Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1625–1626
Tetrahedron Letters

Synthesis of methyl 2-oxo-5-vinyl-2,5-tetrahydrofuran-3-carboxylate

Maximilian A. Silvestri,[a] Chang He,[a] Anita Khoram[b] and Salvatore D. Lepore[a,*]

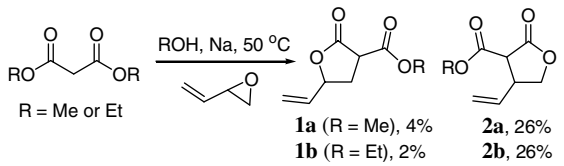
[a]*Department of Chemistry, Florida Atlantic University, Boca Raton, FL 33431, USA*
[b]*Custom Synthesis Inc., Delray Beach, FL 33445, USA*

Received 15 November 2005; revised 19 December 2005; accepted 21 December 2005
Available online 19 January 2006

Abstract—A synthesis of methyl 2-oxo-5-vinyl-tetrahydrofuran-3-carboxylate involving five synthetic steps from commercially available 3,4-dihydroxybutene is reported.

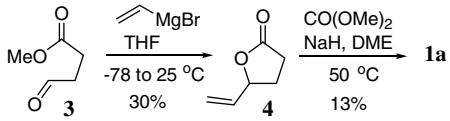
As part of an ongoing total synthesis project, we required a reliable and scaleable procedure for the preparation of methyl 2-oxo-5-vinyl-tetrahydrofuran-3-carboxylate (**1a**).[1] Initial attempts to prepare **1a** centered on a reported one-step procedure for the synthesis of ethyl ester analog **1b** involving the condensation of diethyl malonate with butadiene monoxide.[2] However, repeated attempts to condense malonate ester with butadiene monoxide following the reported protocol led to the formation of undesired regioisomers **2** as the major products (Scheme 1).[3] These data suggest that the structure of the lactone product described in earlier reports were incorrectly assigned.[4] In this letter, we describe our attempts to develop an alternative approach to the synthesis of **1a**.

We initially envisioned a two-step approach for the preparation of **1a** beginning with the addition of vinyl Grignard to commercially available aldehyde ester **3** to give lactone **4** following a related procedure.[5] Subsequent methoxycarbonylation would be expected to yield **1a** (Scheme 2).[6] Although the addition of Grignard reagents to **3** has been previously described,[5a] we were not able to obtain the desired lactone in reasonable yields even after extensive optimization.



Scheme 1. Condensation of butadiene monoxide with dimethyl and diethyl malonate.

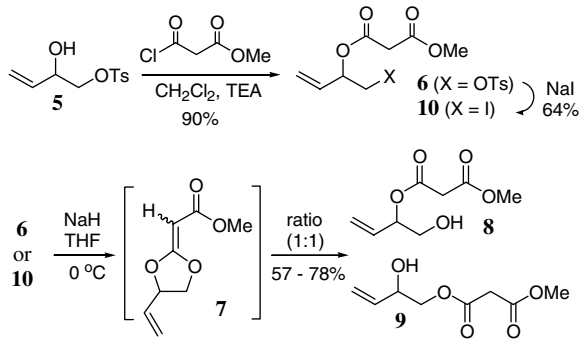
We next attempted a three-step synthesis of **1a** starting from 3,4-dihydroxybutene, which is commercially available as the racemate and non-racemic forms. Mono-tosylation of 3,4-dihydroxybutene[7] to give **5** was followed by the formation of malonate ester **6**.[8] The addition of sodium hydride to **6** failed to give intramolecular C–C bond formation leading to **1a**. Instead, malonic esters **8** and **9** were isolated as a mixture (1:1) after aqueous workup of the reaction. We hypothesize that these two regioisomers arise from ketene acetal intermediate **7** formed by O-alkylation, which is rapidly hydrolyzed to afford observed products **8** and **9** (Scheme 3). Alternatively, intermediate **7** may be hydrolyzed under workup conditions to afford either product **8** or **9**, which are subsequently equilibrated to the observed 1:1 mixture via an acyl migration mechanism. In an attempt to increase the likelihood of C-alkylation, the tosylate leaving group of malonate **6** was converted to the softer iodide in intermediate **10**.[9] However, attempts



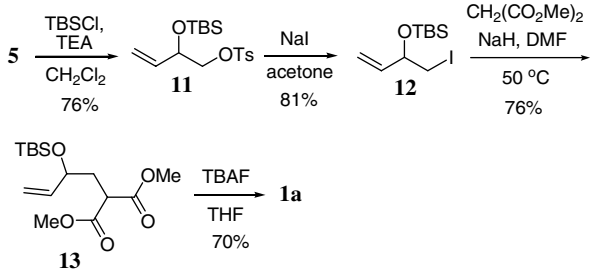
Scheme 2. Two-step synthesis of **1a**.

* Corresponding author. Tel.: +1 561 297 0330; fax: +1 561 297 2759; e-mail: slepore@fau.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.114



Scheme 3. Attempted intramolecular synthesis of **1a** from 3,4-dihydroxybutene.



Scheme 4. Intermolecular synthesis of **1a**.

to cyclize iodide **10** under basic conditions also led to the exclusive formation of **8** and **9** (1:1) in similar yields.

To accomplish an intermolecular malonate addition to **5** the secondary hydroxyl group of **5** was protected using TBSCl to give ether **11** using standard conditions (Scheme 4).[10] An attempt to condense the tosylate **11** with dimethylmalonate using sodium hydride as a base in DMF at 90 °C failed to yield the desired condensation product. Further alkylation attempts involving the use of a variety of solvents and added crown ether catalysts also failed to yield the desired alkylation product. However, conversion to iodide **12** followed by condensation with dimethyl malonate (9 equiv) using sodium hydride as a base in DMF successfully yielded coupling product **13** in 76% yield.[11] This intermediate was then converted to the desired lactone **1a** as a 1:1 mixture of diastereomers in 70% yield in the presence of TBAF.[12]

In conclusion, we have explored alternative synthetic approaches and identified a reliable synthesis of **1a** starting from 3,4-dihydroxybutene. Given the accessibility of non-racemic 1,2-diols through highly selective catalytic asymmetric dihydroxylation, we anticipate that the optimized procedure described in this letter can be used to obtain a variety of γ-butyrolactones containing π-conjugating substituents at the γ-position. Finally, the present work provides a correction to earlier reports involving malonate additions to vinyl oxirane.

Acknowledgements

We thank the Florida Center of Excellence in Marine Biotechnology for financial support. This work was also supported by a grant from the National Institute of General Medical Science (GM067635-01) and the National Science Foundation Division of Undergraduate Education (NSF-0311369) for the 400 MHz NMR used in this study.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.12.114.

References and notes

1. Morizawa, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 2297.
2. (a) Van Zyl, G.; Van Tamelen, E. E. *J. Am. Chem. Soc.* **1950**, *72*, 1357; (b) Russell, R. R.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1947**, *69*, 11.
3. The observed preference for malonate ion attack at the vinyl substituted position of the oxirane has been explained in terms of charge delocalization by the vinyl p-orbitals in the transition state. Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 3531. The preference for 1,2-attack by soft nucleophiles is likely due to metal ion coordination to the epoxide oxygen. Jamie, C.; Ortuno, R. M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139.
4. ^{1}H NMR (including COSY) and ^{13}C NMR spectra of the major product formed in this reaction clearly support the assignment of structure **2b**. Specifically, the methyne malonate proton appears as a doublet whereas in structure **1b** it should appear as a doublet of doublets. Also the chemical shift of methylene protons of **2b** indicates bonding of the methylene carbon to the lactone oxygen.
5. (a) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731; (b) Janowitz, A.; Kunz, T.; Handke, G.; Reissig, H. U. *Synlett* **1989**, 24.
6. Quesada, M. L.; Schlessinger, R. H. *J. Org. Chem.* **1978**, *43*, 346.
7. (a) Marguet, F.; Cavalier, J. F.; Verger, R.; Buono, G. *Eur. J. Org. Chem.* **1999**, 1671; (b) Kabalka, G. W.; Varma, M.; Varma, R. S.; Srivastava, P. C.; Knapp, F. F., Jr. *J. Org. Chem.* **1986**, *51*, 2386.
8. Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.
9. Ali, S.; Bittman, R. *J. Org. Chem.* **1988**, *53*, 5547–5549.
10. Drury, W. J.; Zimmermann, N.; Keenan, M.; Hayashi, M.; Kaiser, H. S.; Goddard, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 70.
11. (a) Fujita, K.; Mori, K. *Eur. J. Org. Chem.* **2001**, 493; (b) Lorca, M.; Kuroso, M. *Tetrahedron Lett.* **2001**, *42*, 2431.
12. Experimental procedures are provided in Supplementary Data for compounds **5**, **6**, **8**–**10**, **11**–**13**, and **1a**. Copies of NMR spectra for compounds **1a** (^{1}H and ^{13}C), **2b** (^{1}H, ^{1}H–^{1}H COSY, and ^{13}C), **5**, **6**, and **8**–**13** (^{1}H) are also provided.