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Tetrahedron Letters 47 (2006) 189–192
Tetrahedron Letters

Ring-rearrangement metathesis of bicyclic amino acid derivatives

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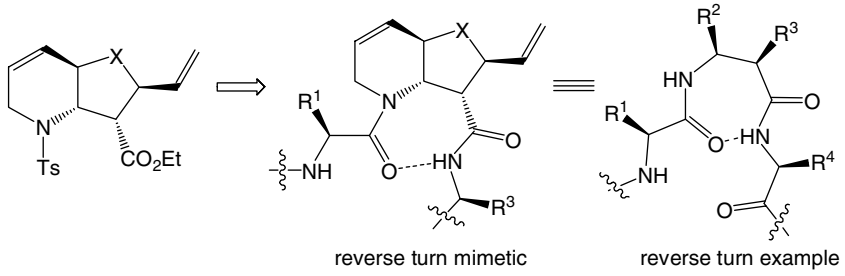
Received 13 October 2005; revised 26 October 2005; accepted 28 October 2005

Abstract—In this letter, we describe the ring-rearrangement metathesis (RRM) of bicyclic amino acid derivatives. The procedure is of use for the synthesis of constrained amino acid and peptide derivatives with potential as reverse-turn inducers.

Conformationally restricted amino acids and peptides are of great interest, and have assumed a prominent role in drug design and development.[1,2] Incorporation of constrained amino acid derivatives into a native peptide in place of naturally occurring amino acids can lead to compounds which may exhibit enhanced potency over their parent sequences.[3] One particular common structural feature targeted for replacement by a constrained analogue is the reverse-turn.[4] Reverse-turns play an important role in proteins, acting as both structural elements and functional scaffolds (Scheme 1); evidenced by the fact that reverse turns usually occur on the exposed surface of proteins. These motifs are likely to be involved in intermolecular recognition processes between proteins and in the interactions between peptide substrates and receptors.[5]

Olefin metathesis is an ideal reaction for the synthesis of conformationally constrained peptide and amino acid derivatives. Now an established synthetic tool in organic synthesis, ring-closing metathesis (RCM) has been widely used for constraining amino acids and peptide sequences.[6] However, ring-rearrangement metathesis (RRM) has not yet been utilised so extensively and to date has mainly been used to prepare molecules with carbocyclic and oxacyclic frameworks,[7–9] with only relatively few reports concerning systems containing other heteroatoms, such as nitrogen.[10,11] As part of a study towards a simplified methodology for the synthesis of conformationally constrained amino acid and peptide derivatives we chose to explore the use of RRM in the synthesis of bicyclic amino acid derivatives. The readily available α and β amino acids chosen for this



Scheme 1.

Keywords: Metathesis; Amino acids; Peptides; Peptidomimetics.
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doi:10.1016/j.tetlet.2005.10.155

study are based on known norbornene and oxanorbornene systems **1**, **2** and **3**, from which **4**, **10** and **13** were readily prepared, following the literature procedures (Fig. 1).[12,13]

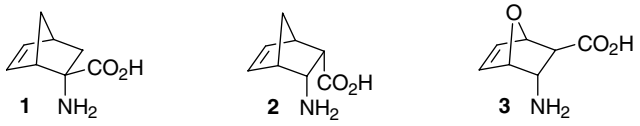
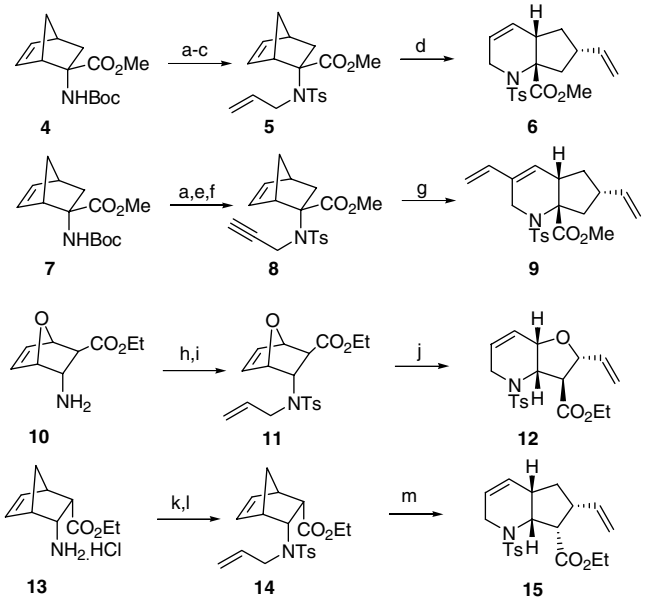


Figure 1.

Elaboration of the core to afford RRM precursors **5**, **8**, **11** and **14** involved protection of the nitrogen and alkylation. In all cases, N-tosylation and subsequent alkylation with allyl bromide or propargyl bromide proceeded in good to excellent yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) 4 N HCl in dioxane, 0 °C, 1 h [quant.]; (b) *p*-TsCl, Et_3N, CH_3CN, 18 h [84%]; (c) allyl bromide, Cs_2CO_3, DMF, 5 h; [98%]; (d) Grubbs I catalyst (10 mol %), ethylene (1 atm), CH_2Cl_2, 15 h, [88%]; (e) *p*-TsCl, Et_3N, CH_3CN [86%]; (f) propargyl bromide, Cs_2CO_3, DMF, 5 h; [93%]; (g) Grubbs I catalyst (10 mol %), ethylene (1 atm), CH_2Cl_2, 15 h, [89%]; (h) *p*-TsCl, Et_3N, CH_2Cl_2 [87%]; (i) allyl bromide, Cs_2CO_3, DMF, 5 h; [98%]; (j) Grubbs I catalyst (10 mol %), ethylene (1 atm), CH_2Cl_2, 15 h, [83%]; (k) *p*-TsCl, Et_3N, CH_2Cl_2; (l) allyl bromide, Cs_2CO_3, DMF, 18 h [98%]; (m) Grubbs 1 catalyst (20 mol %), ethylene (3 atm), CH_2Cl_2, 50 °C, 48 h [88%].

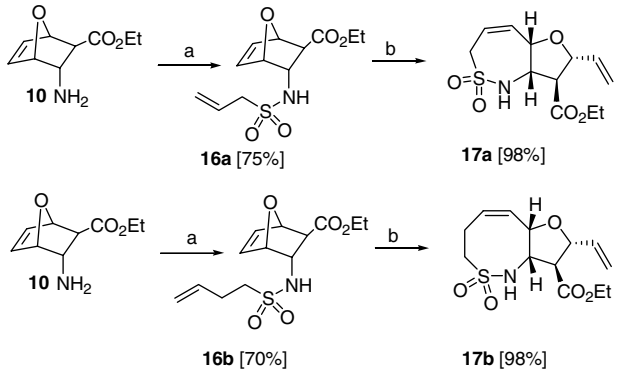
RRM was performed with the Grubbs 1 **[$RuCl_2(PCy_3)_2CH{=}Ph$]**[14] (pre)catalyst under an ethylene atmosphere and RRM proceeded in good yield.[15] For example, **5** was transformed to **6** in 88% isolated yield overnight, and ene-yne derivative **8** was smoothly converted into **9** in 89% yield.[16] RRM of oxanorbornene derivative **11** was also successful, delivering **12** in an 83% isolated yield.

Unfortunately, substrate **14** proved slightly more problematic. ^1H NMR studies showed that the ring-opening metathesis (ROM) step was sluggish, perhaps due to internal coordination of the propagating ruthenium species to the *endo* orientated ester. Therefore, by increasing the catalyst loading to 20 mol % and a reaction pressure of 3 atmospheres ethylene, complete conversion to **15** could be achieved in 48 h.[17]

Recently, peptide sulfonamides have emerged as an important class of constrained amino acids.[18] It was hoped that the synthesis of allylic or homoallylic sulfonamides within the bicyclic framework would allow facile entry into this class of molecule.

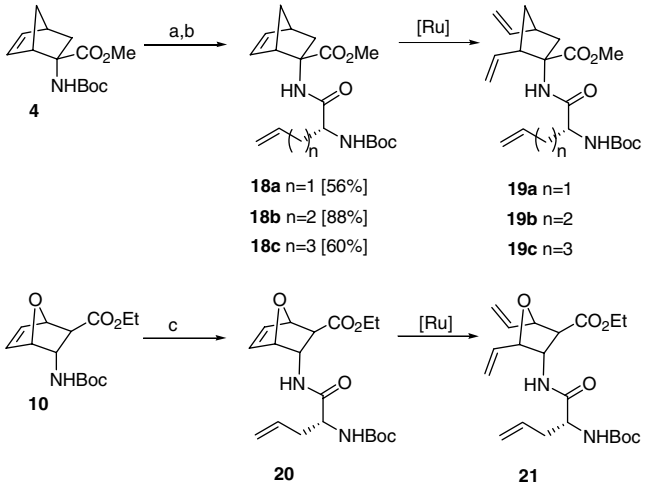
Therefore, the corresponding sulfonyl chloride[19] was coupled with compound **7** to yield the peptidosulfonamides **16a**–**b** in good yields. Unfortunately in this example, the Grubbs 1 (pre)catalyst led only to recovery of unreacted starting material.

It was decided to investigate the use of the more reactive Grubbs 2 **[$RuCl_2PCy_3H_2IMesCH{=}Ph$]**,[20] and after extensive experimentation, the optimum conditions were determined to be at 40 °C with 1 mol % of Grubbs 2 using a highly dilute solution (0.0005 M). The RRM was successfully carried out affording **17a**–**b** in excellent yields (Scheme 3).



Scheme 3. Reagents and conditions: (a) allyl or homoallyl sulfonyl chloride, DMAP, CH_2Cl_2; (b) Grubbs 2 catalyst (1 mol %), CH_2Cl_2, 35 °C, 2 h.

Encouraged by these results, synthesis of a number of dipeptides was undertaken. It was anticipated that after successful RRM the bicyclic products would make ideal candidates for dipeptide reverse-turn mimetics after incorporation into a peptide sequence. In light of the ability of constrained dipeptide surrogates to adopt conformations similar to natural β-turns,[21] this practical methodology would also be of general utility for research in peptide science and medicinal chemistry. Synthesis of RRM precursors proceeded in a straightforward manner, following N-Boc deprotection with 4 N HCl in dioxane and amide bond formation with commercially available coupling reagents, dipeptides **18a**–**c** and **20** were synthesised in good yields (Scheme 4).



Scheme 4. Reagents and conditions: (a) 4 N HCl in dioxan, 0 °C, 1 h, [quant.]; (b) BocNHCH$(CH_2)_n$COOH, PyBOP, DIEA, CH_2Cl_2, 18 h; (c) 4 N HCl in dioxane, 0 °C, 1 h, [quant.]; HBTU, DMF, *i*-Pr_2EtNH, 0 °C, [68%].

Ring rearrangement metathesis was attempted on **18a–c** and **20** using the Grubbs 1 or Grubbs 2 (pre)catalysts and various conditions (DCM/DCE/toluene), at different temperatures 20–110 °C, under both under ethylene and nitrogen atmosphere. To our disappointment, in all cases, the only isolable products were those that arose from an initial ROM of the strained bicyclic ring to give **19a–c** and **21**. Attempts were made to carry out a subsequent RCM reaction on isolated **19a–c** and **21**, but no productive reactions were observed. The lack of reactivity towards RCM can be attributed to the high preference for a *transoid* amide bond conformation as noted by Williams and Liu,[22] and others.[23]

In conclusion, we have demonstrated a successful RRM strategy to synthesise bicyclic amino acid derivatives. The RRM reaction proceeded in good to excellent yields. Attempts of RRM on dipeptides derived from these bicyclic systems were unsuccessful. The work represents a new entry into this important class of molecule. Further studies into the area are underway and will be reported in due course.

Acknowledgements

We are grateful to the EPSRC, the Fonds der Chemischen Industrie and the Graduiertenkolleg 'Synthetische, mechanistische und reaktionstechnische Aspekte von Metallkatalysatoren' for financial support.

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15. Representative procedure: A stirred solution of the substrate (1 equiv) in DCM was saturated with ethylene gas by bubbling the gas through the solution. The catalyst (10 mol %) was then added and the reaction mixture allowed to stir for the appropriate time under a balloon of ethylene.
16. Data for compound **12**. Colourless oil (83%). $R_f = 0.30$ (ether/PE; 30:70). ^{1}H NMR ($CDCl_3$, 500 MHz) 1.26 (3H, t, $J = 7.0$ Hz, C***H***$_3$CH$_2$), 2.40 (3H, s, CH$_3$), 2.89 (1H, t, $J = 10.0$ Hz, C***H***), 3.72–3.76 (1H, m, C***H***), 4.10–4.44 (3H, m, C***H***, CH$_3$C***H***$_2$), 4.55 (1H, t, $J = 10.0$ Hz, C***H***), 4.97 (1H, dd, t, $J = 2.5$, 7.5 Hz, C***H***), 5.13 (1H, d, $J = 10.0$ Hz,

C***H***), 5.54 (1H, app. d, $J = 17.0$ Hz, C***H***), 5.65–5.80 (3H, m, C***H***═C***H***, C***H***═CH_2), 7.26 (1H, d, $J = 8.5$ Hz, $2 \times$ C***H***Ar), 7.66 (2H, d, $J = 8.5$ Hz, $2 \times$ C***H***Ar). ^{13}C NMR ($CDCl_3$, 125 MHz) 14.2 (***C***H_3), 21.5 (***C***H_3), 39.5 (***C***H_2), 50.4 (***C***H), 58.1 (***C***H), 61.5 (***C***H_2), 69.9 (***C***H), 81.5 (***C***H), 117.5 (***C***H_2), 123.7 (***C***H), 127.1 ($2 \times$ ***C***HAr), 127.3 (***C***H), 129.8 ($2 \times$ ***C***HAr), 136.9 (***C***), 137.1 (***C***H), 143.7 (***C***), 170.5 (***C***═O). IR ν_{max} (thin film)/cm^{-1} 3005, 1695, 1395, 1200, 1190. HRMS *m/z* found 377.1301 requires $C_{19}H_{23}N_1O_5$ 377.1297.

17. Data for compound **15**. Colourless oil (88%). $R_f = 0.35$ (ether/PE; 50:50). ^{1}H NMR ($CDCl_3$, 250 MHz) 1.20 (3H, t, $J = 8.5$ Hz, C***H***$_3$CH$_2$), 1.81–2.18 (2H, m, C***H***$_2$), 2.41 (3H, s, C***H***$_3$), 2.60–2.84 (2H, m, $2 \times$ C***H***), 3.18 (1H, t, $J = 7.0$ Hz, C***H***), 3.47–3.64 (1H, m, C***H***), 3.80–4.18 (3H, m, C***H***, CH$_3$C***H***$_2$), 4.62 (1H, dd, $J = 7.5$, 3.0 Hz, C***H***), 4.85–5.10 (2H, m, CH═C***H***$_2$), 5.44–5.82 (3H, m, C***H***═C***H***, C***H***═CH_2), 7.27 (1H, d, $J = 8.5$Hz, $2 \times$ C***H***Ar), 7.68 (2H, d, $J = 8.5$Hz, $2 \times$ C***H***Ar). ^{13}C NMR ($CDCl_3$, 63 MHz) 14.4 (***C***H_3), 21.9 (***C***H_3), 34.3 (***C***H), 35.7 (***C***H_2), 41.4 (***C***H_2), 44.9 (***C***H), 53.0 (***C***H), 56.8 (***C***H), 60.7 (***C***H_2), 116.5 (***C***H_2), 127.3 ($2 \times$ ***C***HAr), 128.5 (***C***H═***C***H), 129.7 ($2 \times$ ***C***HAr), 137.3 (***C***H═CH_2), 137.7 (***C***), 143.1 (***C***), 172.1 (***C***═O). IR ν_{max} (thin film)/cm^{-1} 3005, 1700, 1400, 1200, 1190. MALDI-TOF MS *m/z* found 397.88 (MNa^+), 413.65 (MK^+), requires $C_{33}H_{30}N_{10}O_{15}Na$ 398.14 (MNa^+), $C_{33}H_{30}N_{10}O_{15}K$ 414.11 (MK^+).
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