ORGANIC LETTERS

2001
Vol. 3, No. 5
671−674

A Double Ring Closing Metathesis Reaction in the Rapid, Enantioselective Synthesis of NK-1 Receptor Antagonists

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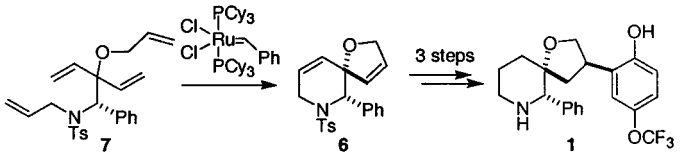
Received December 5, 2000

ABSTRACT

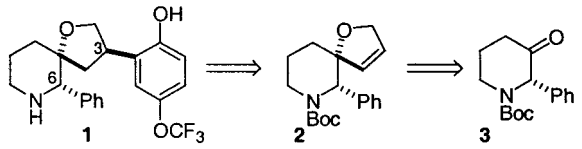


The NK-1 receptor antagonist 1 has been prepared in seven steps from phenylglycine methyl ester. The key steps are a double ring closing metathesis reaction of tetraene 7 to prepare spirocycle 6 and a reductive Heck reaction to introduce the aryl moiety. This latter reaction discriminates the olefins of compound 6 and proceeds in a highly regio- and stereoselective manner.

As part of our ongoing program to prepare selective NK-1 receptor antagonists, we required an efficient enantioselective synthesis of the 1-oxo-7-azaspirodecane **1**. Such a synthesis should be suitable for generating multigram quantities to allow for systematic variation of alkyl groups on nitrogen and oxygen.

The initial route to this compound used a reductive Heck reaction of spiroalkene **2** with an aryl iodide to set the final stereocenter (Scheme 1).[1] The spiroalkene was obtained in

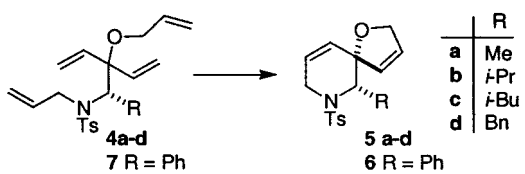
Scheme 1



three steps from ketone **3**; however, this itself required a seven-step synthesis including a resolution.[1c] For further development purposes, a shorter and more practical synthesis of compound **1** was required.

We were attracted to the possibility of forming both the spirocyclic rings in a single step using a double ring closing metathesis (RCM) reaction.[2] We have recently reported the diastereoselective double RCM reaction of amino acid derived tetraenes **4a**−**d**.[3] This reaction afforded the spirocyclic compounds **5a**−**d** in >90% ds, and we envisaged that this approach could be extended to spirodiene **6** (R = Ph) (Scheme 2).[4] In this case, suppression of epimerization at the labile benzylic stereocenter during the synthesis of the metathesis precursor **7** would be needed. Selective functionalization of the two olefins in product **6** would also be a significant synthetic challenge.

Scheme 2



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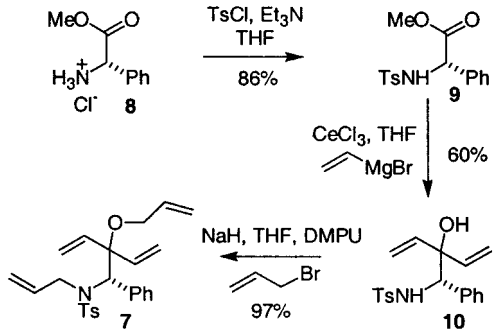
10.1021/ol006958g CCC: $20.00
Published on Web 02/16/2001

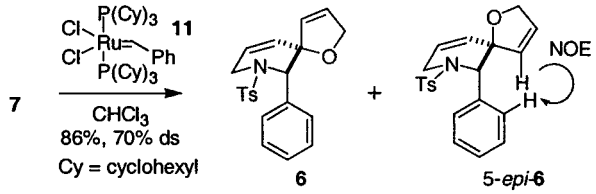
On the basis of our previous work, the tosyl group was chosen as a suitable *N*-protecting group, and hence, commercially available phenylglycine ester **8** was converted to its *N*-tosyl derivative **9** by reaction with tosyl chloride and triethylamine (Scheme 3). Cerium-mediated addition of vinylmagnesium bromide to ester **9** afforded the tertiary alcohol **10** without loss of optical purity as determined by chiral HPLC methods (Diacel Chiracel OD-R 0.46 × 25 cm column). As expected, in the absence of cerium chloride, 1,4-addition to the enone intermediate (structure not shown) was a significant side reaction. *N*,*O*-Diallylation of **10** was achieved in a single step by reaction with excess sodium hydride and allyl bromide to give tetraene **7** in excellent yield.

Scheme 3



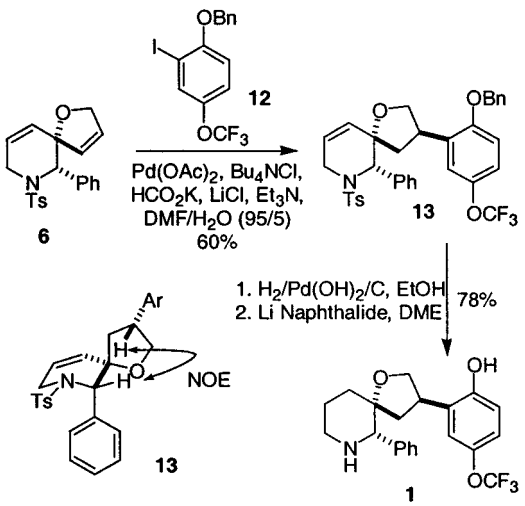
The key double RCM reaction of **7** proceeded smoothly under our previously optimized conditions employing the Grubbs' catalyst **11**[5] (Scheme 4). With only 4 mol % of catalyst, this gave the two chromatographically distinct and crystalline diastereoisomers **6** and 5-*epi*-**6** in 86% yield and 70% ds, favoring the desired compound.[6] The stereochemistry of the products was determined by NOE studies. In particular, the minor isomer 5-*epi*-**6** gave an NOE enhancement as shown that was absent in the major isomer **6**. A single-crystal X-ray determination and subsequent conversion of the major isomer to known intermediates (vide infra) confirmed this assignment. The pseudoaxial orientation of the phenyl group was also ascertained by NOE studies, and this may be significant to the stereochemical outcome of the RCM reaction. When employing benzyl protecting groups on nitrogen (Bn or PMB), the selectivity of the related double RCM reaction was reversed, i.e., 5-*epi*-**6** was favored over **6** in Scheme 4 (Bn protecting group instead of Ts, 65% ds). NMR studies of these spirocyclic compounds then indicated that the 6-phenyl group was equatorial.[7]

Scheme 4



To complete the synthesis of target **1**, selective functionalization of the two olefins of **6** was now required. Initial studies looked at the selective removal of the piperidine olefin; however, this led to mixtures of reduced products. An ambitious approach was to perform the reductive Heck reaction on the diene and hope for a regio- and stereoselective reaction. In theory, provided only single addition occurs, eight different isomeric products could result. We were gratified to find that reaction of spirodiene **6** with aryl iodide **12**, in the presence of catalytic palladium acetate, afforded the desired compound **13** in 60% yield with 90% ds (Scheme 5). Notably the addition of water (5%) to the reaction solvent

Scheme 5



was found to be key for obtaining high selectivities for this transformation.[8] While the exact role of the water is unclear,

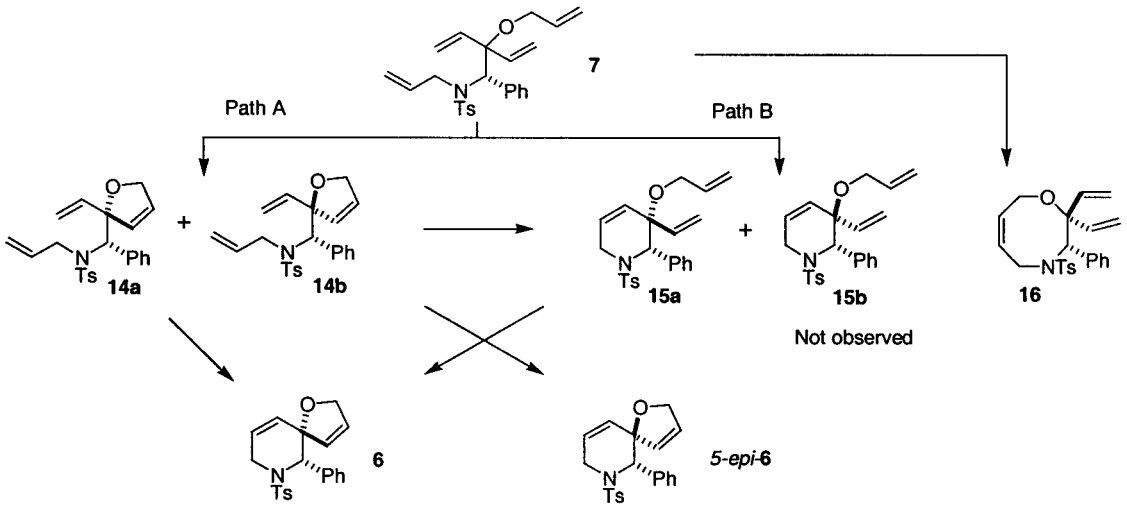
(1) (a) Baker, R.; Curtis, N. R.; Elliott, J. M.; Harrison, T.; Hollingworth, G. J.; Jackson, P. S.; Kulagowski, J. J.; Rupniak, N. M. WO 97/49710. (b) Kulagowski, J. J.; Curtis, N. R.; Swain, C. J.; Williams, B. J. *Org. Lett* **2001**, *3*, 667. (c) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.

(2) For recent reviews of the metathesis reaction in synthesis, 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; Vol. 55, p 8141. (e) Alkene Metathesis in Organic Synthesis; Furstner, A., Ed. *Top. Organomet. Chem.* **1998**, 1. (f) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(3) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 2027.

(4) For other examples of diastereoselective double RCM reactions, see: (a) Lautens, M.; Hughes, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 129. (b) Bassindale, M. J.; Hamley, P.; Leitner, A.; Harrity, J. P. A. *Tetrahedron Lett.* **1999**, *40*, 3247. (c) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421. (d) Bassindale, M. J.; Edwards A. S.; Hamley, P.; Adams, A.; Harrity, J. P. A. *J. Chem. Soc., Chem. Commun.* **2000**, 1035. (e) Lautens, M.; Hughes, G.; Zunic, V. *Can. J. Chem.* **2000**, *78*, 868. (f) Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817. (g) Wallace, D. J.; Bulger, P. G.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U.-H. *Synlett.* In press.

Scheme 6



in the absence of this additive significant quantities of regioisomeric products were observed. In line with previous studies, the arylpalladium species approached from the less hindered face of the dihydrofuran to give the desired epimer. This stereochemical outcome was deduced by a single NOE interaction as shown and confirmed by later comparison with known intermediates.

Hydrogenation of **13** using Pearlman's catalyst cleaved the phenolic protecting group and reduced the remaining double bond. Removal of the tosyl protecting group was achieved by reaction with sodium naphthalide to give **1** in 78% yield over the final two steps. This completed the synthesis of an important NK-1 receptor antagonist in optically pure form from a commercially available starting material in just seven steps, without the need for a resolution. Formation of the *N*-Boc derivative of **1** gave material identical in all respects (NMR, HPLC, α_D) to that synthesized previously.[1]

With the synthesis of compound **1** completed, we turned our attention to the mechanistic aspects of the double RCM reaction. We were surprised by the lower selectivity obtained for the RCM of tetraene **7**[9] compared with those of related tetraenes **4a**−**d** (70% ds vs >90% ds).[3] To obtain an insight into this differing selectivity and the origin of the stereocontrol, molecular modeling studies were carried out. Analysis of the previously synthesized structures **5a** (R = Me), **5b** (R = *i*-Pr), and their C-5 epimers using the MM2* force field[10] as implemented in Macromodel 5[11] showed that in each case there was little energetic difference between the two diastereoisomers.[12] This suggests that these reactions do not proceed under thermodynamic control as good selectivity was obtained in RCM reactions to produce **5a** and **5b** (>90% ds). In contrast, when comparing **6** (R = Ph) with *5-epi*-**6**, a larger energy difference (ca. 10 kJ/mol) in favor of **6** was calculated. Hence, it would have been expected, on the basis of thermodynamic considerations, that a higher selectivity would be obtained for this compound rather than the observed lower selectivity.

We have also resubjected purified **6** and *5-epi*-**6** to the metathesis reaction and found that they do not equilibrate under these conditions, even under an ethylene atmosphere. In view of this it is worth considering that as two rings are formed, the order of ring formation is important, i.e., the reaction could proceed by the initial formation of either a five- or a six-membered ring (Path A or Path B in Scheme 6). The relative energy levels of monocyclized intermediates may be more significant in determining the stereochemical outcome than those of the final product.

In an attempt to detect these intermediates and elucidate the mechanistic pathway, a reaction was carried out with reduced catalyst load. Hence, treatment of the starting material **7** with catalyst **11** (1 mol %) and quenching after 30 min led to a mixture containing 20% spirodienes (70% ds), 20% residual starting material, and four intermediates.[13] Purification of this mixture by preparative HPLC allowed for isolation and identification of these four compounds. The major intermediates observed were the dihydrofurans **14a**

(5) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(6) Isomer ratios quoted were determined by hplc analysis (Zorbax Eclipse XDB-C8 0.46 × 25 cm column). Yields are for the isolated compounds after column chromatography.

(7) (a) Scott, J. W.; Durham, L. J.; deJongh, H. A. P.; Burckhardt, U.; Johnson, W. S. *Tetrahedron Lett.* **1967**, 2381. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.

(8) For examples of the use of water in Heck reactions, see: (a) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (b) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2003. (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

(9) Despite screening a range of reaction conditions (temperature, solvent, additives and other catalysts), this selectivity could not be improved.

(10) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

(11) Mohamedi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(12) Chang, G.; Guida, W. C.; Still, W. C. Monte Carlo searches were performed to ensure that all low-energy conformations had been included in the calculations. *J. Am. Chem. Soc.* **1989**, *111*, 4379.

(13) Relative ratios were determined by HPLC analysis.

and **14b** formed in approximately equal amounts. Additionally, small quantities of the six-membered ring **15a** and the eight-membered ring **16** were produced. Moreover, the relative ratios of **14a**, **14b**, and **15a** to each other remain constant throughout the course of the reaction. On the basis of these observations, the predominant pathway operating is the initial formation of the five-membered ring (Path A).[14]

When re-subjecting the monocyclic compounds to the reaction conditions, the isolated intermediates **14a** and **15a** both reacted to afford the expected metathesis product **6** as the sole spirocycle. Surprisingly, when **14b** was re-subjected to the reaction conditions, a 65:35 mixture of 5-*epi*-**6** and **6** was obtained. We believe this mixture results from the expected formation of *5-epi*-**6** as well as cyclization of the pendant allyl group onto the preformed dihydrofuran ring (to give **15a**).[15] The exclusive conversion of **14a** and **15a** to give **6**, together with the nonequilibration of the final spirocycles, provides evidence that the reaction selectivity is usually based on the first cyclization. However, the conversion of **14b** into a mixture of *5-epi*-**6** and **6** indicates that competing pathways can operate.[16]

To summarize, three intermediates in the double ring closing metathesis reaction of tetraene **7** have been isolated. This has allowed us to propose that the predominant pathway operating is the initial formation of the dihydrofurans. Resubjection of these intermediates to the reaction conditions has provided further insight into the reaction mechanism. In conjunction with the regio- and stereoselective reductive Heck reaction, this chemistry has allowed for a new seven-step synthesis of a key NK-1 receptor antagonist.

Acknowledgment. We thank Richard Ball and Nancy Tsou for the crystallographic studies, Andrew Gibson for preliminary experiments, and Paul Byway for mass spectrometry.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, *N*-Boc-**1**, **6**, *5-epi*-**6**, **7**, **9**, **10**, **13 14a 14b 15b**, and **16**. Tables of molecular modeling data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) It is possible that **15a** and **15b** are formed in significant quantities but that their further cyclization is faster than that for the dihydrofurans **14a** and **14b**. However, the consistent ratio of the two product isomers throughout the reaction (70:30 at *all conversions*) does not support this.

(15) No acyclic compounds were observed during this reaction.

(16) Details of modeling studies on the intermediate compounds are provided in the Supporting Information.