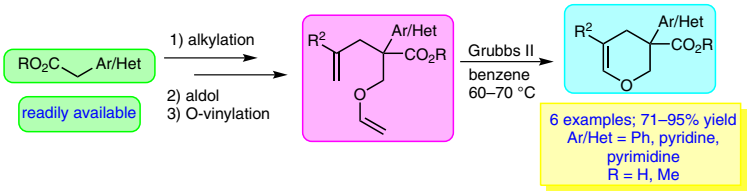
Synlett A.-M. Dechert-Schmitt et al. Letter

Development of an O-Vinylation–Ring-Closing Metathesis Strategy to Access 3,3′-3,4-Dihydropyrans

Anne-Marie Dechert-Schmitt*
Shawn Cabral
Daniel W. Kung

Pfizer Inc., Eastern Point Road, Groton, CT 06340, USA
anne-marie.dechertschmitt@pfizer.com



Received: 17.08.2016
Accepted after revision: 09.09.2016
Published online: 05.10.2016
DOI: 10.1055/s-0036-1588615; Art ID: st-2016-r0536-l

Abstract Dihydropyrans are common structural motifs that appear in both natural products and pharmaceuticals and are intermediates for the synthesis of tetrahydropyrans. Currently, no reports exist in the literature for the synthesis of 3,3′-differentially disubstituted-3,4-dihydro-2-pyrans. We describe an approach employing abundant esters as starting materials that allows access to these heterocyclic scaffolds through a unique O-vinylation–RCM sequence.

Key words cyclization, heterocycles, metathesis, ring closure, aldol reaction

Dihydropyrans are privileged heterocyclic structures that are present in both biologically active natural products and pharmaceuticals, including zanamivir (anti-flu), the lamiridosin family of natural products (hepatitis C virus entry inhibitor) and laulimalide (anti-cell growth, Figure 1).[1]

In addition to being biologically relevant, dihydropyrans are also useful synthetic intermediates for the synthesis of functionalized tetrahydropyrans.[2] Due to their structural significance and biological profile, various methods have been developed to access dihydropyrans including [4+2] cycloadditions,[3] Prins cyclizations,[4] a Michael–hemiacetalization approach,[5] cascade reactions,[6] a dioxanone–Claisen rearrangement,[7] Trost metal-catalyzed cycloisomerization,[8] and ring-closing metathesis (RCM).[9] RCM approaches to dihydropyran synthesis typically utilize allyl-homoallyl ethers which provide access to the 3,6-dihydro-2*H*-pyran regioisomer (Scheme 1). While RCM of vinyl ethers to access dihydropyrans is known with both ruthenium and molybdenum catalysts,[10] only one example producing a 3,3′-disubstituted dihydropyran has been reported; however, this approach only demonstrates the RCM to form trisubstituted olefins.[11] Herein we describe an approach to the synthesis of 3-quaternary dihydropyrans through an O-vinylation–RCM sequence from hydroxyl alkenes.

Our initial approach to the desired dihydropyran was via an intramolecular ruthenium-catalyzed cycloisomerization of the primary alcohol **1** (Scheme 2), a strategy recently described by Merck in the synthesis of a tetrahydropyran DPP4 inhibitor.[8a] The reaction delivered the product in low yields (<20% in most cases), and the product was difficult to separate from the triphenylphosphine from the reaction mixture. We reasoned that our heteroaryl substrate was problematic and perhaps chelated to the ruthenium metal center of the catalyst.[12]

Based on the limited success of known procedures, and limited strategies to access the desired 3,3′-3,4-dihydropyran, we sought an alternative approach to the synthesis of

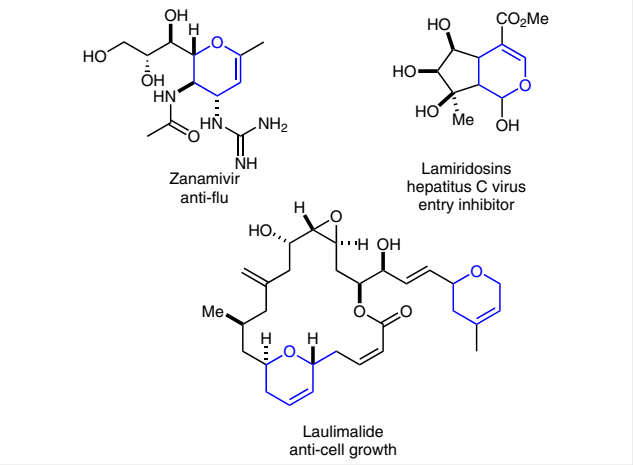
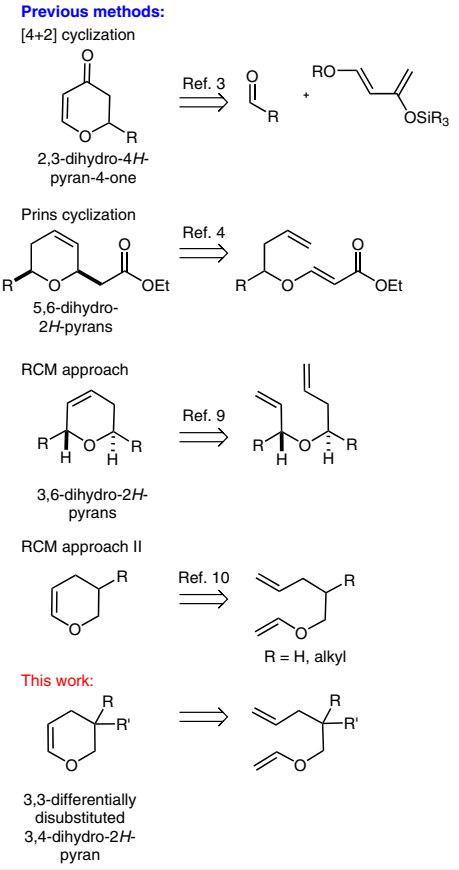
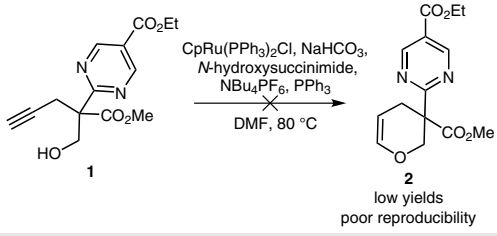


Figure 1 Biologically active dihydropyrans



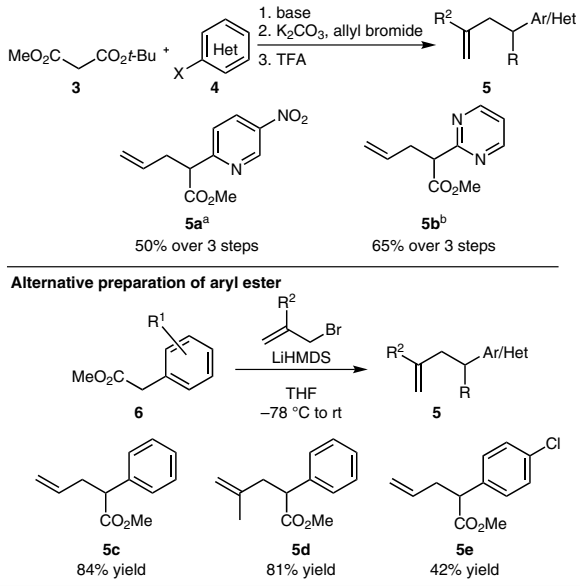
Scheme 1 Synthetic approaches to dihydropyrans



Scheme 2 Cycloisomerization approach to access dihydropyran

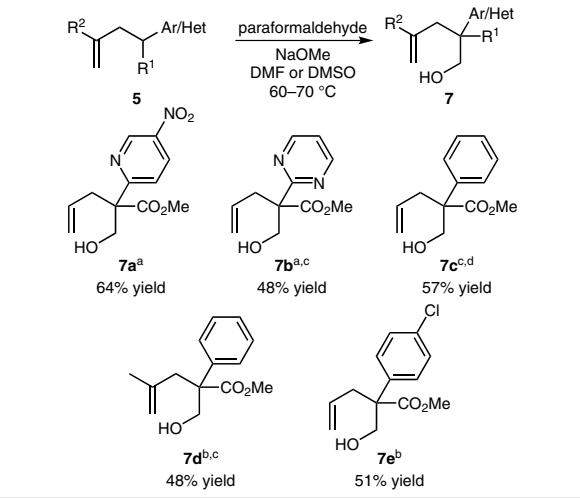
dihydropyrans through the use of an O-vinylation–RCM sequence. The O-vinylation precursors were prepared from the aryl halides via a three-step sequence: S_NAr with malonate **3** and aryl halide **4**, allylic alkylation, and decarboxylation under acidic conditions to deliver product **5**. Alternatively, alkylation of aryl acetic acid derivatives **6** with allyl bromide or methallyl bromide delivered the aryl allyl ester precursors **5** in a reliable manner (Scheme 3).

With the aryl allyl esters **5** in hand, the bishomoallylic alcohol **7** was installed using an aldol reaction of paraformaldehyde. Several bases were explored, including triethylamine, LDA, LiHMDS, but the most general base for the reaction was found to be sodium methoxide, which allowed



Scheme 3 Preparation of the aryl ester. Base: [a] NaH; [b] K_2CO_3.

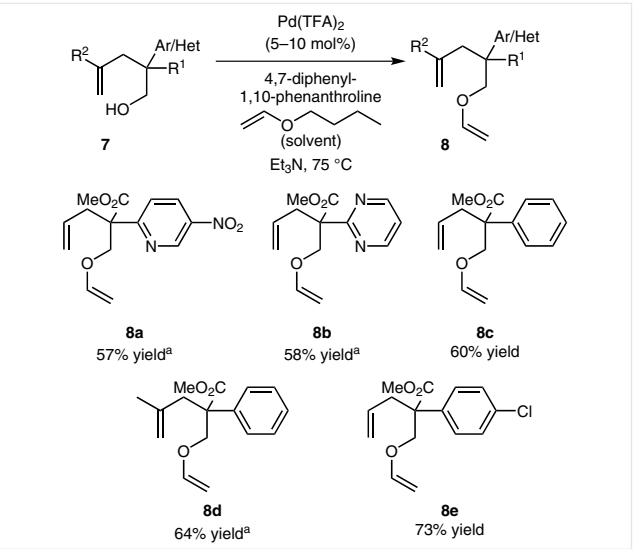
for the formation of the product on the various substrates shown. Less acidic substrates such as the methyl phenyl acetate gave comparable yields using LiHMDS as a base compared to sodium methoxide. Attempts to perform the aldol reaction with other aldehydes under various conditions were unsuccessful, presumably due to the increased steric demands of the product (Scheme 4).



Scheme 4 Aldol reaction with paraformaldehyde. [a] DMSO, 60 °C; [b] DMF, 70 °C; [c] average of two runs; [d] DMSO, 75 °C.

Our next step was the O-vinylation of primary alcohols **7**. Historically, O-vinylation has been accomplished through the use of stoichiometric quantities of mercury or hydroetherification of acetylene.[13] Modern methods have shown that several metals catalyze this reaction and circumvent the use of mercury or the harsh conditions associated with

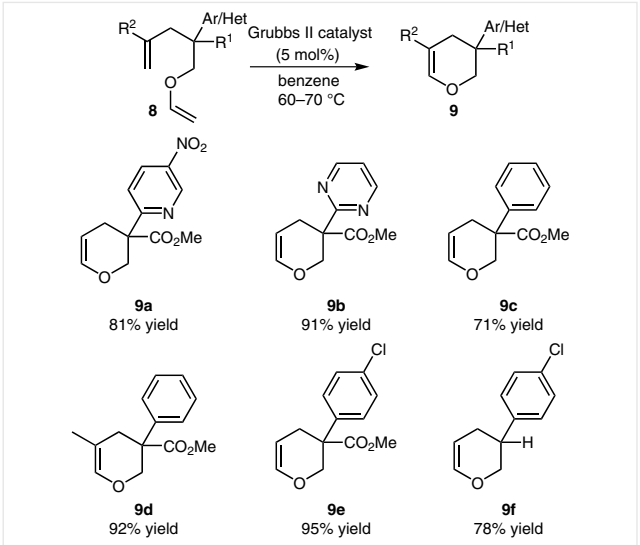
acetylene hydroetherification.[14] We explored several methods (Ir, Pd, Au/Ag) and found that both the palladium- and gold/silver-catalyzed reactions delivered the desired product **8** successfully, while the iridium catalyst proved to be unsuitable (Scheme 5).[14e] In the case of the gold/silver reaction,[14g] the reaction was slow and required 72 hours to obtain an acceptable yield, with acetal byproduct formation also occurring. Attempts to improve the yield by increasing the temperature and changing the reaction solvent resulted in no appreciable yield increase.[14g]



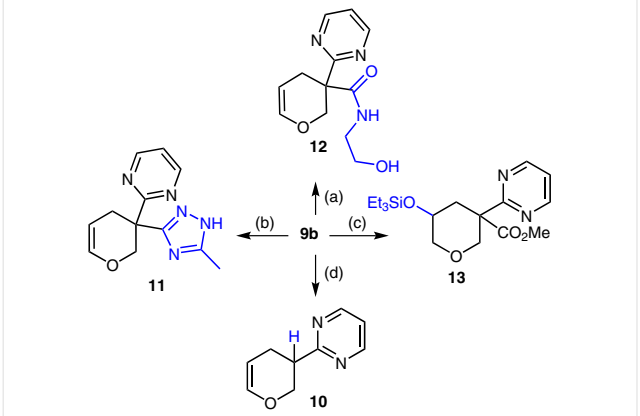
Scheme 5 Pd-catalyzed O-vinylation. [a] Average of two runs.

RCM with Grubbs second-generation catalyst delivered the dihydropyrans in excellent yields, with no dimerization or other byproducts being detected (Scheme 6). It is worth noting that enol ethers are generally poor substrates in cross-metathesis reactions with ruthenium–alkylidene catalysts.[15] However, the intramolecular RCM is highly favorable likely due to initial insertion into the terminal olefin followed by ring closure. To explore the possibility of a Thorpe–Ingold effect in the substrates below, the des-ester substrate was prepared and subjected to the RCM conditions. The product **9f** was generated in 78% yield with no appreciable formation of byproducts, indicating that the quaternary center likely does not have a strong effect on the RCM reaction.

To further demonstrate the utility of the approach to access 3,4-dihydropyrans, the pyrimidine **9a** was further elaborated into compounds of synthetic interest (Scheme 7). The methyl ester could be hydrolyzed and decarboxylated using 1 M NaOH in THF at 0 °C to deliver the des-ester **10** in 62% yield. The ester could also be transformed into a 1,2,4-triazole **11** by first treatment with hydrazine-hydrate followed by addition of acetonitrile under microwave conditions. Following a procedure by Caldwell, the amido alcohol **12** could be prepared using BEMP as a catalyst in 80% yield.[16] The silyl-protected 3-hydroxy tetrahydropyran **13** was prepared using a hydroboration–oxidation sequence followed by protection with TESOTf to deliver a 1.7:1 mixture of diastereomers in 38% yield over two steps.



Scheme 6 RCM with Grubbs second-generation catalyst



Scheme 7 Elaboration of the dihydropyran. *Reagents and conditions*: (a) BEMP, ethanolamine, MeCN, 40 °C (80%); (b) 1) N_2H_4–H_2O, MeOH, 70 °C, 2) MeCN, 150 °C, MW (66%, 2 steps); (c) 1) 9-BBN, THF, then MeOH, pH 8 buffer, H_2O_2, 2) TESOTf, 2,6-lutidine (38%, 2 steps); (d) NaOH, THF (62%).

In summary, we have developed a novel strategy to access 3,3′-disubstituted 3,4-dihydro-2-pyrans using robust chemistry that is tolerant of N-heterocycles.[17] In this sequence, a readily accessed aryl allyl ester is subjected to an aldol reaction with paraformaldehyde. The resultant primary alcohol is O-vinylated under palladium-catalyzed conditions, and subjected to a high yielding RCM with Grubbs second-generation catalyst. Further elaboration of the products has allowed for highly substituted dihydropyrans

and tetrahydropyrans to be accessed. Moreover, our approach allows access to 3,3′-disubstituted 3,4-dihydropyrans which are not commonly accessible through the standard methods to access other dihydropyrans.

Acknowledgment

Andy Tsai, Matt Dowling, and Kevin Hesp are gratefully acknowledged for their help in preparing this manuscript.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588615.

References and Notes

(1) (a) Magano, J. *Chem. Rev.* **2009**, *109*, 4398. (b) Atta-ur-Rahman; Nasreen, A.; Akhtar, F.; Shekhani, M. S.; Clardy, J.; Parvez, M.; Choudhary, M. I. *J. Nat. Prod.* **1997**, *60*, 472. (c) Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem.* **2005**, *70*, 8533. (d) Smith, A. B.; Sperry, J. B.; Han, Q. *J. Org. Chem.* **2007**, *72*, 6891. (e) Kumar, S.; Malachowski, W. P.; DuHadaway, J. B.; LaLonde, J. M.; Carroll, P. J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem.* **2008**, *51*, 1706. (f) Yoo, N. H.; Jang, D. S.; Yoo, J. L.; Lee, Y. M.; Kim, Y. S.; Cho, J.-H.; Kim, J. S. *J. Nat. Prod.* **2008**, *71*, 713. (g) Xu, Z.; Li, Y.; Xiang, Q.; Pei, Z.; Liu, X.; Lu, B.; Chen, L.; Wang, G.; Pang, J.; Lin, Y. *J. Med. Chem.* **2010**, *53*, 4642. (h) Zhang, H.; Rothwargl, K.; Mesecar, A. D.; Sabahi, A.; Rong, L.; Fong, H. *J. Nat. Prod.* **2009**, *72*, 2158. (i) Lichtenthaler, F. W.; Nakamura, K.; Klotz, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5838. (j) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 5838.

(2) (a) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis*; Wiley-VCH: Weinhein, **2003**. (b) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237. (c) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348. (d) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (e) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (f) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (g) Smith, A. B.; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. (h) Li, P.; Chai, Z.; Zhao, S.-L.; Yang, Y.-Q.; Wang, H.-F.; Zheng, C.-W.; Cai, Y.-P.; Zhao, G.; Zhu, S.-Z. *Chem. Commun.* **2009**, 7369. (i) Li, G.; Kaplan, M. J.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1960. (j) Alemán, J.; Marcos, V.; Marzo, L.; García Ruano, J. L. *Eur. J. Org. Chem.* **2010**, 4482. (k) Zacuto, M. J.; Tomita, D.; Pirzada, Z.; Xu, F. *Org. Lett.* **2010**, *12*, 684. (l) Wang, H.-F.; Li, P.; Cui, H.-F.; Wang, X.-W.; Zhang, J.-K.; Liu, W.; Zhao, G. *Tetrahedron* **2011**, *67*, 1774. (m) Zhu, X.-B.; Wang, M.; Wang, S.-Z.; Yao, Z.-J. *Tetrahedron* **2012**, *68*, 2041.

(3) (a) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. *J. Am. Chem. Soc.* **1987**, *109*, 8119. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (c) Leconte, S.; Dujardin, G.; Brown, E. *Eur. J. Org. Chem.* **2000**, 639. (d) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558. (e) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662. (f) Krauss, I. J.; Mandal, M.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 5576. (g) Ashtekar, K. D.; Staples, R. J.; Borhan, B. *Org. Lett.* **2011**, *13*, 5732. (h) Fujiwara, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2012**, *134*, 5512. (i) Yao, W.; Xiaowei, D.; Lu, Y. *J. Am Chem. Soc.* **2015**, *137*, 54.

(4) (a) Yadev, V. K.; Kumar, N. V. *J. Am. Chem. Soc.* **2004**, *126*, 8652. (b) Sultana, S.; Indukuri, K.; Deka, M. J.; Saikia, A. K. *J. Org. Chem.* **2013**, *78*, 12182.

(5) Feng, J.; Fu, X.; Chen, Z.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2013**, *15*, 2640.

(6) Chouthaiwale, P. V.; Tanaka, F. *Chem. Commun.* **2014**, *50*, 14881.

(7) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, 4320. (b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

(8) (a) Xu, F.; Zacuto, M. J.; Kohmura, Y.; Rosen, J.; Gibb, A.; Alam, M.; Scott, J.; Tschaen, D. *Org. Lett.* **2014**, *16*, 5422. (b) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482. (c) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528.

(9) (a) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958. (b) Shu, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4794. (c) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032.

(10) (a) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231. (b) Sharma, H.; Santra, S.; Debnath, J.; Antonio, T.; Reith, M.; Dutta, A. *Bioorg. Med. Chem.* **2014**, *22*, 311. (c) Sturion, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623.

(11) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153.

(12) Poyatos, M.; McNamara, W.; Incarvito, C.; Clot, E.; Peris, E.; Crabtree, R. H. *Organometallics* **2008**, *27*, 2128.

(13) (a) Reppe, W. *Justus Liebigs Ann. Chem.* **1956**, *601*, 84. (b) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1956**, *79*, 2828.

(14) (a) McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 227. (b) McKeon, J. E.; Fitton, P. *Tetrahedron* **1972**, *28*, 233. (c) Handerson, S.; Schraf, M. *Org. Lett.* **2002**, *4*, 407. (d) Bosch, M.; Schraf, M. *J. Org. Chem.* **2003**, *68*, 5225. (e) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590. (f) Nakagawa, H.; Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2003**, *44*, 103. (g) Nakamura, A.; Tokunaga, M. *Tetrahedron Lett.* **2008**, *49*, 3729.

(15) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(16) Caldwell, N.; Jamieson, C.; Simpson, I.; Tuttle, T. *Org. Lett.* **2013**, *15*, 250.

(17) **Example Experimental Procedure for the Preparation of 9c Methyl 2-(Hydroxymethyl)-2-phenylpent-4-enoate (7c)**
An oven-dried vial equipped with a stir bar was charged with methyl 2-phenylpent-4-enoate (**5c**, 700 mg, 3.68 mmol) and paraformaldehyde (365 mg, 4.05 mmol). The vial was purged with nitrogen for 15 min, then DMSO (7.36 mL, 0.05 M) was added followed by NaOMe (219 mg, 4.05 mmol) at 25 °C. The reaction was heated to 75 °C for 16 h. The reaction was then poured into HCl solution (1 M, 20 mL), extracted with EtOAc (3 × 15 mL). The combined organic extracts were concentrated under reduced pressure and purified via column chromatography (0–70% EtOAc–heptane) to provide the product (422.4 mg, 52%). The reaction was run a second time and a yield of 61% was obtained.
Alternatively, similar yields could be obtained using LiHMDS as a base. An oven-dried round-bottom flask equipped with a stir bar was charged with methyl 2-phenylpent-4-enoate (**5c**, 700 mg, 3.68 mmol). The flask was purged with nitrogen and to this was added THF (0.5 M, 7.36 mL). The reaction was cooled to –78 °C, and LiHMDS (1 M in THF, 4.05 mmol, 4.05 mL) was added dropwise over 15 min. The reaction was aged for 15 min, then paraformaldehyde was added (365 mg, 4.05 mmol), and the reaction was warmed to 25 °C for 16 h. The reaction mixture

was then poured into HCl (1 M, 15 mL), extracted with EtOAc (3 × 15 mL), dried over $MgSO_4$, and concentrated. The crude material was purified via column chromatography (0–60% EtOAc–heptane) to provide the product as a clear oil (407 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (br s, 1 H). 2.91–2.89 (dd, *J* = 7.2 Hz, 1 Hz, 1 H), 3.75 (s, 3 H) 4.10–4.01 (q, *J* = 11.4 Hz, 2 H), 5.21–5.10 (m, 2 H), 5.82–5.71 (m, 1 H), 7.40–7.28 (m, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 28.47, 52.19, 56.00, 66.37, 118.82, 126.70, 127.37, 128.64, 133.58, 139.64, 175.20. ESI-HRMS: *m/z* calcd for $C_{13}H_{16}O_3$ [M + H]: 243.10; found: 243.09.

Methyl 2-Phenyl-2-[(vinyloxy)methyl]pent-4-enoate (8c)

To a vial equipped with a stir bar was added $Pd(TFA)_2$ (3.15 mg, 0.00949 mmol, 1 mol%) and 4,7-diphenyl-1,10-phenanthroline (3.15 mg, 1 mol%). Butyl vinyl ether (1 mL) was added, and the reaction mixture was aged 15 min. Methyl 2-(hydroxymethyl)-2-phenylpent-4-enoate (**7c**, 209 mg, 0.949 mmol) was added in butyl vinyl ether (1.5 mL) followed by Et_3N (13.2 µL, 10 mol%) at 25 °C. The reaction was heated to 75 °C for 48 h and then concentrated under reduced pressure. The crude reaction mixture was purified via MPLC (0–15% EtOAc–heptane) to provide the product (139 mg, 60%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93–2.92 (d, *J* = 7.6 Hz, 2 H), 3.69 (s, 3 H), 4.01–4.00 (dd, *J* = 7.0, 1.8 Hz, 1 H), 4.13–4.11 (d, *J* = 9.4 Hz, 1 H), 4.26–4.24 (m, 2 H), 5.11–5.06 (m, 2 H), 5.59–5.52 (m, 1 H), 6.47–6.43 (dd, *J* = 14.4, 6.7 Hz, 1 H), 7.29–7.24 (m, 3 H), 7.36–7.34 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 37.81, 52.24, 54.05, 69.03, 86.64, 119.21, 126.32, 127.29, 128.55, 133.04, 139.55, 151.62, 173.93. ESI-HRMS: *m/z* calcd for $C_{15}H_{18}O_3$ [M + Na]: 269.12; found: 269.11.

Methyl 3-Phenyl-3,4-dihydro-2*H*-pyran-3-carboxylate (9c)

To a vial equipped with a stir bar was added methyl 2-phenyl-2-[(vinyloxy)methyl]pent-4-enoate (**8c**, 139 mg, 0.56 mmol) in benzene (8.06 mL, 0.07 M). The reaction mixture was sparged with nitrogen for 15 min at which point Grubbs II catalyst (24 mg, 0.028 mmol) was added. The vial was sealed, and the reaction was heated to 70 °C for 16 h. The reaction mixture was concentrated under reduced pressure and purified via column chromatography (0–50% EtOAc–heptane) to provide the product as a clear oil (88 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66–2.38 (m, 1 H), 2.87–2.81 (m, 1 H), 3.61 (s, 3 H), 4.10–4.08 (d, *J* = 10.5 Hz, 1 H), 4.55–4.52 (dd, *J* = 10.7, 2.1 Hz, 1 H), 4.78–4.74 (ddd, *J* = 6.0, 4.5, 3.1 Hz, 1 H), 6.31–6.29 (dt, *J* = 6.1, 1.8 Hz, 1 H), 7.29–7.17 (m, 5 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 29.37, 46.64, 52.54, 69.82, 99.36, 125.92, 127.61, 128.79, 139.58, 143.75, 173.58. ESI-HRMS: *m/z* calcd for $C_{13}H_{14}O_3$ [M + Na]: 241.08; found: 241.08.