√	√	*Hindered extended acrylamide olefin.* Activated *via (i)* asymmetric hydrogenation and *(ii)* CM with ethylene/2-butene.

[a] √ = Reactive olefin, X = Unreactive olefin, — = Unreactive dicarba bridge, Act = Olefin activation step, CM–H = Cross-metathesis–homodimerisation, CM = Cross-metathesis.

unfavourable competition between the rising concentration of terminal olefins and **2** for binding to the ruthenium catalyst.[5] Exposure to an atmosphere of 2-butene overcame this problem, facilitating catalysis *via* the more stable ruthenium–ethylidene intermediate. The newly formed disubstituted olefin **6** was then readily homodimerised to the expected unsaturated dimer **7** with 5 mol% of second generation Grubbs' catalyst (Scheme 1). Exposure of the newly formed olefin to a hydrogen atmosphere and Wilkinson's catalyst resulted in quantitative conversion to the saturated dicarba bridge **8**. Once again, the sterically and electronically compromised olefin **3** remained a spectator over the three reactions used to form the *second* diaminosuberic acid derivative.

The remaining acrylate-type olefin **3** was then used to form the final dicarba bridge. A *double activation* sequence needed to be employed to render this remaining olefin reactive to homodimerisation. This was achieved through the use of asymmetric hydrogenation and cross-metathesis. Homogeneous hydrogenation of dienamide **3**[6] using chiral (*S,S*)-Rh(I)-Et-DuPHOS (Burk's catalyst)[7] gave (*S*)-configured prenylglycine derivative **9** in excellent enantioselectivity (>99% ee), chemoselectivity and conversion.[8] No evidence of over-reduction of the *C*4 carbon–carbon double bond was observed. The resulting prenyl olefin **9** was then converted to the crotylglycine analogue **10** *via* butenolysis (Scheme 1). Exposure of this olefin **10** to the previously described cross-metathesis and hydrogenation conditions then led to the formation of the final dicarba bond and the *third* diaminosuberic acid derivative **11** *via* alkene intermediate **12** (Scheme 1). The product mixture resulting from the nine homogeneous catalytic transformations was separated by column chromatography to afford diamidosuberic acid esters **5**, **8** and **11** in 70, 81 and 73% yields respectively. Significantly, no other byproducts were isolated which demonstrates the high chemoselectivity exhibited by each catalytic step.

The homogeneous catalytic methodology described in this communication could find widespread use in peptidomimetics and total product synthesis where multiple C–C bonds and/or rings need to be selectively constructed. This methodology is currently being applied to the preparation of several biologically active and naturally occurring cyclic molecules and peptides.

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Notes and references

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