Pergamon

Tetrahedron Letters 43 (2002) 9035–9038

TETRAHEDRON LETTERS

Synthesis of α,β-disubstituted cycloalkenones through a sequence of olefin metathesis and oxidative rearrangement

Dongfang Meng* and Dann L. Parker, Jr.

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

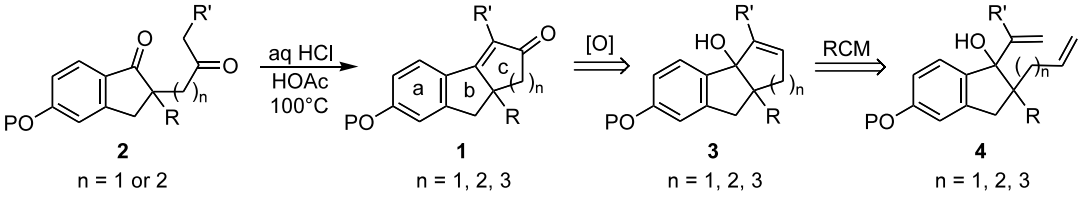
Received 13 September 2002; accepted 15 October 2002

Abstract—Efficient syntheses of five-, six-, and seven-membered α,β-disubstituted cycloalkenones were achieved. Ring-closing metathesis and allylic oxidative rearrangement were the key steps in this route. To make substituted cycloalkenes from triene substrates constituted of two monosubstituted double bonds and one α,α-disubstituted double bond, ethylene was found to successfully promote equilibria among ring closing-ring opening-ring closing processes. © 2002 Published by Elsevier Science Ltd.

Phenolic tetrahydrofluorenones **1** ($n=2$, P = H, Scheme 1) are a new class of potent ligands for estrogen receptors.[1] The synthesis of the tetrahydrofluorenone C-ring, an α,β-disubstituted cyclohexenone with a quatenary γ-center, presents an interesting synthetic challenge. These compounds, as well as compounds with a five-membered C-ring, have been constructed through aldol-type condensation (**2**→**1**), but this method often required harsh conditions. These conditions are incompatible with targets in which R contains an acid sensitive moiety, for example a cyclopropyl ring or an alkenyl halide. Furthermore, we found no mature, efficient methods for preparing cycloheptenone targets.[2] The need to efficiently make a variety of these potentially important ER ligands prompted us to develop a new synthetic route.

One of the most exciting synthetic methods developed in the past 10 years is olefin metathesis, especially ring-closing metathesis (RCM).[3] This powerful reaction has gained enormous popularity as catalysts became more active, air stable, and commercially available.[4] We sought a route toward tetrahydrofluorenones and their five- and seven-membered cousins which would employ a sequence of RCM followed by oxidative rearrangement of the methathesis product. If RCM furnishes allylic alcohols **3** from dienes **4**, targets **1** could be reached easily through allylic oxidative rearrangement (AOR). This route strategically avoids ring construction in the crowded area of the tetrasubstituted olefin and quartenary center, which makes it possible to be both efficient and mild enough to tolerate desirable functional groups on R.

This idea was quickly tested as shown in Scheme 2. Indanones **5**,[1] known and readily available to us, were alkylated to introduce a terminal alkenyl group at the quaternary center. The neat ketones **6** were stirred with excess (3–5 equiv.) isopropenyl Grignard to give the RCM substrates **7** as 1:1 mixtures of diastereomers. The metathesis reaction was then attempted using Grubbs' first-generation ruthenium catalyst[5] $(Pcy_3)_2Cl_2Ru{=}CHPh$, which completely consumed the substrate **7** yet failed to generate any desired product.



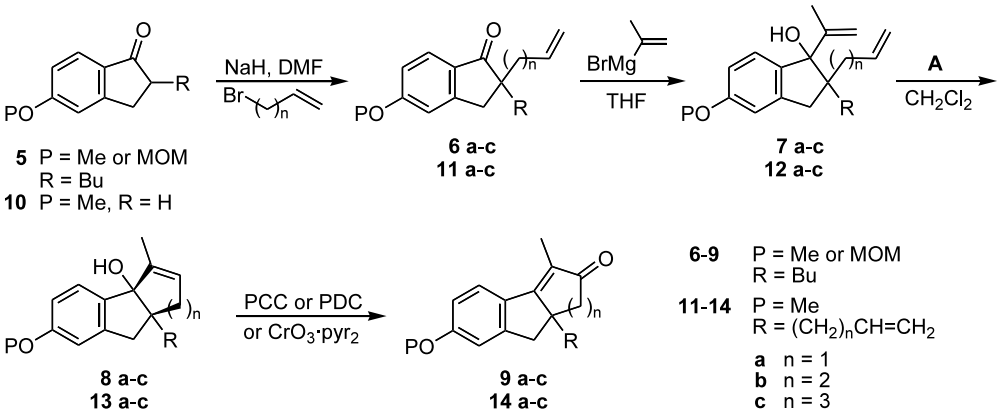
2 n = 1 or 2 **1** n = 1, 2, 3 **3** n = 1, 2, 3 **4** n = 1, 2, 3

Scheme 1.

Keywords: cycloalkenones; olefin metathesis; allylic oxidative rearrangement.

* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)02307-9



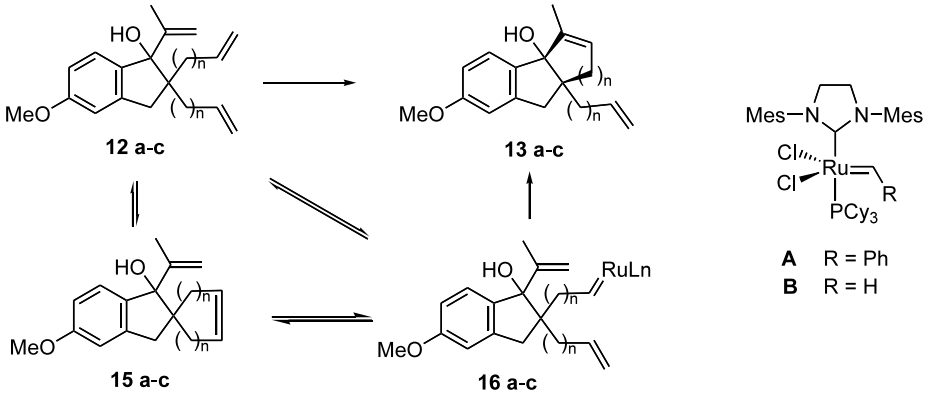
Scheme 2.

Schrock's molybdenum catalyst[6] is more active for making trisubstituted alkenes, but the higher Lewis acidity of Mo makes it incompatible with a free alcohol and protection of our tertiary alcohol was impractical. Fortunately, shortly after facing this dilemma, Grubbs' more active, second-generation ruthenium catalyst[7] tricyclohexylphosphine[1,3 - bis(2,4,6 - trimethyl - phenyl)-4,5-dihydro-imidazol-2-ylidene]benzylidine ruthenium(IV) dichloride (A) became commercially available. Much to our delight, this reagent successfully cyclized one diastereomer of dienes **7** to yield the desired products **8**, presumably the *cis*-fused ring, in about 45% yield. Allylic tertiary alcohols **8** rearranged cleanly to the desired cycloalkenones **9** with either PDC or PCC,[8] even though the isolated yields (30–40%) were surprisingly lower than expected based on NMR examination of the crude reaction mixtures (>60%). Final deprotection of the phenol could be carried out through several known methods.[1]

These early studies encouraged us to improve this route. Double alkylation of the indanone with the requisite alkene would generate several advantages. First, symmetrically substituted indanones **11a–c** are more easily prepared than **6a–c**. Second, the theoretical yield of the metathesis step would now be 100% since there would be a 1,2-*cis* arrangement of alkenyl groups in the metathesis substrate **12a–c**. Finally, the final products **14a–c** would possess an R group amenable to functionalization. Because RCM is a thermodynamic process,[9] all possible kinetic products from a triene like **12** (see Scheme 3) should be driven to the more stable, trisubstituted alkene **13**. Furthermore, the trisubstituted alkene is less likely to be attacked by the RCM catalyst. Thus, under high dilution, the desired product should be obtained without polymerization.

Trienes **12** were easily prepared (see Scheme 2) from the commercially available indanone **10** using a sequence similar to that previously described for diene **7**.[10] When trienes **12a–c** were treated with catalyst A, they behaved quite differently. Cycloheptenone precursor **12c** cyclized slowly at room temperature, but was consumed in 3 h at 40°C to yield **13c** as the major product. The spiro-product **15c** (see Scheme 3), in this case a cyclononene, was not detected. In contrast, **12a** and **12b** cyclized quickly at room temperature, but the major products were spiro-cycloalkenes **15**. After 1 h, the ratios of **13**:**15** were about 1:2. Longer reaction times at either room temperature or 40°C slowly improved the **13**:**15** ratio, but it never got better than 2:1 even after 4 days (16 h ratio of **13b**:**15b** still smaller than 1:1).

This dominance of the disubstituted olefin product is a general problem for RCM of trienes constituted from two monosubstituted double bonds and one disubstituted double bond.[11] We hypothesized that this prob-



Scheme 3.

lem could be solved by running the reactions in the presence of ethylene.[12] We proposed that ethylene would accelerate the ring-opening metathesis (ROM) of spiro-cycloalkenes **15** but leave the fused, substituted cycloalkenes **13** untouched. Thus, running the metathesis reaction in the presence of ethylene should drive the equilibrium toward our desired product. Gratifyingly, after 12 h under these conditions, the ratios of **13a**:**15a** and **13b**:**15b** were found to be greater than 4:1 based on NMR integration of crude reaction mixtures. Additional catalyst and longer reaction times slightly improved the ratio but side products started to appear.

In order to obtain more information about the reaction mechanism, **15a** was isolated and treated with A under an atmospheres of either nitrogen or ethylene. After 16 h under nitrogen, no trisubstituted alkene **13a** was detected by NMR. By contrast, a 3:1 ratio of **13a**:**15a** was reached under ethylene. It is very likely that catalyst **A** was transformed to the more efficient catalyst **B** through reaction with either **12** or ethylene. Since the highly congested α,β-disubstituted double bond is kinetically less favored, **B** opens the spiro-cycloalkene to give two diastereomeric Ru-carbenes **16**. If *cis*-**16** cyclizes to **13** intramolecularly, it would be unlikely to ring-open again. *trans*-**16** Would either cyclize back to **15**, metathesize to *cis*-**16** intramolecularly, or give **12** through cross-metathesis. To our knowledge, this is the first example to use ethylene as a modulator in RCM to drive the reaction in the desired trisubstituted alkene direction via a ring closing-ring opening-ring closing process.

To complete the synthesis, oxidant was introduced to the reaction solution of RCM. AOR always went smoothly, but was probably still the lowest yielding step in this four-step sequence. PDC gave less high polarity side-products than PCC. Addition of powdered molecular sieves accelerated the reaction but did not give higher isolated yields. It was interesting to find that Ratcliffe reagent[13] (CrO_3 and pyridine) worked better on **13c** than the other chromium sources, but required 12–18 equiv. of reagent to drive the reaction to completion.

In summary, we have developed a novel procedure for the synthesis of α,β-disubstituted cycloalkenones with a functionalized γ side-chain. Furthermore, cycloheptenone **14c** was synthesized with remarkable efficiency relative to existing alternative methods. From commercially available reagents, this four-step sequence requires just one final purification.[14] These methods should allow rapid access to analogs which previously had to be prepared by more laborious routes. Finally, these studies revealed that ethylene promoted the RCM–ROM–RCM equilibrium between disubstituted cycloalkene and tri-substituted cycloalkene, allowing the preparation of tri-substituted cycloalkene as the major metathesis product of triene substrates containing two monosubsituted and one α,α-disubstituted olefins.

References

1. Published Merck patent application: Parker, D.; Ratcliffe, R.; Wilkening, R.; Wildonger, K. WO 0182923-A1.
2. For a recent method to make β-monosubstituted cycloheptenones, see: Piers, E.; Walker, S. D.; Armherst, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 635.
3. Danishefsky, S. J. *C & EN* 2002, Feb. 11, 36.
4. For a thorough list of references about RCM, please see references in: Furstner, A.; Radkowski, K.; Wirz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061.
5. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.
6. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.
7. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
8. Dauben, W. G.; Michno, D. *J. Org. Chem.* **1977**, *42*, 682.
9. Miller, S. J.; Kim, S.; Chen, Z.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.
10. All allylic/benzylic tertiary alcohols like **7**, **8**, **12**, and **13** were acid sensitive and used crude. Because of this instability, it was difficult to follow RCM and AOR reactions by TLC or LCMS.
11. Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991.
12. Professor Hoveyda and colleagues have reported using ethylene to mediate ring opening–ring closing metathesis in the synthesis of chromenes. Thermodynamically more stable cyclostyrenes (chromenes) were made from diene substrates containing one styrene and one cycloalkene (in one case, one styrene and two monosubstituted alkenes). The major function of ethylene in their case was to prevent oligomerization under relatively high substrate concentration (usually 0.1 M). In our system to make substituted cycloalkenes from trienes, oligomerization was not a problem at low concentration (0.005 M), even without ethylene. By contrast, at 0.1 M reactions were messier (oligomerization?) regardless of the presence or absence of ethylene. (a) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343; (b) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488.
13. Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
14. Representative procedures. (A) Five- and six-membered cycloalkenones: To a solution of **12a** (~0.2 mmol, 10% of crude product prepared in two steps from 2 mmol of 10) in CH_2Cl_2 (40 mL) at −78°C was added catalyst A (32 mg, ~0.04 mmol). Ethylene gas in a balloon was charged through three repetitions of a vacuum/ethylene sequence. The solution was stirred at room temperature overnight. At timepoints of 1 and 15 h, 1 mL aliquots were syringed out for NMR evaluation and not added back. After about 16 h, PDC (150 mg, 0.4 mmol) was added and the reaction mixture was stirred for 4 h. The solution was diluted with Et_2O (50 mL) and filtered through a plug of silica. The filtrate was concentrated

and purified by PLC. The product bands provided **14a** (9.8 mg, 20%) and **13a** (8.0 mg, about 60% purity). RCM equilibrium to make **13b** was usually slower so additional A in CH_2Cl_2 was injected into the reaction after several hours. (B) Cycloheptenone: **12c** and A (0.2 equiv.) in CH_2Cl_2 (0.005 M) was stirred at 40°C for 2–3 h, then cooled to room temperature and treated with PDC (2 equiv., 40°C) or freshly prepared Ratcliffe reagent (18 equiv., rt). After 1 h, the reaction was worked up and purified as above. Overall yields of **14a–c** from **10** were ~20%.