A Ring Closing Metathesis Based Approach for the Spiroannulation of Cyclopentanes and Cyclohexanes. Formal Synthesis of (±)-Acorones

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Received 17 September 2001; revised 18 October 2001

Abstract: An efficient ring closing metathesis (RCM) reaction based approach was developed for the spiroannulation of cyclopentanes and cyclohexanes and its utility demonstrated in the formal synthesis of the spirosesquiterpenes acorones.

Key words: spiroannulation, spiro compounds, metathesis reaction, Claisen rearrangement, acorones

The last decade has witnessed a dramatic growth in the application of the olefin metathesis reaction in organic synthesis. The substoichiometric nature of the reaction in combination with the operational simplicity, remarkable tolerance of Grubbs' catalyst to various functional groups and its stability to various conditions are key factors responsible for the increased utility of this reaction, particularly the intramolecular version, i.e. the ring-closing metathesis (RCM)[1] reaction, using Grubbs' catalyst [$PhCH=RuCl_2(PCy_3)_2$]. Spiro-fused cyclopentanes and cyclohexanes[2] are encountered in a variety of natural products, but, even though a few examples of RCM reaction generating heteroatom containing spirosystems have been reported,[1c] its utility in the construction of carbocyclic spiro-systems has received little attention.[3] Herein, we wish to report a general methodology based on an efficient RCM reaction for the spiroannulation of cyclopentanes and cyclohexanes, and its application in the formal synthesis of the acorone spirosesquiterpenes.

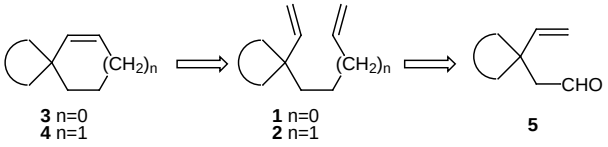
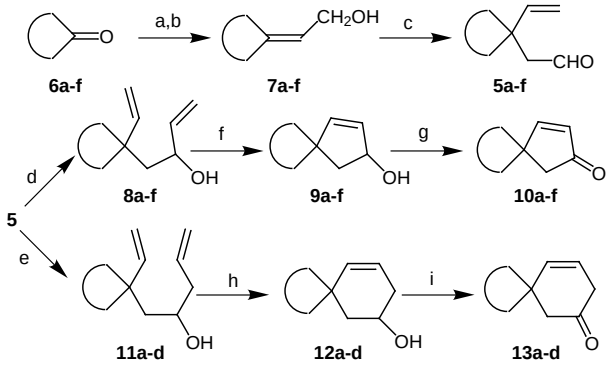


Figure 1

It was considered that RCM reaction of the 1,6-heptadienes **1** and 1,7-octadienes **2** would generate the spiro compounds **3** and **4**, respectively, while the aldehyde **5** could serve as a common precursor for the generation of the dienes **1** and **2** (Figure 1). Synthesis of γ,δ-unsaturated aldehydes **5,** from the corresponding cyclic ketones **6**, via the Claisen rearrangement of the allyl alcohol **7**, is well established.[4] The general methodology is depicted in Scheme 1. Initially, the cyclic ketones **6a**–**f** were transformed into the allyl alcohols **7a**–**f** via Horner-Wadsworth–Emmons reaction followed by reduction of the resultant α,β-unsaturated esters with lithium aluminium hydride (LAH). One pot Claisen rearrangement of the allyl alcohols **7a**–**f** with ethyl vinyl ether and mercuric acetate furnished the aldehydes **5a**–**f**.[4] Reaction of the aldehydes **5a**–**f** with vinylmagnesium bromide in THF at room temperature generated the hepta-1,6-dien-3-ols **8a**–**f** in 85–90% yield. The RCM reaction[5] of the dienols **8a**–**f** in methylene chloride in the presence of 6–8 mol% of Grubbs' catalyst for 6–8 h at room temperature furnished the spiro compounds **9a**–**f** in near quantitative yield. Oxidation using pyridinium chlorochromate (PCC) and sodium acetate in methylene chloride transformed the allyl alcohols **9a**–**f** into the spiroenones **10a**–**f** (Scheme 1).



Scheme 1 Reagents, conditions and yields: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, reflux, 8 h, 92–98%;[4] (b) $LiAlH_4$, Et_2O, –70 °C, 2 h, 90-95%;[4] (c) $CH_2=CHOEt$, $Hg(OAc)_2$, sealed tube, 180 °C, 60–65%;[4] (d) $CH_2=CHMgBr$, THF, r.t., 1 h, 82–90%; (e) Zn, $CH_2=CHCH_2Br$, THF, sonication, 15 min, 84–88%; (f) 6–8 mol% Grubbs' catalyst, CH_2Cl_2, r.t., 6 h; (g) PCC, NaOAc, CH_2Cl_2, r.t., 1 h. (h) 6–8 mol% Grubbs' catalyst, C_6H_6, reflux, 16–18 h; (i) PCC, CH_2Cl_2, 1 h.

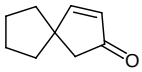
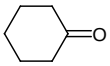
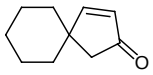
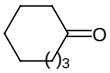
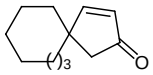
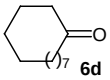
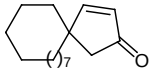
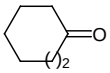
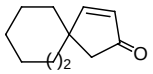
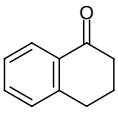
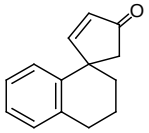
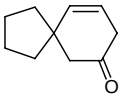
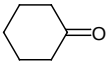
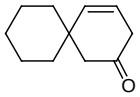
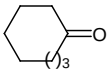
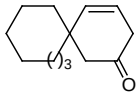
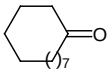
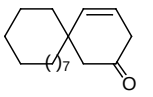
In a similar manner, sonochemically accelerated reaction of the aldehydes **5a**–**d** with zinc and allyl bromide in THF furnished the octa-1,7-diene-4-ols **11a**–**d** in 84–88% yield. RCM reaction[5] of the octadienols **11a**–**d** with 6–8 mol% of Grubbs' catalyst in refluxing benzene for 16-18 h furnished the spiro compounds **12a–d** in 84–90% yield. PCC oxidation in methylene chloride transformed the alcohols **12a**–**d** into the spiroenones **13a**–**d** (Table). It is worth noting that the RCM reaction of the octadienols **11a**–**d** failed to proceed at room temperature. The results

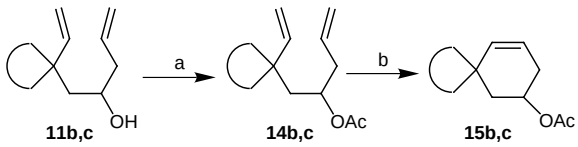
Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1986,1988,ftx,en;D21901ST.pdf.

ISSN 0936-5214

are summarized in the table. The corresponding acetates **14b**,**c** also underwent RCM reaction with Grubbs' catalyst in refluxing benzene to furnish the spiroacetates **15b**,**c** (Scheme 2). After successfully demonstrating the methodology, as an application, it has been extended to the formal synthesis of the spiro sesquiterpenes acorones **16**.

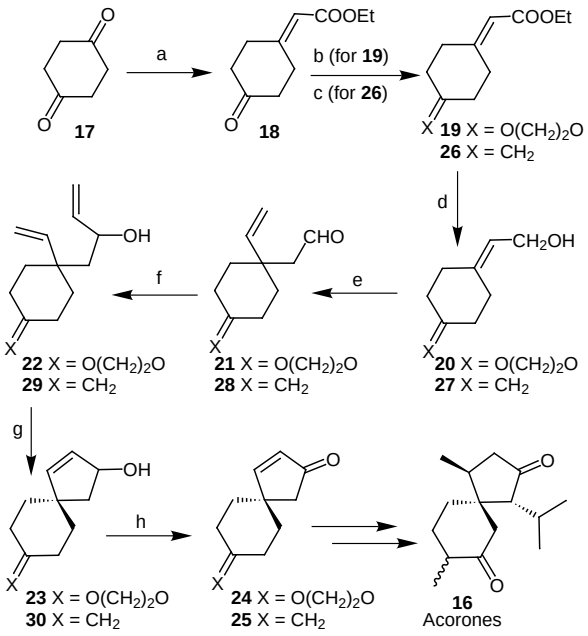
Table Annulation Reactions

Starting ketone	Yield in RCM reaction	Oxidation	Annulated product
	96%	92%	
6a			**10a**
	98%	92%	
6b			**10b**
	97%	92%	
6c			**10c**
	98%	92%	
6d			**10d**
	95%	90%	
6e			**10e**
	99%	94%	
6f			**10f**
	87%	85%	
6a			**13a**
	89%	88%	
6b			**13b**
	89%	86%	
6c			**13c**
	90%	86%	
6d			**13d**



Scheme 2 Reagent, conditions and yields (a) Ac_2O, py, DMAP, CH_2Cl_2, r.t., 4 h; 90–92%; (b) 8 mol% Grubbs' catalyst, C_6H_6, reflux, 18 h, 84–86%.

Sorm and coworkers reported the isolation of the spirosesquiterpenes acorone and isoacorone **16** from the oil of sweet flag, *Acorus calamus L*, and established the presence of a novel spiro[4.5]decane carbon framework.[6] Further phytochemical investigations led to the characterization of a number of acorane sesquiterpenes.[6] The interesting spirocyclic carbon framework made acoranes challenging synthetic targets,[7] the most important aspect in the synthesis of acoranes being the stereocontrolled construction of the spiro system. Based on the methodology described above, a formal synthesis of acorones **16**, depicted in Scheme 2, was conceived starting from cyclohexane-1,4-dione **17**. Thus, selective Horner–Wadsworth–Emmons reaction of the dione **17** generated the ketoester **18**. Two alternate strategies were explored. In the first strategy, the ketone in **18** was protected as its ethylene ketal to furnish the ketalester **19**, which on regioselective reduction with LAH furnished the allyl alcohol **20**. One pot Claisen rearrangement of the allyl alcohol **20** with ethyl vinyl ether and propionic acid generated the aldehyde **21**, which on reaction with vinylmagnesium bromide furnished the dienol **22**. The RCM reaction of the dienol **22** in methylene chloride with 7 mol% of Grubbs' catalyst at room temperature furnished the spiro alcohol **23**, which on oxidation with PCC and NaOAc in methylene chloride generated the spiroenone **24**. Conversion of the spiroenone **24** into the spiroenone **25** via hydrolysis of the ketal and selective Wittig reaction has already been reported.[7] In the second strategy it was envisaged that, instead of the protection of the ketone in **18**, Wittig methylenation followed by spiroannulation would directly generate the spiroenone **25**, thereby eliminating the protection-deprotection protocol. Thus, reaction of the ketoester **18** in benzene with methylenetriphenylphosphorane at room temperature followed by regioselective reduction of the resultant compound **26** with LAH furnished the allyl alcohol **27**. Claisen rearrangement followed by addition of vinylmagnesium bromide to the resultant aldehyde **28**, transformed the allyl alcohol **27** into the dienol[#] **29**. The RCM reaction of the dienol **29** in methylene chloride with 7 mol% of Grubbs' catalyst at room temperature furnished the spiro alcohol[#] **30**, which on oxidation with PCC and NaOAc in methylene chloride generated directly the spiroenone[#] **25**. Since the spiroenone **25** has already been transformed into (±)-acorones,[7] the present sequence constitutes a formal synthesis of the spirosesquiterpenes **16** (Scheme 3).



Scheme 3 Reagents, conditions and yields: (a) $(EtO)_2P(O)CH_2COOEt$, NaH, 0 °C, 10 min, 92%; (b) $(CH_2OH)_2$, *p*-TSA, C_6H_6, reflux, 10 h, 90%; (c) $Ph_3P{=}CH_2$, C_6H_6, r.t., 3 h, 75%; (d) $LiAlH_4$, Et_2O, –70 °C, 2 h, 92%, 90%; (e) $CH_2{=}CHOEt$, EtCOOH (for **21**) or $Hg(OAc)_2$ (for **28**), sealed tube, 175 °C, 61%, 60%; (f) $CH_2{=}CHMgBr$, THF, r.t., 1 h, 93%, 86%; (g) 7 mol% Grubbs' catalyst, CH_2Cl_2, r.t., 5 h, 95%, 96%; (h) PCC, NaOAc, CH_2Cl_2, r.t., 1 h, 94%, 91%.

In conclusion, we have developed a convenient and efficient methodology based on the RCM reaction for the spiroannulation of cyclopentanes and cyclohexanes starting from cyclic ketones, which has the flexibility to be extended further to spiroannulation of other rings. The overall efficiency of the methodology points to its high potential in organic synthesis. As an illustration, the formal synthesis of the spirosesquiterpenes acorones has been accomplished, demonstrating the utility of the present methodology in the natural product synthesis.

Acknowledgement

We thank the Council of Scientific and Industrial Research, New Delhi for the award of research fellowships to SJG and NCB.

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(5) *Typical Procedure:* The dienol (**8** or **11**, 0.2-0.3 mmol) was added to a solution of Grubbs' catalyst (10–12 mg) in methylene chloride (for **8**) or benzene (for **11**) and the solution was stirred at room temperature for 6 h (for **8**) or refluxed for 16–18 h (for **11**). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column furnished the spiro compounds.

(6) (a) Sorm, F.; Herout, V. *Collect. Czech. Chem. Commun.* **1948**, *13*, 177. (b) Sorm, F.; Herout, V. *Collect. Czech. Chem. Commun.* **1949**, *14*, 723. (c) Sykora, V.; Herout, V.; Pliva, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1958**, *23*, 1072. (d) Tomita, B.; Isono, T.; Hirose, H. *Tetrahedron Lett.* **1970**, 1371; and reference cited therein.

(7) For the earlier formal and total syntheses of acorones see: Srikrishna, A.; Kumar, P. P. *Tetrahedron* **2000**, *56*, 8189; and references cited therein.

(8) All the compounds exhibited spectral data consistent with their structures. Selected spectral data for the alcohol **29**: IR(neat): ν_{max}/cm^{-1} 3406, 916, 885. ^1H NMR (300 MHz, $CDCl_3$ +CCl_4): δ 5.81 (1 H, dd, *J* 17.4 and 10.8 Hz), 5.90–5.75 (1 H, m), 5.30–4.95 (4 H, m), 4.56 (2 H, s), 4.30–4.20 (1 H, m), 2.20–2.05 (4 H, m), 1.90–1.20 (7 H, m). ^{13}C NMR (75 MHz, $CDCl_3$ +CCl_4): δ 148.9 (C), 146.1 (CH), 142.3 (CH), 114.3 (CH_2), 113.6 (CH_2), 107.0 (CH_2), 70.1 (CH), 48.4 (CH_2), 39.5 (C), 38.0 (CH_2), 36.6 (CH_2), 31.0 (2 C, CH_2). For the spiroalcohol **30**: IR(neat): ν_{max}/cm^{-1} 3346, 887. ^1H NMR (300 MHz, $CDCl_3$ +CCl_4): δ 5.87 (1 H, d, *J* 6 Hz), 5.73 (1 H, dd, *J* 6 and 1.8 Hz), 4.90–4.80 (1 H, m), 4.60 (2 H, s), 2.26–2.10 (5 H, m), 1.70–1.20 (6 H, m). ^{13}C NMR (75 MHz, $CDCl_3$ +CCl_4): δ 148.2 (C), 143.3 (CH), 131.9 (CH), 107.5 (CH_2), 76.9 (CH), 49.1 (C), 45.7 (CH_2), 40.4 (CH_2), 39.1 (CH_2), 32.4 (CH_2), 32.2 (CH_2). For the spiroenone **25**: IR(neat): ν_{max}/cm^{-1} 1715, 890. ^1H NMR (300 MHz, $CDCl_3$ +CCl_4): δ 7.48 (1 H, d, *J* 5.6 Hz), 6.06 (1 H, d, *J* 5.6 Hz), 4.68 (2 H, s), 2.28 (2 H, s), 2.50–2.00 (4 H, m), 1.80–1.50 (4 H, m). ^{13}C NMR (75 MHz, $CDCl_3$ +CCl_4): δ 209.2 (C), 171.6 (CH), 146.7 (C), 132.1 (CH), 108.6 (CH_2), 46.3 (CH_2), 45.8 (C), 37.9 (2 C, CH_2), 32.1 (2 C, CH_2).