Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 8883–8885

TETRAHEDRON LETTERS

A sequential Claisen/ring-closing metathesis approach to the synthesis of spirocyclic cyclopentanes and cyclohexanes☆

Patrick Beaulieu and William W. Ogilvie*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

Received 20 August 2003; revised 18 September 2003; accepted 19 September 2003

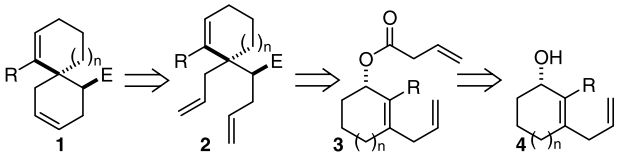
Abstract—A new method for the formation of spirocycles is described using a sequential Ireland–Claisen/Metathesis strategy to construct spirocyclic systems. Optimization of the Ireland–Claisen conditions provides the key metathesis substrates. The metathesis reactions were highly regioselective by virtue of steric hindrance in the substrate olefins.

The formation of carbon–carbon bonds in an asymmetric manner is a central goal of modern synthetic chemistry. Many methods have been developed, however the asymmetric formation of quaternary carbons is still a formidable challenge.[1] Spirocycles, found in many natural products, represent a special case with added synthetic difficulties[2] because of the requirements for ring formation and facial selectivity during the creation of a quaternary carbon. In this paper we report a methodology based on ring-closing metathesis that produces spirocyclopentanes and -hexanes. The formation of the quaternary center is set by an Ireland–Claisen rearrangement,[3,4] thus controlling the configuration of the quaternary center by virtue of suprafacial migration.

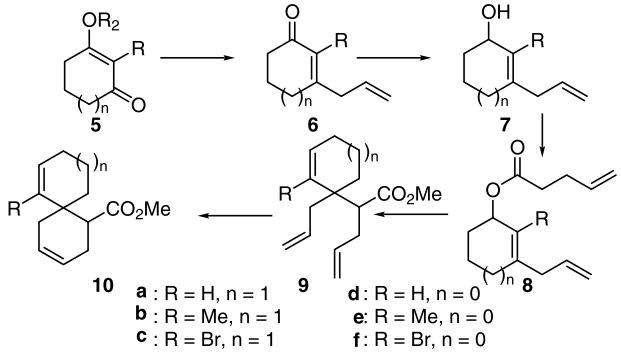
In our strategy, the configuration of the quaternary carbon would be dictated by the configuration of the starting alcohol **4** (Scheme 1). The enantioselective production of products such as **4** is well precedented[5] and provides stereochemical information to set the absolute configuration of the spiro center. Acylation of **4** would give compounds such as **3**. Ireland–Claisen rearrangement[6] of the derived silyl enol ethers would produce products such as **2**. These compounds could be cyclized to spirocycles **1** using olefin metathesis.[7]

The allylic alcohols required for this work were prepared as shown in Scheme 2. Addition of allylmagnesium chloride to enol ethers **5** gave the α,β-unsaturated ketones **6**. Selective reductions using $NaBH_4/CeCl_3$ gave allylic alcohols **7** that were acylated to afford esters **8**. These transformations proceeded extremely well providing esters **8** in 61 to 86% overall yields.

We then proceeded to optimize the rearrangement.[8] The use of KHMDS[9] was essential to realize synthetically useful yields (Table 1, entry 4). LDA, LiHMDS or NaHMDS gave significantly decreased recoveries (entries 1–3). Attempts to form the silyl ethers using TIPS triflate and Hunig's base resulted in decomposition (entry 5).



Scheme 1.



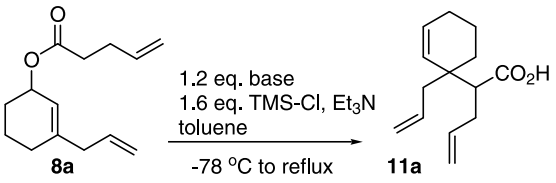
Scheme 2.

☆ Supplementary data associated with this article can be found at doi:10.1016/j.tetlet.2003.09.190

* Corresponding author. Tel.: +1-613-562-5800; fax: +1-613-562-5170; e-mail: wogilvie@science.uottawa.ca

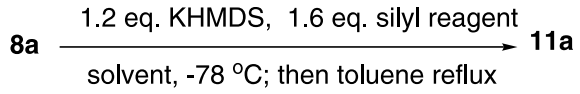
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.190

Table 1. Effect of base on the Ireland–Claisen rearrangement of **8a**



Entry	Base	Yield (%)	dr
1	LDA	0	
2	LiHMDS	12	2.1:1
3	NaHMDS	44	1.4:1
4	KHMDS	76	3:2
5	DIPEA/TIPSOTf	0	

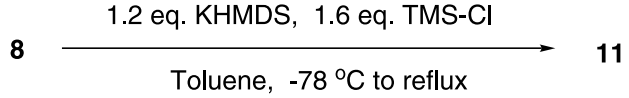
Table 2. Effect of solvent and silyl reagent on the Ireland–Claisen rearrangement of **8a**



Entry	Solvent	Silyl reagent	Yield (%)	dr
1	THF[a]	TMS-Cl/Et_3N	47	4.5:1
2	Ether[a]	TMS-Cl/Et_3N	79	2:1
3	Toluene	TMS-Cl/Et_3N	76	3:2
4	THF/HMPA[b]	TMS-Cl/Et_3N	44	4:1
5	Toluene	TBS-Cl	0	–
6	Toluene	TIPS-OTf	79[c]	2:1

[a] Solvent for silyl ether formation. Rearrangement performed in toluene.
[b] LDA was used as base.
[c] Yield after deprotection of the TIPS ester with aqueous HF in CH_3CN.

Table 3. Results of the Ireland–Claisen rearrangement of various substrates



Entry	Substrate	Yield (%)	dr
1	**8a**	76	3:2
2	**8b**	51	1.6:1
3	**8c**	47	1.9:1
4	**8d**	74	1.3:1
5	**8e**	0	–
6	**8f**	41	4.6:1

Toluene was superior as a rearrangement solvent (Table 2, entry 3). Selectivity was slightly higher when the silyl ether was formed in THF or ether. In these cases, the ethereal solvent was removed in vacuo and the rearrangement was completed in refluxing toluene (entries 1–3). The use of HMPA did not invert the ratio of products obtained (entry 4, see below) and led to lower recoveries. Among the silyl reagents used, the combination of TMS-Cl/TEA gave the best yields and reproducibility.

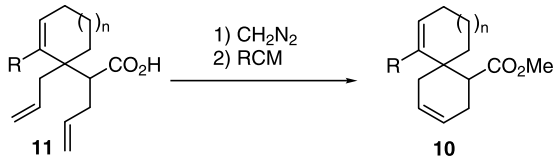
Surprisingly, TBS-Cl gave no product at all and only starting material was recovered (entry 5). Improvements in reproducibility were achieved using a slight excess of TIPSOTf as the silylating agent (entry 6). The TIPS silyl ketene acetals proved to be stable toward flash chromatography allowing us to purify the intermediates (in quantitative yield) if warranted. Brief exposure to HF in CH_3CN was required in these cases after the rearrangement in order to obtain the desired carboxylic acids.

Using KHMDS and TMS-Cl in toluene, we were able to rearrange substrates **8** to obtain the acids **11** in good yields and verify the effect of the R group on yield and selectivity (Table 3). The rearrangement of substrates incorporating no substituent proceeded in excellent yield and modest diastereoselectivity. We investigated the reactions of **8c** and **8f** incorporating bromo substituents as a possible means to increase diastereoselectivity. Substrate **8f** gave improved selectivity over **8d**. However only a small effect was observed for derivative **8c**.

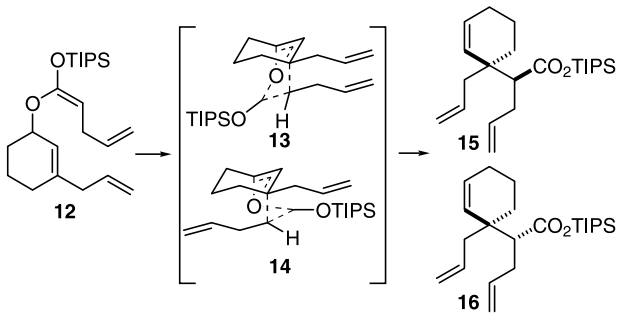
The rearrangements of **8d** and **8e** proved to be challenging. Both substrates were unstable and quickly decomposed under the mildly acidic conditions required for isolation. The former substrate **8d** could be converted to **9d** if the rearrangement was carried out immediately after the isolation of **8d**. Compound **8e** proved to be too unstable and could not be rearranged.

With substrates **11** in hand we then explored the ring-closing metathesis to obtain the various spirocyclic cores. After treating the substrates **11** with excess diazomethane, we subjected the methyl esters to metathesis. The metathesis reactions proceeded extremely rapidly and cleanly giving the desired products **10** in 82–97% yields (Table 4). In all cases except **9d** the endocyclic olefins of the starting materials were untouched and we obtained the desired spirocycles only. Compound **9d** gave a mixture of products resulting from opening of the five-membered ring.[10] This was

Table 4. Ring-closing metathesis of various substrates



Entry	Substrate	Catalyst loading (mol%)	Yield (%)
1	**9a**	7	97
2	**9b**	7	91
3	**9c**	10	82
4	**9d**	5	–
5	**9f**	5	96



Scheme 3.

unexpected given the proximity of the endocyclic olefin to the quaternary center and the excellent regioselectivity observed for all the other substrates. Substrate **9f**, possessing a more sterically hindered endocyclic double bond, did not suffer ring-opening under the conditions employed (entry 5).

We explored the possibility of cyclizing the TIPS ester products as isolated directly after the rearrangement. The reactions proceeded extremely rapidly, however small amounts of side products, that were difficult to remove, were formed. We therefore found it prudent to hydrolyze the TIPS esters and convert the resulting acids to the methyl esters for metathesis.

The rearrangement of pure enolates to give mixtures of diastereomers is not unknown for other cyclic substrates.[3,6] Calculations performed by Houk[6b] indicate that this is a consequence of the rearrangements occurring through both chair and boat-like transition states. We were able to confirm this by experiments performed using substrate **8a**. Treatment of **8a** with KHMDS and TIPSOTf resulted in exclusive formation of the *E* enolate **12** as evidenced by the characteristic chemical shift of the enolate carbon (85 ppm as opposed to 75 ppm for the *Z* enolate).[3] Rearrangement of this compound gave a 2:1 mixture of products in favor of epimer **15**[11] (Scheme 3). This suggests that the rearrangement was proceeding via both boat- and chair-like transitions states in agreement with calculations performed by Houk.[6b]

The described method provides a rapid and reliable way to assemble spirocycles. Using the Claisen protocol, one can set the configuration of the spiro carbon by virtue of the well-precedented[3,6] suprafacial migration. By exploiting the steric hindrance of the endocylcic double bond, ring-closing metathesis proceeds extremely selectively, affording in all cases studied except one, the desired compounds in excellent yield. We are currently exploring this method in the synthesis of natural products.

Acknowledgements

Financial support from the University of Ottawa, NSERC, Canada Foundation for Innovation and the Ontario Innovation Trust is gratefully acknowledged.

References

1. (a) Fuji, K. *Chem. Rev*. **1993**, *93*, 2037–2066; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 388–401; (c) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed*. **2001**, *40*, 4591–4597.
2. Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071.
3. Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem*. **1991**, *56*, 3572–3582.
4. For other applications of Claisen rearrangements in the formation of spiro systems, see: (a) Srikrishna, A.; Vijaykumar, D.; Jagadeeswar Reddy, T. *Tetrahedron* **1997**, *53*, 1439–1446; (b) Dickson, J. K.; Tsang, R., Jr.; Llera, J. M.; Fraser-Reid, B. *J. Org. Chem*. **1989**, *54*, 5350–5356; (c) Ladouceur, G.; Paquette, L. A. *Synthesis* **1992**, 185–191; (d) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith Strickland, S. M.; Saunders, J. O. *J. Org. Chem*. **1981**, *46*, 2400–2402.
5. (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed*. **1998**, *37*, 1986–2012; (b) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc*. **1999**, *121*, 6771–6772.
6. (a) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928; (b) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem*. **2003**, *68*, 572–577.
7. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.
8. Related rearrangements have been reported with considerable variation in yield and selectivity. See: Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem*. **1981**, *46*, 3896–3900 and Ref. 3.
9. Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett*. **2002**, *4*, 2877–2880.
10. Metathesis of **9d** was complete in less than 2 min at 0°C. Reaction at −78°C gave 64% conversion after 10 min with the same distribution of ring-opened products.
11. This was consistent with NMR observations on the subsequent metathesis product **10a**. The proton α to the ester in the spectrum of the minor isomer shows couplings of 9.9 Hz and 5.4 Hz. The same hydrogen in the major product gives 6.6 and 6.8 Hz couplings. NOE measurements are consistent with this assignment.