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### Synthesis of 5-cyclodecenones via RCM and a three-pot sequence for bisannulation

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Abstract: 5-Cyclodecenones were made by RCM, using the first generation Grubbs catalyst and infinite dilution in refluxing dichloromethane. A convenient one-pot procedure for making 2,6-disubstituted cyclohexanones was developed, which allowed for the synthesis of a bridged bicyclo compound, containing a 5-cyclodecenone. Transannular cyclization of this substrate led to a tricyclic product. The overall three-pot sequence of dialkylation, RCM and transannular cyclization results in bisannulation on a pre-existing ring.

Keywords: 2,6-Disubstituted cyclohexanones; Ring-closing metathesis; 5-Cyclodecenones; Transannular cyclization; Bisannulation; Perhydrophenalene

#### Introduction

Our research group has prepared a number of 5-cyclodecenones via anionic oxy-Cope rearrangements of 1,2-dialkenylcyclohexanols in which the two alkenyl groups are trans, as illustrated in equation 1.<sup>1-7</sup> In general the stereochemistry of the resulting alkene is trans with respect to the cyclodecene ring both in our work and in the work of others.<sup>1-23</sup>



In considering other routes to 5-cyclodecenones, we were inspired by the work of Nevalainen and Koskinen<sup>24-25</sup> who prepared 4-cyclodecenones via ring-closing metathesis (RCM) (equation 2). Their optimized procedure involved adding 10 mol % of first-generation Grubbs catalyst **2** to a 0.56 mM solution of dienone **1** pre-complexed with 10 mol% of  $Ti(O'Pr)_4$  in refluxing CH<sub>2</sub>Cl<sub>2</sub>, resulting in a mixture of 4-cyclodecenones **3a-c**. When the RCM was done without  $Ti(O'Pr)_4$ , the same mixture of products was obtained albeit it in a slightly altered ratio and slightly lowered yield.<sup>24</sup>



We report herein our preliminary investigations into the preparation of 5-cyclodecenones via RCM.

#### Dodeca-1,11-dien-6-one and its RCM

We began our work with the model compound dodeca-1,11-dien-6-one (4), which has been made by several routes.<sup>26-28</sup> We prepared 4 from commercially available 5-bromopent-1-ene and hept-6-enenitrile in one pot via addition of the Grignard reagent to the nitrile, followed by hydrolysis of the intermediate imine (equation 3).<sup>29</sup>



Attempted RCM of dienone **4**, using the conditions of Nevalainen and Koskinen (0.35 mM in refluxing  $CH_2CI_2$ ), led to a less than 10% yield of the products from RCM. This led us to explore a variety of conditions for promoting RCM. It turned out that the  $Ti(O'Pr)_4$  was unnecessary for our substrate, but infinite dilution conditions were. Addition of dienone **4** over a 24-hour period to a refluxing solution of first-generation Grubbs catalyst **2** in refluxing dichloromethane containing 22 mol% of **2** followed by addition of activated carbon and filtration though Celite<sup>30-31</sup> led to a 1.5:1 ratio of the two possible 5-cyclodecenones<sup>32</sup> that slightly favored the trans isomer in a combined yield of 46%.<sup>33</sup>



The ratio of products is most likely a kinetic result, given the low reactivity of **2** towards disubstituted alkenes. We observed that shortening the time for the addition did not alter the product ratio, only the yield of products. Furthermore, when a mixture of 1.66 equivalents of allyl ether (to insure conversion of the pre-catalyst **2** to its propagating form) and the trans isomer **5** was added over 24 hours to 0.21 equivalents of **2** under the otherwise identical conditions used to make **5** and **6**, 85% of **5** was recovered and no trace of either the cis isomer **6** or of oligomers was detected by either TLC or NMR, indicating that **5** does not react with the active form of the catalyst.

We examined the effect that temperature had on RCM of dienone **4**. At room temperature in dichloromethane we isolated less than 10% of the compounds **5** and **6**, and substantially more of the oligomeric products. Higher temperatures are known to aid RCM using second-generation ruthenium catalysts,<sup>34-35</sup> but reaction with first-generation Grubbs catalyst **2** at 75-80 °C<sup>36</sup> in either benzene or 1,2-dichloroethane led to partial recovery of **4** and little or none of **5** and **6**.

We also examined alternative ruthenium catalysts.<sup>37</sup> Use of second-generation Grubbs catalyst **7** in refluxing dichloromethane resulted in isolation of a mixture of **5** and **6** in a combined yield of less than 10%.<sup>38</sup> We prepared the first-generation Hoveyda-Grubbs catalyst **8**<sup>39</sup> and the

second-generation Hoveyda-Grubbs catalyst **9**,<sup>40-41</sup> but in refluxing dichloromethane neither led to significant amounts of the desired compounds **5** and **6**.



#### 2,6-Disubstituted Cyclohexanones and RCM

In reflecting on alternative substrates that would also lead to 5-cyclodecenones upon RCM, we considered incorporating a ring into the 1,11-dodecadiene. A pre-existing ring might aid RCM relative to oligomerization, and transannular cyclization of the product from RCM would lead to tricyclic products. A few examples of RCM to add a cyclodecene ring to a pre-existing six-membered ring are known.<sup>42,43</sup> In these examples, the products from RCM are fused bicyclo compounds from 1,2-disubstituted benzene and cyclohexene rings.

We were interested in the RCM of cyclohexanone **10** whose RCM would lead to a bridged bicyclo compound. In principal, the previously unknown 2,6-disubstitued cyclohexanone **10** could be made by alkylation of either of the known monosubstituted cyclohexanones **11**<sup>44</sup> or **12**.<sup>45</sup> In practice, alkylation under standard conditions (LDA, THF/HMPA, -78 °C) with the appropriate alkyl bromide or iodide lead to low yields of a mixture of the cis and trans isomers of **10** along with side products such as the 2,2-disubstituted cyclohexanones.



In considering alternative methods for making 2,6-substituted cyclohexanones,<sup>46</sup> we were attracted to the alkylation of the metalloenamine from deprotonation of imine  $13^{47}$  with *n*-BuLi and hydrolysis of the alkylated imine to prepare  $11^{48}$  in very high yield, as it allowed for possible sequential alkylation and one-pot preparation of the desired cyclohexanone 10. In practice, this worked as illustrated in equation 5, to prepare 10a and 10b in a 1:1.2 ratio in 70% yield that favored the trans isomer 10b.<sup>49</sup>



The assigned relative stereochemistry of **10a** and **10b** is consistent with an NMR sample of trans isomer **10b** in unfiltered CDCl<sub>3</sub> slowly isomerizing to a slightly greater than 3:1 ratio in favor of the more stable cis isomer **10a**.<sup>50</sup> The cis isomer is also the faster eluting diastereomer by flash chromatography, as observed in the separation of diastereomeric pairs of other 2,6-disubstituted

cyclohexanones.<sup>51,52</sup> The stereochemistry was further confirmed by reducing the cis isomer **10a** with NaBH<sub>4</sub> and converting the mixture of alcohols to their acetate derivatives (equation 6). The approximately 4:1 ratio of diastereomers could be partially separated. In the minor diastereomer **15** the hydrogen alpha to the acetoxy group was a triplet with a  ${}^{3}J_{ax-ax} = 10.1$  Hz, indicating that all three substituents on the cyclohexane ring are equatorial, as in **15**, which is only possible if the 2,6-disbutstitued cyclohexanone it was derived from has the cis stereochemistry of **10a**. By inference, **10b** must be the trans diastereomer. The trans stereochemistry of **10b** is also consistent with the relative stereochemistry of the products derived from **10b** (*vide infra*).



With the cyclohexanones **10a** and **10b** in hand we investigated their RCM. The cis isomer **10a** when treated with **2** under infinite dilution conditions gave only compounds that appeared to be oligomers. However, the trans isomer led to clean conversion to the bridged bicyclo compound **16** in 55% yield (equation 7) along with small amounts of oligomeric products.



The chemical shifts of the vinylic hydrogens of **16** were observed to be 5.49 ppm (td, J =11.3, 11.3, 3.0 Hz) and 5.36 ppm (tdd, J = 11.3, 11.3, 5.7, 1.8 Hz). The coupling constant of J =11.3 Hz between the vinylic hydrogens suggested a probable configuration of *cis* for the alkene. but due to the nearness of this coupling value to the limit of the characteristic coupling of a *cis* alkene further NMR experiments were used to confirm this assignment. The chemical shifts of the allylic hydrogens adjacent to each vinyl hydrogen were assigned using selective 1D TOCSY experiments with increasing mixing times. Only the resonance signals of the hydrogens nearest each vinyl hydrogen were apparent in the 1D TOCSY spectra with the shortest mixing times (Figures S9 and S10 in the Supporting Information), while the remaining hydrogens in the spin system were observed with longer mixing times. The resonances at 5.49 ppm and 2.23 ppm were observed to correspond to one set of vinylic-allylic vicinal hydrogens and the resonances at 5.36 ppm and 2.45 ppm were observed to correspond to the other pair of vinylic-allylic vicinal hydrogens (Figure 1). A 2D NOESY experiment was then used to identify NOEs between hydrogens in relatively close proximity to each other. Unfortunately, the NOE between the two vinylic hydrogens was obscured by the diagonal cross-peaks in the 2D NOESY spectrum and could not be observed. Due to this absence of direct evidence, indirect evidence from the NOESY spectrum was used to confirm the configuration of the alkene. The absence of NOEs between each vinylic hydrogen and the allylic hydrogens on the opposite side of the alkene suggested that the configuration was cis. Observation of NOEs between the vinylic hydrogens and their adjacent allylic hydrogens indicated that the absence of observed NOEs was not due to weak signals.

Additionally, a signal corresponding to the NOE between the allylic hydrogens on opposite sides of the alkene at 2.23 and 2.45 ppm provided further evidence for the cis configuration.



Figure 1. Correlations from TOCSY and NOESY experiments used to assign the geometric configuration of the geometry of the alkene group in 16.

### Transannular cyclization and determination of relative stereochemistry

Given our interest in transannular cyclizations of 5-cyclodecenones,<sup>1-7</sup> we treated the 5-cyclodecenone **16** with trifluoroacetic acid, which led to the tricyclic alcohol **17** in 70% yield (equation 8). A small amount (less than 3% by mass) of another product was isolated, but its structure was not determined.



Based on the downfield shift of the chemical shifts of the hydrogens on C4 (+0.42 ppm) and C5 (+0.26) in pyridine-d<sub>5</sub> compared to their chemical shifts in CDCl<sub>3</sub>,<sup>53</sup> the hydrogens on C4 and C5 are syn to the hydroxyl group on C13, which is the same relative stereochemistry observed in the analogous transannular cyclization of *cis*-5-cyclodecenone (**6**) with CF<sub>3</sub>CO<sub>2</sub>H in which a cis alkene leads to a cis ring fusion between C13 and C5, and the cis relationship between the alkene hydrogens that correspond to the hydrogens on C4 and C5 of the product is maintained. It could further be determined that one of the other methine hydrogens on either C1 or C9 was syn and one was anti to the hydroxyl group on C13 based on a downfield (+0.15 ppm) and an upfield shift (-0.25 ppm) in their chemical shifts in pyridine-d<sub>5</sub> compared to their chemical shifts in CDCl<sub>3</sub>, which is consistent with the trans stereochemistry of **10b**. This left two possible structures, **17** and **18**, for the product from transannular cyclization of **16**.



In order to distinguish between these two diastereomers, 2D COSY, HSQC and HMBC experiments were used to assign the chemical shift of the resonances of C1, C3, C4, C5, C6, C9 and C13 (Figure 2). The chemical shift in DMSO-d<sub>6</sub> of the hydrogen on C4 was assigned as 5.52 ppm, with its downfield resonance caused by deshielding from the trifluoroacetoxy group. Crosspeak signals with this hydrogen in the COSY spectrum allowed the assignment of the chemical shifts of the hydrogens at C3 as 1.71 ppm and 1.66 ppm and at C5 as 1.87 ppm. Further examination of the COSY spectrum led to the assignment of the chemical shifts of the hydrogens on C6 (Figure 2). A <sup>1</sup>H-<sup>13</sup>C HSQC experiment enabled the assignment of the chemical shifts of C3-C6 (Table S1 in the Supporting Information). With these assignments made, a <sup>1</sup>H-<sup>13</sup>C HMBC experiment was used to assign the chemical shift of C1 and C9. Specifically, correlations in the HMBC experiment were observed from 1.66 ppm (C3-Hb) to 155.8, 78.7, 47.0, and 32.0 ppm, corresponding to the carbonyl carbon of the trifluoroacetate, C4, C5 and C1, respectively. Based on these assignments, a 2D NOESY experiment was then used to identify hydrogens that were syn to the C13 hydroxyl group. NOE signals between the hydrogens on C4 and C5 and the C13 hydroxyl group indicated that these hydrogens were syn to each other, while the absence of a NOE signal between the hydrogen on C1 and those on C4, C5 and the C13 hydroxyl group indicated that the hydrogen on C1 was anti to the other hydrogens. Additionally, an NOE signal between the C13 hydroxyl group and the hydrogen on C9 indicated that these two hydrogens were also syn to each other (Figure 3). These results supported the conclusion that the configuration of the product of the transannular cyclization was that of 17.



**Figure 2.** Selected correlations from COSY and HMBC experiments used to assign the chemical shift of the resonances of C1, C4, C5 and C13 and their attached hydrogens in **17**. Assignments of the chemical shifts of hydrogens to their respective carbons were made based on the results of an HSQC experiment.



**Figure 3.** Correlations from a 2D NOESY experiment used to assign the relative configuration of **17**.

#### Conclusion

For the first time 5-cyclodecenones have been made by RCM, using Grubbs first generation catalyst and infinite dilution in refluxing dichloromethane. To enable the synthesis of more complex substrates, a convenient one-pot procedure was used to make 2,6-disubstituted cyclohexanones **10**, which allowed for the synthesis of a bridged bicyclo compound, containing a 5-cyclodecenone (**16**). The success of the RCM reaction to prepare the bridged bicyclo compound was dependent on the stereochemistry of substrate **10**. Whereas the model substrate **4** for the RCM led to a mixture of cis and trans isomers of the resultant alkene, the more substituted compound **10b** underwent RCM to give only the product with the cis alkene (**16**). As such, this compliments the use of the oxy-Cope rearrangement to make 5-cyclodecenones from 1,2-dialkenylcyclohexanols, which generally lead to a trans alkene in the product.

Transannular cyclization of **16** led to the tricyclic product **17**. The overall three-pot sequence of  $13 \rightarrow 10b \rightarrow 16 \rightarrow 17$  results in bisannulation to a pre-existing ring and the generation of five chiral centers. This methodology rapidly increases molecular complexity and has the potential to make a variety of tricyclic structures by altering the size of the starting ring and the length of the two tethers by which the two alkenyl groups are attached to the cycloalkanone, as illustrated in equation 9. Such studies are in progress and will be reported in due course.



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### Supplementary data

Supplementary data (characterization data and procedures) associated with this article can be found, in the online version, at

### **References and notes**

- 1. Li Jisheng, Teresa Gallardo, and James B. White, J. Org. Chem. 1990, 55, 5426-5428.
- 2. Weiming Fan and James B. White, *Tetrahedron Lett.* **1993**, *34*, 957-960.
- 3. Weiming Fan and James B. White, *J. Org. Chem.* **1993**, *58*, 3557-3562.
- 4. David Colclough, James B. White, William B. Smith and Yongliang Chu, *J. Org. Chem.* **1993**, *58*, 6303-6313.

- 5. Yongliang Chu, David Colclough, David Hotchkin, Myla Tuazon, and James B. White, *Tetrahedron* **1997**, *53*, 14235-14246.
- 6. Weiming Fan and James B. White, *Tetrahedron Letters* **1997**, *38*, 7155-7158.
- 7. Yongliang Chu, James B. White and Brian A. Duclos, *Tetrahedron Letters* **2001**, *42*, 3815-3817.
- 8. Still, W. C. J. Am. Chem. Soc. 1977, 99, 4186-4187.
- 9. Still, W. C. J. Am. Chem. Soc. 1979, 101, 2493-2495.
- 10. Clive, D. L. J.; Russell, C. G.; Suri, S. C. J. Org. Chem. 1982, 47, 1632-1641.
- 11. Schreiber, S. L.; Santini, C. J. Am. Chem. Soc. 1984, 106, 4038-4039.
- 12. Zhao, R.; Wu, Y. Acta Chimica Sinica (English Edition) 1989, 86-87.
- 13. Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331-2332.
- 14. Paquette, L. A.; Shi, Y. J. J. Org. Chem. 1989, 54, 5205-5207.
- 15. Paquette, L. A.; Shi, Y. J. Am. Chem. Soc. 1990, 112, 8478-8489.
- 16. Janardhanam, S.; Shanmugam, P.; Rajagopalan, K. Synth. Commun. 1993, 23, 311-323.
- 17. Paquette, L. A. Tetrahedron 1994, 50, 4071-4086.
- 18. Dimartino, G.; Gelbrich, T.; Hursthouse, M. B.; Light, M. E.; Percy, J. M.; Spencer, N. S. *Chem. Commun.* **1999**, 2535-2536.
- 19. Von Zezschwitz, P.; Voight, K.; Noltemeyer, M.; De Meijere, A. Synthesis 2000, 1327-1340.
- 20. Rajapaksa, N. S.; Jacobsen, E. N. Org. Lett. 2013, 15, 4238-4241.
- 21. Roosen, P. C.; Vanderwal, C. D. Org. Lett. 2014, 16, 4368-4371.
- 22. For exceptions in which a cyclodecene with a cis alkene is obtained from anionic oxy-Cope rearrangement of a 1,2-dialkenylcyclohexanols in which the two alkenyl groups are trans, see references 1e, 2h, 2j and 2l.
- 23. For a reference to a methodology that makes 1,2-dialkenylcycloalkanols in which the alkenyl substituents are cis, see: White, B. H.; Snapper, M. L. J. Am. Chem. Soc. 2003, 125, 14901-14904. The stereochemistry of the alkene of the ring-expanded cycloalkenes from anionic oxy-Cope rearrangement depends on both the size of the ring and the substituents on one of the alkenyl groups.
- 24. Nevalainen, M.; Koskinen, A. M. P. Angew. Chem. Int. Ed. 2001, 40, 4060-4062.
- 25. Nevalainen, M.; Koskinen, A. M. P. J. Org. Chem. 2002, 67, 1554-1560.
- 26. Harato, N.; Tomisaka, Y.; Ogawa, A. Kidorui 2003, 42, 68-69.
- 27. Brocard, J.; Moinet, G; Conia, J.-M. Bull. Soc. Chim. France 1973, (5) (Pt.2), 1711-1717.
- 28. Moinet, G; Brocard, J.; Conia, J.-M. Tetrahedron Lett. 1972, (43), 4461-4464.
- 29. We prepared dodeca-1,11-dien-6-one (4) in 61% yield by adapting the procedure for the preparation and addition of *cis*-3-hexenylmagnesium bromide to a nitrile: Matsuda, I.; Murata, S.; Izumi, Y. *J. Org. Chem.* **1980**, *45*, 237-240.
- 30. Cho, J. H.; Kim, B. M. Org. Lett. 2003, 5, 531-533.
- For a review of methods for removal of Ru byproducts, see: Arumugasamy, J.; Arunachalam, K.; Bauer, D.; Becker, A.; Caillet, C. A.; Glynn, R.; Latham, G. M.; Lim, J.; Liu, J.; Mayes, B. A.; Moussa, A.; Rosinovsky, E.; Salanson, A. E.; Soret, A. F.; Stewart, A.; Wang, J.; Wu, X. Org. Process. Res. Dev. 2013, 17, 811-828.
- 32. In preparing this manuscript, we discovered that the NMR data we previously reported<sup>4</sup> for *cis*-5-cyclodecenone (**6**) was incorrect. The corrected data for **6**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz)  $\delta$ (ppm) 5.31-5.48 (m, 2H), 2.51 (dd, *J* = 6.4, 5.8 Hz, 2H), 2.40-2.34 (m, 2H), 1.29-2.21 (m, 10H);

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 50 MHz) δ (ppm) 215.2, 132.3, 129.1, 46.3, 35.1, 28.9, 24.8, 23.7, 23.6, 21.3.

- 33. Small amounts of oligomers were also obtained in this reaction. For an excellent review that includes a discussion on the competition between intramolecular RCM versus intermolecular metathesis that leads to oligomerization see: Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783-3816.
- 34. Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297-3299.
- 35. Aïssa, C.; Riveiros, R.; Ragot, J.; Fürstner, A. J. Am. Chem. Soc. 2003, 125, 15512-15520.
- 36. First-generation Grubbs catalyst **2** has been used successfully at 70 °F in toluene to prepare a ten-membered lactone: Fürstner, A.; Müller, T. *Synlett* **1997**, 1010-1012.
- 37. For a review of how the choice of ruthenium catalyst affects the stereochemistry of the alkene product and cyclization versus dimerization and oligomerization, see: Nolan, S. P.; Clavier, H. *Chem. Soc. Rev.* **2010**, *39*, 3305-3316.
- 38. That we got even a low yield of products 5-6 with the second-generation Grubbs catalyst 7 is somewhat surprising given the results published by Hiller and Percy for the reaction of dodeca-1,11-diene with catalyst 7: Nelson, D. J.; Ashworth, I. W.; Hillier, I. H.; Kyne, S. H.; Pandian, S.; Parkinson, J. A.; Percy, J. M.; Rinaudo, G.; Vincent, M. A. *Chem. Eur. J.* 2011, *17*, 13087-13094.
- 39. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J. Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791-799.
- 40. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.
- 41. Gessler, S.; Randl, S.; Blechert, S. Tetrahedron Lett. 2000, 41, 9973-9976.
- 42. For examples of RCM of *cis*-1,2-disubstituted cyclohexene rings to make cyclodecene rings, see: (a) Telser, J.; Beumer, R.; Bell, A. A.; Ceccarelli, S. M.; Monti, D.; Bennari, C. *Tetrahedron Lett.* 2001, *42*, 9187-9190; (b) Castoldi, D.; Caggiano, L.; Bayón, P.; Costa, A. M.; Cappella, P.; Sharon, O.; Gennari, C *Tetrahedron* 2005, *61*, 2123-2139; (c) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* 2006, *12*, 51-62.
- 43. For an example of a RCM of a 1,2-disubstituted benzene derivative to make a cyclodecene ring, see: Takao, K.; Nanamiya, R.; Fukushima, Y.; Namba, A.; Yoshida, K.; Tadano, K. *Org. Lett.* **2013**, *15*, 5582-5585.
- 44. Liu, R.; Gutierrez, O.; Tantillo, D. J.; Aubé, J. J. Am. Chem. Soc. 2012, 134, 6528-6531.
- 45. Molander, G. A.; McKie, J. A. J. Org. Chem. 1992, 57, 3132-3139.
- 46. For a lead reference on the preparation of 2,6-disubstituted cyclohexanones, see: Kobayashi, Y.; Feng, C. Ikoma, A.: Ogawa, N.; Hirotsu, T. *Org. Lett.* **2013**, *16*, 760-763.
- 47. Imine 14 was prepared by mixing equimolar amounts of cyclohexanone and cyclohexylamine in benzene with azeotropic removal of water, evaporation of the solvent and vacuum distillation of the product. For physical properties and NMR data of 14, see: Gingerich, S. B.; Jennings, P. W. J. Org. Chem. 1983, 48, 2606-2608.
- 48. Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. J. Am. Chem. Soc. **1988**, *110*, 3588-3597.
- 49. To the best of our knowledge, this is the first example of a one-pot dialkylation to prepare a 2,6-disubstituted cyclohexanone. There is precedent in the sequential dialkylation of SAMP-/RAMP-hydrazones of 2,2-dimethyl-1,3-dioxan-5-one; see: Job, A.; Janeck, C. F.; Bettray, W.;

Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253-2329. Doing the second alkylation step at -78 °C and allowing it to slowly warm to -15 °C before quenching the reaction with oxalic acid and water did not alter the ratio of **10a** and **10b**. Also, extending the length of time for hydrolysis with oxalic acid from two hours to overnight did not alter the ratio of **10a** and **10b**.

- 50. Johnson, F.; Duquette, L. G. J. Chem. Soc. D, Chem. Commun. 1969, 1448.
- 51. Henderson, K. W.; Kerr, W. J.; Moir, J. H. Tetrahedron 2002, 58, 4573-4587.

- 52. Hatakeyama, T.; Ito, S.; Yamane, H.; Nakamura, M.; Nakamura, E. *Tetrahedron* **2007**, *63*, 8440-8448.
- 53. Demarco, P. V.; Farkas, E.; Doddrell, D.; Mylari, B. L.; Wenkert, E. *J. Am. Chem. Soc.* **1968**, *90*, 5480-5486.



- Synthesis of 5-cyclodecenones via ring-closing metathesis. •
- Synthesis of bridged bicyclic compound via ring-closing metathesis •
- A convenient, one-pot synthesis of 2,6-disubstituted cyclohexanones. •
- Transannular cyclization to prepare a perhydrophenalene tricyclic compound. ٠

Acception