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Stereoconvergent Palladium-Catalyzed Carbonylation of Both *E* and *Z* Isomers of a 2-Trifloxy-1,3-butadiene

Matthew M. Bio and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York, 10027

leighton@chem.columbia.edu

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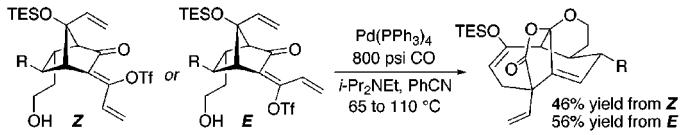
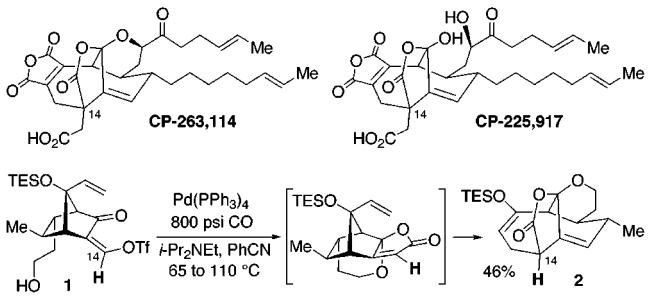
ABSTRACT



Carbonylation of the illustrated *Z*-tetrasubstituted enol triflate followed by tandem silyloxy-Cope rearrangement leads to the CP-263,114 core ring system with the all-carbon quaternary stereocenter intact in 46% yield. Subjection of the corresponding *E* isomer to the same conditions gives the same product in 56% yield. This observation is explained by a mechanism involving isomerization of a π-allyl palladium species involving an allenic intermediate.

CP-263,114 and CP-225,917[1] have, due primarily to their unique and challenging molecular architecture, attracted the attention of synthetic chemists. In addition to many diverse strategies,[2] total syntheses have been reported by Nicolaou,[3] Danishefsky,[4] and Shair.[5] Our own approach revolves around a late-stage tandem carbonylation-Cope rearrangement that delivers the entire core ring system of the CP structures (**1** → **2**, Scheme 1).[6] One of the many challenges posed by these targets—and one which was unaddressed in our model study—is the all carbon quaternary stereocenter at C(14) (highlighted proton, Scheme 1).[7] Herein we describe our efforts to extend our approach to incorporate an appropriate substituent at C(14), and an unusual observation regarding the chemistry of 2-trifloxy-1,3-butadienes.

Scheme 1



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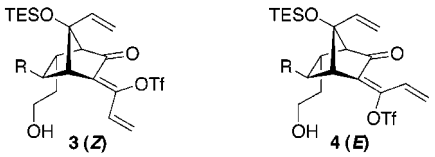
After considering several options, we targeted a vinyl group for the C(14) substituent because it was deemed unlikely to interfere with the carbonylation-Cope sequence, and due to its synthetic equivalence to the requisite acetic acid. This decision seemingly necessitated the stereoselective synthesis of (*Z*)-tetrasubstituted enol triflate **3** (Scheme 2).

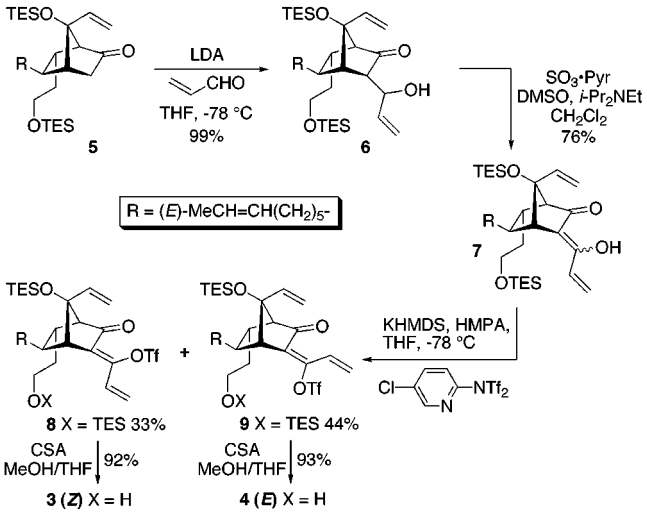
Scheme 2



We were intrigued, however, by the possibility that the (*E*)-enol triflate **4** might also serve as an effective precursor to the desired carbonylation-Cope rearrangement product. If so, the strategic advantage would be substantial in that an (*E*)-selective or even a nonselective synthesis of the enol triflates **3** and **4** would be equally useful.

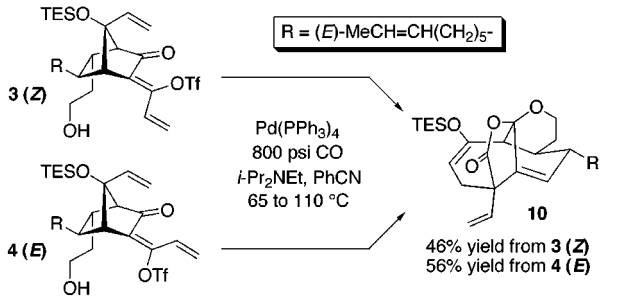
Our studies commenced with ketone **5**.[8] Attempted Claisen condensation with acrylate esters under a variety of conditions proved fruitless, and as a result an aldol-oxidation sequence was investigated. Treatment of ketone **5** with lithium diisopropylamide (LDA) and treatment of the resultant enolate with acrolein in THF at −78 °C led to a nearly quantitative yield of aldol **6** as a single diastereomer (stereochemistry unassigned). Oxidation according to the Parikh−Doering protocol[9] then delivered *β*-diketone **7** in 76% yield. The critical enol triflate formation was then investigated under a variety of conditions.[10] While the regioselectivity for the exocyclic enol triflate was consistently >10:1 (controlled by the strain in the endocyclic enolate), the stereoselectivity of exocyclic enol triflate formation was found to vary widely with conditions. Enolization of **7** with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of hexamethylphosphoramide (HMPA) in THF at −78 °C, and treatment of the resulting anion with Comin's triflating reagent[11] gave a 1:1.3 mixture of *Z*:*E*-enol triflates **8** and **9** in 77% yield. Conditions that resulted in a *Z* selective (>10:1) reaction were identified (KHMDS, Tf_2O, Et_2O, −78 °C), however the yield of **3 (*Z*)** was an unacceptable 44%. In preparation for the carbonylation-Cope rearrangement, the primary triethylsilyl (TES) ethers of **8** and **9** were hydrolyzed with catalytic camphorsulfonic acid (CSA) in MeOH/THF giving **3** (*Z*) and **4** (*E*) in 92% and 93% yields, respectively.

Scheme 3



We first examined the carbonylation−Cope rearrangement of enol triflate **3** to confirm that the C(14) vinyl group would not interfere with the reaction. Indeed, subjection of **3** to the carbonylation conditions developed previously resulted in the isolation of the CP-core fragment **10** in 46% yield (Scheme 4). We then turned our attention to the "wrong"

Scheme 4



E-enol triflate **4**. Remarkably, subjection of **4** to the same carbonylation conditions led to the isolation of **10** in 56% yield.

Mechanistically, we propose the scenario depicted in Scheme 5. Following insertion of Pd(0) into the *E*-enol triflate **4**, CO migratory insertion would be expected to be facile. However, this should be a mechanistic dead-end in that the only potential trap for the palladium-acyl is an *intermolecular* reaction with the primary alcohol. The high dilution of the reaction is likely helpful in this regard. Thus,

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(4) Meng, D.; Qiang, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197−3201.

(5) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424.

(6) Bio, M. M.; Leighton, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 890−891.

(7) Clive has addressed the construction of the C(14) quaternary stereocenter with a Cope rearrangement strategy. See ref 2k,l.

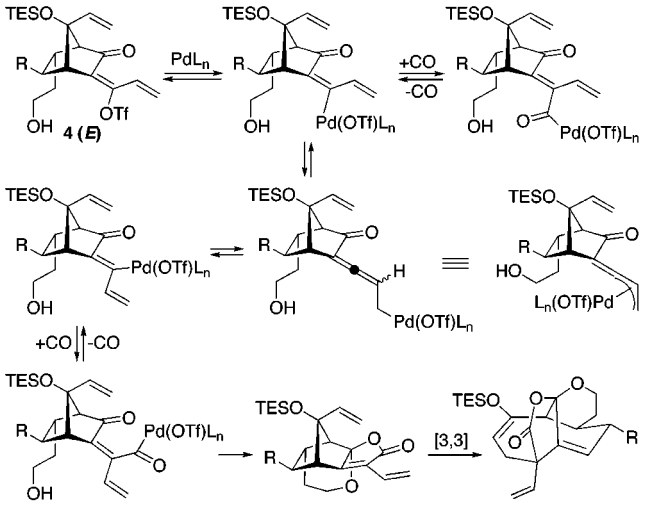
(8) The synthesis of ketone **5** is straightforward and proceeds in 11 steps from comercially available materials. Details will be reported elsewhere.

(9) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(10) For a review on the preparation and uses of enol triflates, see: Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47−54

(11) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

Scheme 5



the initially formed *E*-vinylpalladium species may be expected to isomerize via the indicated π-allyl palladium complex to the *Z*-vinylpalladium complex. From there, CO insertion and trapping of the resultant palladium-acyl with the hemiketal formed from the ketone and primary alcohol lead to the illustrated unsaturated lactone, which then rearranges to give the observed product.

The generation of allenic π-allyl palladium complexes of the type proposed here from buta-2,3-dien-1-ols and their derived acetates, carbonates and phosphates is well-precedented.[12] Various traps have been used (alkyl Zn and Mg, sodium ethylmalonate, CO/MeOH, CO/H_2O, organoboranes) and with the exception of the malonate reaction the products are 2-substituted-1,3-butadienes. 1,3-Diene syntheses involving similar intermediates but starting from 2-butyne-1,4-diol dicarbonates are known as well.[13] The present work constitutes the first example of the isomerization of one geometric isomer of a 2-substituted-1,3-butadiene to the other. Synthetically this discovery has important ramifications in that the need for a relatively difficult stereospecific synthesis of the *Z*-enol triflate has been obviated. In essence, a stereospecific synthesis of the C(14) quaternary stereocenter has been "paid for" with a nonselective synthesis of the tetrasubstituted enol triflate. The application of this strategy to a total synthesis of CP-263,114 is in progress.

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Supporting Information Available: Experimental procedures and characterization data for **6**−**9**, **3**, **4**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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