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Stereoselective double ring closing metathesis reactions in the synthesis of spirocyclic compounds

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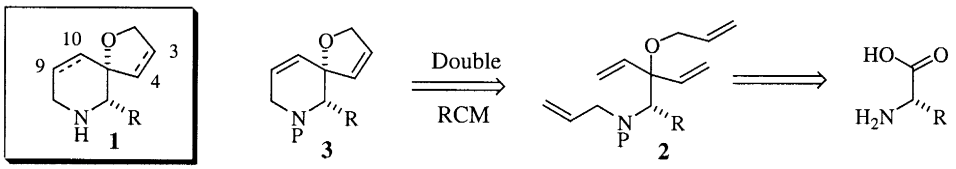
Abstract

The first diastereoselective double ring closing metathesis reaction to afford a spirocyclic compound is reported. Cyclisation of amino acid derived tetraenes **7** selectively afforded spirocyclic compounds **8**.

Keywords: ring closing metathesis; stereoselective; spirocyclic.

The ring closing metathesis (RCM) reaction has recently evolved to become a major tool for synthetic organic chemists. This is largely due to the introduction of the well defined molybdenum and ruthenium catalysts developed by Schrock[1] and Grubbs,[2] respectively. The RCM has now been applied to a range of synthetic targets with great success.[3] Despite this surge in interest, reports of double RCM reactions are still rare[4] although the possibility of forming two rings, in a single reaction, offers great scope for the rapid synthesis of complex cyclic systems.

As part of our ongoing program to develop selective NK-1 receptor antagonists[5] we required a convenient synthesis of compounds with general structure **1** (Scheme 1). We were attracted to the



Scheme 1.

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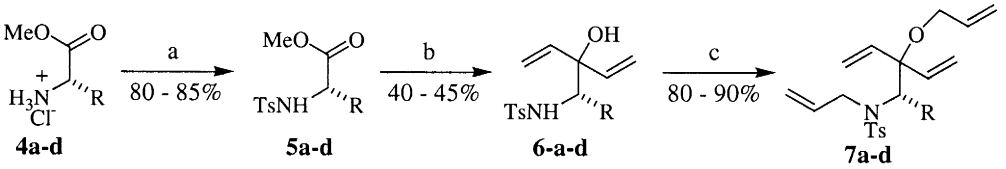
possibility of forming the spirocyclic rings of such a compound in a single step using a double RCM. For instance, the double RCM reaction of tetraene **2** could afford spirodiene **3**. This approach would require the existing stereocentre in **2** to differentiate the enantiotopic vinyl groups. While diastereoselectivity has been achieved in a double RCM reaction to form a decalin system,[4b] to the best of our knowledge, only achiral spirocyclic compounds have previously been accessed in this way.[4d] In this paper we report our preliminary studies on the first diastereoselective double RCM to give a spirocyclic compound.

A range of *N*-tosyl protected metathesis precursors were synthesised from commercially available amino acid esters as outlined in Scheme 2. Reaction of the hydrochloride salts **4a–d** with tosyl chloride and triethylamine afforded the *N*-tosyl esters **5a–d** in good yields. Cerium-mediated addition of vinylmagnesium bromide to these esters gave the tertiary alcohols **6a–d** in moderate yields. Subsequent allylation on oxygen and nitrogen was then achieved in a single step to give the tetraenes **7a–d** in excellent yields.[6]



Tetraene	R	Yield[a]	Diastereoselectivity[b]
7a	Me	74%	92%
7b	iPr	84%	92%
7c	iBu	76%	92%
7d	CH_2Ph	87%	92%

a. Isolated yield of both isomers after column chromatography
b. Isomer ratio determined by HPLC analysis

Scheme 2. Reagents and conditions: (a) TsCl, Et_3N, THF, 20°C, 16 h; (b) vinylmagnesium bromide, $CeCl_3$, THF, 0°C, 1 h; (c) NaH, THF, DMPU, allyl bromide, 20°C, 16 h; (d) $RuCl_2(PCy_3)_2$=CHPh, $CHCl_3$, 20°C, 2 h

The optimum conditions for the key double RCM reaction were treatment of a 0.05 M chloroform solution of the tetraene with 5–7 mol% of the Grubbs catalyst at room temperature. This led to complete consumption of the starting material within 2 h and in all cases the easily separable spirocyclic compounds **8a–d** and **9a–d** were isolated in good to excellent yields.[6] We were gratified to find that the diastereoselectivity was strongly in favour of the desired 5*R*,6*S* isomers **8a–d** and surprisingly was not affected by the alkyl substituent.

The stereochemistry of the products was elucidated by NOE studies (Fig. 1), which also indicated that the C_6 substituent adopted a pseudoaxial position. Interactions between the C_6 equatorial proton and a C_2 proton in the major isomer (e.g. shown for **8d**), or the C_4 proton and, for **9d**, the benzylic protons in the minor isomer allowed for stereochemical assignment.

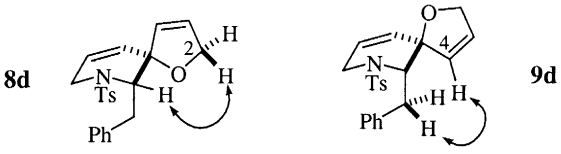


Fig. 1.

In conclusion, we have reported the first example of a diastereoselective double RCM reaction to form a spirocyclic compound. Further studies on the scope of this reaction and the factors controlling the stereochemical induction are underway and will be reported in due course.

References

1. Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc*. **1991**, *112*, 6899 and references cited therein.
2. (a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; *J. Am. Chem. Soc*. **1992**, *114*, 3974 (b) Wu, Z.; Nguyen, S. T.; Grubbs, R. H.; Ziller, J. W. *J. Organomet. Chem*. **1995**, *497*, 195. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 2039. (d) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100.
3. For recent reviews of the metathesis reaction, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) *Tetrahedron Symposium in Print*; Snapper, M. L.; Hoveyda, A. H., Eds; **1999**, *55*, 8141. (e) Alkene Metathesis in Organic Synthesis; Furstner, A., Ed.; *Top. Organomet. Chem*. **1998**, 1.
4. (a) Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354. (b) Lautens, M.; Hughes, G. *Angew. Chem. Int. Ed. Engl*. **1999**, *38*, 129. (c) Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem*. **1998**, *63*, 8628. (d) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247. (e) Trevitt, M.; Gouverneur, V. *Tetrahedron Lett.* **1999**, *40*, 7333. (f) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 7324.
5. Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrison, T.; Hollingworth, G. J.; Jackson, P. S.; Kulagowski, J. J.; Seward, E. M.; Swain, C. J.; Williams, B. J. International Patent WO97/49710, 1997.
6. All new compounds gave satisfactory spectroscopic and HRMS data.