



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

Kevin J. Quinn*, John M. Curto, Kevin P. McGrath, Neal A. Biddick

Department of Chemistry, College of the Holy Cross, Worcester, MA 01610-2395, United States

ARTICLE INFO

Article history:

Received 14 September 2009

Revised 25 September 2009

Accepted 30 September 2009

Available online 4 October 2009

Keywords:

Heterocycle synthesis

Olefin metathesis

Ring-size selectivity

ABSTRACT

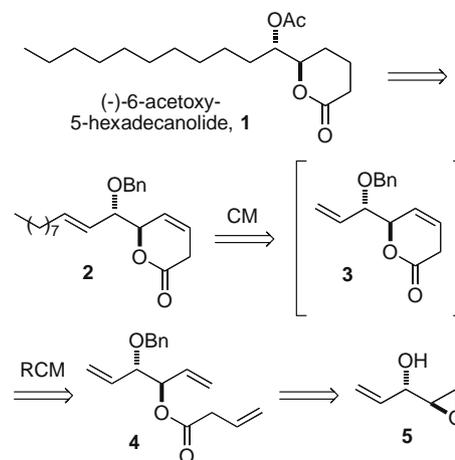
A total synthesis of (–)-6-acetoxy-5-hexadecanolide, in six steps and 37% overall yield from (2*R*,3*S*)-1,2-epoxy-4-penten-3-ol is reported. The key synthetic step is a size-selective ring-closing/cross metathesis reaction in which lactone formation and alkyl chain extension are accomplished in an efficient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

© 2009 Elsevier Ltd. All rights reserved.

(–)-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

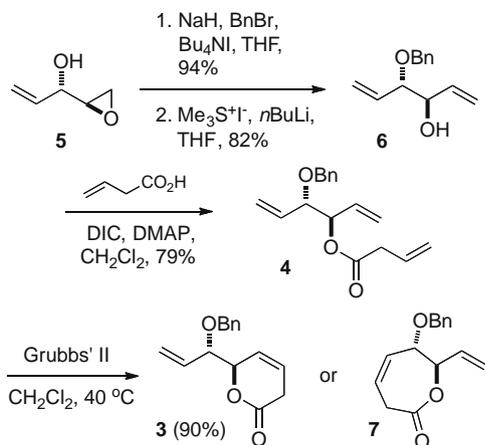


Scheme 1. Retrosynthetic analysis.

homologation upon treatment with dimethylsulfonium methylide⁷ 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).

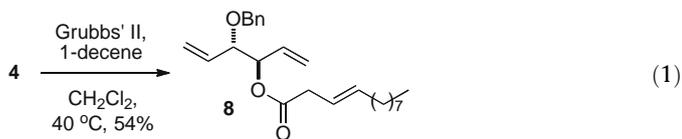
With **4** in hand, we set out to establish the size selectivity of its RCM. As noted earlier, two ring closure products are possible—dihydropyranone **3** or oxepanone **7**—by metathesis between the vinylacetate group and the proximal olefin or the distal olefin, respectively. We found that treatment of **4** with 10 mol % of the second-generation Grubbs' catalyst⁸ [PhCH= RuCl₂(PCy₃)(IMes)]

* Corresponding author. Tel.: +1 508 793 3576; fax: +1 508 793 3530.
E-mail address: kquinn@holycross.edu (K.J. Quinn).

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

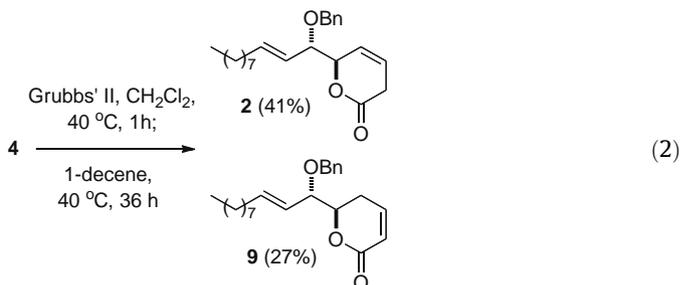
in refluxing CH_2Cl_2 resulted in the exclusive formation of **3** in 90% isolated yield within an hour. The assignment of **3** as dihydropyranone was based on the upfield shift of the $\text{C}=\text{O}$ resonance in its ^{13}C NMR spectra (δ 170.0) relative to the expected position of the corresponding resonance for the isomeric oxepanone ($\delta \sim 175$) 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 alkenes¹⁰ and tandem RCM/intramolecular alkenyl transfer of substituted vinylacetates of divinyl carbinol.¹¹



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 exam-

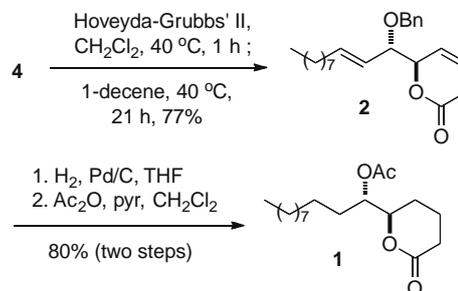
ple of an isomerization of this type has been reported.¹³ As we did not observe isomerization in the RCM of **4** (reaction time of 1 h), we speculate that the extended reaction time required for the CM results in decomposition of the propagating metathesis-active catalyst and corresponding build-up of an isomerization-active Ru species, which promotes the isomerization of **2** subsequent to CM or intermediate **3** prior to CM.



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' catalyst¹⁴ [*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

Financial support of this research by the National Science Foundation (CHE-0848128) and the Pfizer Undergraduate Research Fellowship Program is gratefully acknowledged. Mass spectral data were obtained at the University of Massachusetts Mass Spectrometry Facility, which is supported, in part, by the National Science Foundation.

References and notes

- (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.
- 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.
- 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.
- (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.
- 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.
- Yields cited in the schemes are for chromatographically and spectroscopically homogeneous substances. All structural assignments are supported by ¹H and ¹³C NMR and high-resolution mass spectrometric analyses.
- Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.
- Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
- Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
- Virolleaud, M. A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081.
- Virolleaud, M. A.; Piva, O. *Synlett* **2004**, 2087.
- 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.
- Formentin, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235.
- Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
- Quinn, K. J.; Curto, J. M.; Faherty, E. E.; Cammarano, C. M. *Tetrahedron Lett.* **2008**, *49*, 5238.
- RCM/CM of **4** and *1-decene*. To a solution of triene **4** (202.0 mg, 0.74 mmol) in CH₂Cl₂ (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/Et₂O) gave RCM/CM product **2** (203.1 mg, 77%) as a yellow oil. Data for **2**: [α]_D²² +70.1 (c 1.55, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₃H₃₃O₃ (MH⁺) 357.2430, found 357.2434.
- Data for (–)-*6-acetoxy-5-hexadecanolide* (**1**): [α]_D²² –36.1 (c 0.85, CHCl₃); lit.^{3a} [α]_D²⁰ –35.4 (c 0.85, CHCl₃); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₁₈H₃₃O₄ (MH⁺) 313.2379, found 313.2375.