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Facile synthesis of (−)-6-acetoxy-5-hexadecanolide by size-selective ring-closing/cross metathesis

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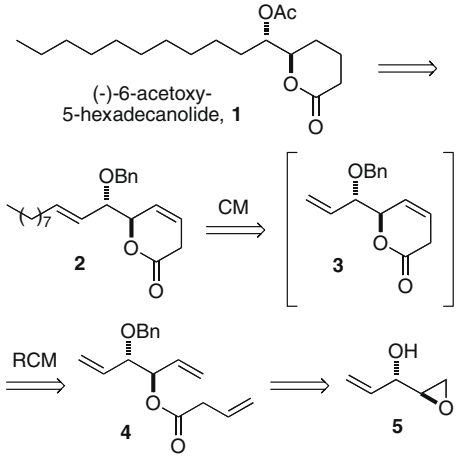
ABSTRACT

A total synthesis of (−)-6-acetoxy-5-hexadecanolide, in six steps and 37% overall yield from (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol is reported. The key synthetic step is a size-selective ring-closing/cross metathesis reaction in which lactone formation and alkyl chain extension are accomplished in an efficient one-pot process.

(−)-6-Acetoxy-5-hexadecanolide (**1**) is the major component of the apical droplets that form on the eggs of the mosquito *Culex pipiens fatigans* and has been shown to attract and induce oviposition in gravid female mosquitoes of this species.[1] *Culex pipiens fatigans* is found throughout the world and is a known vector for filarial infections, malaria, and West Nile virus.[2] Due to the potential of **1** in controlling mosquito populations, it has received considerable attention from the synthetic community, and numerous enantioselective syntheses have been reported.[3] Herein, we report a short and flexible synthesis of **1** employing a one-pot, size-selective ring-closing metathesis (RCM)/cross metathesis (CM) reaction as the key step.

Our retrosynthetic analysis is outlined in Scheme 1. Central to our plan was the assembly of protected 6-(1-hydroxy-2-undecenyl)-3,6-dihydropyranone **2** from acyclic triene **4** by RCM/CM. It was anticipated that initial RCM of vinylacetate **4** would provide six-membered lactone **3**, and subsequent CM between 1-decene and the exocyclic olefin of **3** would complete the process to provide **2**. Although two modes of closure are possible in the RCM (six- vs seven-membered ring formation), our previous studies on size-selective RCM of acrylate esters related to **4** gave us reason to believe that formation of the smaller ring would be preferred.[4] Metathesis substrate **4** was expected to be available by elaboration of known (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol (**5**),[5] which possesses the requisite *erythro* stereochemistry of **1**.

Metathesis substrate **4** was prepared from **5** in three steps as outlined in Scheme 2. Benzylation was followed by one carbon homologation upon treatment with dimethylsulfonium methylide[7] to give allylic alcohol **6**, a desymmetrized analogue of *meso*-hexa-1,5-diene-3,4-diol. Subsequent acylation with vinylacetic acid completed an efficient synthesis of **4** (57% over three steps).



Scheme 1. Retrosynthetic analysis.

With **4** in hand, we set out to establish the size selectivity of its RCM. As noted earlier, two ring closure products are possible—dihydropyranone **3** or oxepanone **7**—by metathesis between the vinylacetate group and the proximal olefin or the distal olefin, respectively. We found that treatment of **4** with 10 mol % of the second-generation Grubbs' catalyst[8] [PhCH=$RuCl_2(PCy_3)$(IMes)]

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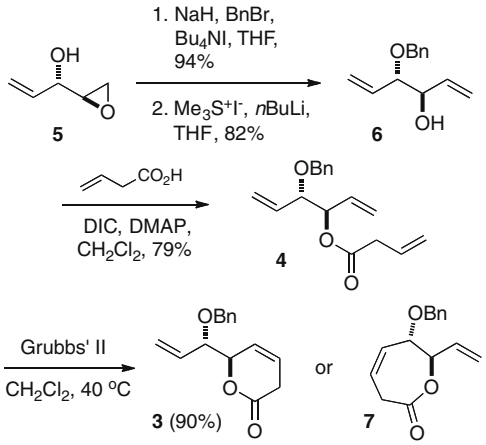
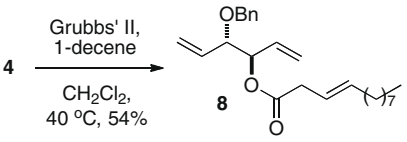


Scheme 2. Preparation and RCM of **4**.[6]

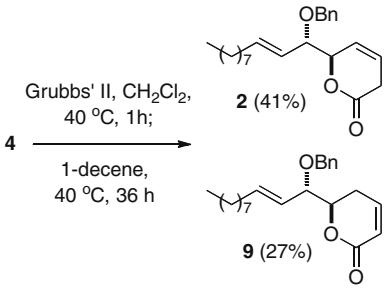
in refluxing CH_2Cl_2 resulted in the exclusive formation of **3** in 90% isolated yield within an hour. The assignment of **3** as dihydropyranone was based on the upfield shift of the C=O resonance in its ^{13}C NMR spectra (δ 170.0) relative to the expected position of the corresponding resonance for the isomeric oxepanone (δ ~175) and later confirmed by comparison (vide infra).

Encouraged by the yield and selectivity observed for RCM of **4**, we turned our attention to its incorporation into the proposed RCM/CM process for the preparation of the chain-extended dihydropyranone **2**. In an attempt to conduct a tandem RCM/CM, second-generation Grubbs' catalyst (10 mol %) was added to a refluxing 0.01 M CH_2Cl_2 solution of triene **4** and five equivalents of 1-decene. Unfortunately, the major product isolated from the reaction was chain-extended triene **8**, which arose from CM between the vinylacetate alkene and 1-decene (Eq. 1). This outcome was not wholly unexpected considering (1) the stoichiometry employed which likely favors initiation with 1-decene, and (2) the relative reactivity of the vinylacetate alkene and 1-decene (both type I) compared to that of the C1–C2 and C5–C6 alkenes (both type II).[9] However, it was somewhat surprising that no trace of the desired RCM/CM product **2** could be isolated under our reaction conditions given reports by Piva and coworkers of successful tandem RCM/CM of vinylacetates of divinyl carbinol with terminal alkenes[10] and tandem RCM/intramolecular alkenyl transfer of substituted vinylacetates of divinyl carbinol.[11]



(1)

In order to prevent the formation of undesired CM product **8**, we turned to a sequential procedure in which a 0.01 M solution of **4** in CH_2Cl_2 and second-generation Grubbs' catalyst (10 mol %) was heated to reflux until RCM was judged to be complete by TLC analysis (1 h) followed by addition of 5 equiv of 1-decene. Heating was then continued until complete consumption of RCM product **3** was observed (36 h). We were surprised to find that this procedure gave a separable mixture of expected dihydropyranone **2** and its isomer **9**, in a roughly 1.5:1 ratio and 68% combined yield (Eq. 2). It is well known that Ru metathesis initiators are capable of catalyzing olefin isomerization, through their presumed conversion to Ru hydride species;[12] however, conjugative isomerization to an α,β-unsaturated system, as in the formation of **9**, is exceedingly rare. To the best of our knowledge, only one previous example of an isomerization of this type has been reported.[13] As we did not observe isomerization in the RCM of **4** (reaction time of 1 h), we speculate that the extended reaction time required for the CM results in decomposition of the propagating metathesis-active catalyst and corresponding build-up of an isomerization-active Ru species, which promotes the isomerization of **2** subsequent to CM or intermediate **3** prior to CM.

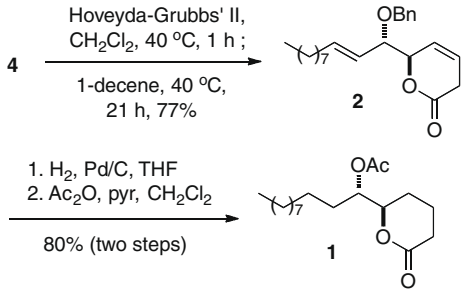


(2)

Although both dihydropyranones **2** and **9** are useful in our synthetic plan, we felt the yield of the RCM/CM process may be improved if isomerization could be prevented. Previously, we found that isomerization could be suppressed by use of the second-generation Hoveyda–Grubbs' catalyst[14] [*o*-isopropoxyPhCH=$RuCl_2$(IMes)] rather than the second-generation Grubbs' catalyst,[15] so we chose to examine its use in the sequential RCM/CM procedure. We were pleased to find that use of 10 mol % of the second-generation Hoveyda–Grubbs' catalyst provided 77% yield of **2** in just 22 h (Scheme 3).[16] Isomerization product **9** was not observed even if the reaction was allowed to run for up to 36 h. Although not important in our synthesis of **1**, it should be noted that CM generated **2** with complete (*E*)-selectivity for the exocyclic olefin as determined by ^1H NMR (J = 15.5 Hz).

Completion of the synthesis was accomplished by catalytic hydrogenation/hydrogenolysis of **2** followed by acetylation of the resulting secondary alcohol to give **1** as a colorless oil in 80% yield. (−)-6-Acetoxy-5-hexadecanolide produced in this manner displayed spectral data and optical rotation consistent with those reported in the literature.[17]

In summary, an efficient strategy for the synthesis of 6-(1-hydroxy-2-alkenyl)-3,6-dihydropyranones via sequential RCM/CM has been demonstrated by its application in a short synthesis of the mosquito oviposition pheromone (−)-6-acetoxy-5-hexadecanolide. The flexibility inherent in this approach and the high degree of functionality present in RCM/CM products like **2** make it broadly applicable. Extension to the synthesis of more complex natural products and studies on the size-selective RCM of unsaturated esters of diene diols are underway and results will be reported in due course.



Scheme 3. Completion of the synthesis of **1**.[6]

Acknowledgments

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References and notes

1. (a) Laurence, B. R.; Pickett, J. A. *J. Chem. Soc., Chem. Commun.* **1982**, 59; (b) Laurence, B. R.; Mori, K.; Otsuka, T.; Pickett, J. A.; Wadhams, L. J. *J. Chem. Ecol.* **1985**, *11*, 643.
2. Anderson, J. F.; Andeadis, T. G.; Vossbrinck, C. R.; Tirrell, S.; Waken, E. M.; French, R. A.; Garmendia, A. E.; Van Kruiningen, H. J. *Science* **1999**, *286*, 2331.
3. For recent syntheses and leading references, see: (a) Singh, S.; Guiry, P. J. *Eur. J. Org. Chem.* **2009**, 1896; (b) Prasad, K. R.; Anbarsan, P. *Tetrahedron: Asymmetry* **2007**, *18*, 2479; (c) Sabitha, G.; Swapna, R.; Reddy, E. V.; Yadav, J. S. *Synthesis* **2006**, 4242; (d) Ikishima, H.; Sekiguchi, Y.; Ichikawa, Y.; Kotsuki, H. *Tetrahedron* **2006**, *62*, 311; (e) Dhotare, B.; Goswami, D.; Chattopadhyay, A. *Tetrahedron Lett.* **2005**, *46*, 6219; (f) Sun, B.; Peng, L.; Chen, X.; Li, Y.; Yamasaki, K. *Tetrahedron: Asymmetry* **2005**, *16*, 1305.
4. (a) Quinn, K. J.; Smith, A. G.; Cammarano, C. M. *Tetrahedron* **2007**, *63*, 4881; (b) Quinn, K. J.; Isaacs, A. K.; DeChristopher, B. A.; Szklarz, S. C.; Arvary, R. A. *Org. Lett.* **2005**, *7*, 1243; (c) Quinn, K. J.; Isaacs, A. K.; Arvary, R. A. *Org. Lett.* **2004**, *6*, 4143.
5. Prepared in gram quantities and high enantiopurity (>98% ee) from commercially available divinyl carbinol via modified Sharpless asymmetric epoxidation using cumene hydroperoxide instead of *t*-butylhydroperoxide, see: Romero, A.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 8264.
6. Yields cited in the schemes are for chromatographically and spectroscopically homogeneous substances. All structural assignments are supported by ^{1}H and ^{13}C NMR and high-resolution mass spectrometric analyses.
7. Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.
8. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
9. Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
10. Virolleaud, M. A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081.
11. Virolleaud, M. A.; Piva, O. *Synlett* **2004**, 2087.
12. For a review of the non-metathetic reactivity of Ru carbene complexes including olefin isomerization, see: Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817.
13. Formentin, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235.
14. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
15. Quinn, K. J.; Curto, J. M.; Faherty, E. E.; Cammarano, C. M. *Tetrahedron Lett.* **2008**, *49*, 5238.
16. *RCM//CM of **4** and 1-decene*. To a solution of triene **4** (202.0 mg, 0.74 mmol) in CH_2Cl_2 (74 mL) was added second-generation Hoveyda–Grubbs' catalyst (46.3 mg, 0.074 mmol). The reaction mixture was heated to reflux for 1 h, at which time TLC analysis indicated that RCM was complete. 1-Decene (0.70 mL, 3.70 mmol) was added by syringe, and heating was continued for an additional 21 h. After cooling to room temperature, the brown solution was filtered through a short pad of silica gel, and the filtrate was concentrated in vacuo. Purification by silica gel chromatography (4:1 hexanes/Et_2O) gave RCM/CM product **2** (203.1 mg, 77%) as a yellow oil. Data for **2**: $[\alpha]_D^{22}$ +70.1 (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.24 (m, 5H), 5.95–5.87 (m, 2H); 5.81 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.33 (ddt, *J* = 15.5, 8.1, 1.5 Hz, 1H), 4.90 (m, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.09 (dd, *J* = 8.1, 3.4 Hz, 1H), 3.12–2.96 (m, 2H), 2.09 (q, *J* = 6.8 Hz, 2H), 1.45–1.22 (m, 12H), 0.88 (t, *J* = 6.9, 3H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 137.9, 137.8, 128.4, 127.8, 127.7, 124.6, 124.0, 121.9, 82.0, 81.6, 70.7, 32.3, 31.9, 30.8, 29.4, 29.3, 29.1, 29.0, 22.6, 14.1; HRMS calcd for $C_{23}H_{33}O_3$ (MH^+) 357.2430, found 357.2434.
17. *Data for (−)-6-acetoxy-5-hexadecanolide* (**1**): $[\alpha]_D^{22}$ −36.1 (*c* 0.85, $CHCl_3$); lit.[3a] $[\alpha]_D^{20}$ −35.4 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.98 (dt, *J* = 7.8, 5.0 Hz, 1H), 4.35 (ddd, *J* = 11.0, 4.8, 3.4 Hz, 1H), 2.60 (m, 1H), 2.46 (m, 1H), 2.08 (s, 3H), 2.02–1.76 (m, 2H), 1.73–1.52 (m, 4H), 1.48–1.20 (m, 16H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 170.5, 80.5, 74.3, 31.9, 29.5, 29.4, 29.3, 25.2, 23.5, 22.7, 21.0, 18.3, 14.1; HRMS calcd for $C_{18}H_{33}O_4$ (MH^+) 313.2379, found 313.2375.