An Approach to the Synthesis of CP-263,114: A Remarkably Facile Silyloxy-Cope Rearrangement

Matthew M. Bio and James L. Leighton*

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

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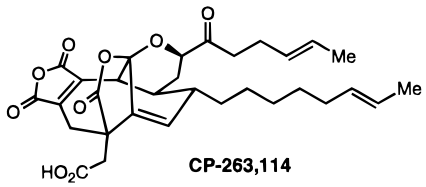
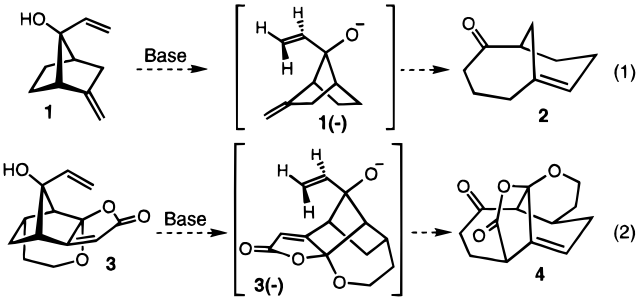
Researchers at Pfizer recently reported the isolation, structural characterization, and biological activity of two natural products termed CP-263,114 and CP-225,917.[1] Both were found to be active against protein farnesyl transferase, a medicinal target of great current interest.[2] As a result, these structurally challenging natural products have generated considerable interest from synthetic chemists.[3]



CP-263,114

Our retrosynthetic analysis began with the recognition of the retron for the anionic oxy-Cope rearrangement[4,5] within the bicyclic core. Stripped of all substituents, this rearrangement is depicted in eq 1 (**1** → **2**). At the time we began our work, no such example of the Cope rearrangement was known,[6] and the question of kinetic feasibility was of concern as inspection of molecular models indicated that the reacting termini of the two olefins of **1** are far from ideally oriented for a Cope rearrangement. In fact, Clive and Sgarbi have reported an anionic oxy-Cope rearrangement similar to **1** → **2**, thus establishing the feasibility of this approach.[3d] However, the reaction conditions (100 °C for 20 h) indicated an unusually sluggish anionic oxy-Cope rearrangement. We had sought from the start to build into our system an extra structural feature designed to promote the Cope rearrangement which, ideally, would be present in the natural product so as not to require additional steps in the synthesis. Analysis of the Cope rearrangement with the lactone spiroketal already built into the starting material reveals that the *exo*-methylene of **1** would be constrained within the lactone ring as in **3** (eq 2). This results



in significant strain and twisting in the bicyclic system (**1(−)** vs **3(−)**), and it was expected that relief of this strain would render the Cope rearrangement substantially more facile. It thus became the central tenet of our synthesis plan that the lactone spiroketal would be built into the Cope rearrangement precursor.

The synthesis commenced from the readily available ketoacid **5** (Scheme 1).[7,8] Prior to functionalization of the endocyclic olefin, we could anticipate very high diastereoselectivity in the addition of Grignard reagents to ketone **5** based on literature precedent[9] and the presence of the *exo*-methyl group that effectively blocks approach to the back face of the ketone. Indeed, treatment of **5** with excess vinylmagnesium bromide gave allylic alcohol **6** with very high diastereoselectivity. The alcohol was then protected as its triethylsilyl (TES) ether **7** in 61% overall yield from **5**. With **7** in hand the next task was a straightforward one-carbon homologation of the carboxylic acid with the Arndt−Eistert sequence. Synthesis of acid chloride **8** was best accomplished by way of the lithium carboxylate of **7**, and was followed by treatment with diazomethane to provide diazoketone **9** in 64% overall yield from **7**. Wolff rearrangement of **9** under photolysis conditions proceeded smoothly to give homologated acid **10** in 92% yield. Chemo- and regioselective functionalization of the endocyclic double bond was accomplished by treatment of acid **10** with $Hg(OAc)_2$, followed by treatment first with $NaBH_4$ to reduce the mercuryalkyl and then with $LiAlH_4$ to reduce the lactone. This procedure, performed without purification of intermediates, provided the desired diol **11** directly in 50% yield. Selective protection of the primary alcohol as its *tert*-butyldimethylsilyl (TBS) ether **12** in 85% yield was followed by Swern oxidation[10] of the secondary alcohol to afford ketone **13** in 92% yield.

With the required template in place, we were faced with the challenge of constructing the strained α,β-unsaturated γ-lactone spiroketal. A well-known method for the synthesis of unsaturated lactones is the palladium-catalyzed carbonylation of alkenyl halides or enol triflates with intramolecular trapping of the resultant palladium-acyl with alcohols and enolizable ketones.[11] Our system would require a novel modification in that the palladium-acyl would be trapped with a hemiketal formed from

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(6) A related anionic oxy-Cope rearrangement has been employed in an approach to the taxane bridgehead double bond: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190−3192.

(7) Ketoacid **5** was obtained from an *endo*-selective Diels−Alder reaction of methyl crotonate and 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, followed by saponification of the ester, dissolving metal reduction to remove the chlorines, and ketal hydrolysis in 81% overall yield. See the Supporting Information for details. See also: Thompson, H. W.; Wong, J. K.; Lalancette, R. A.; Boyko, J. A.; Robertiello, A. M. *J. Org. Chem.* **1985**, *50*, 2115−2121 and references therein.

(8) All new compounds were characterized spectroscopically. Full details are provided in the Supporting Information.

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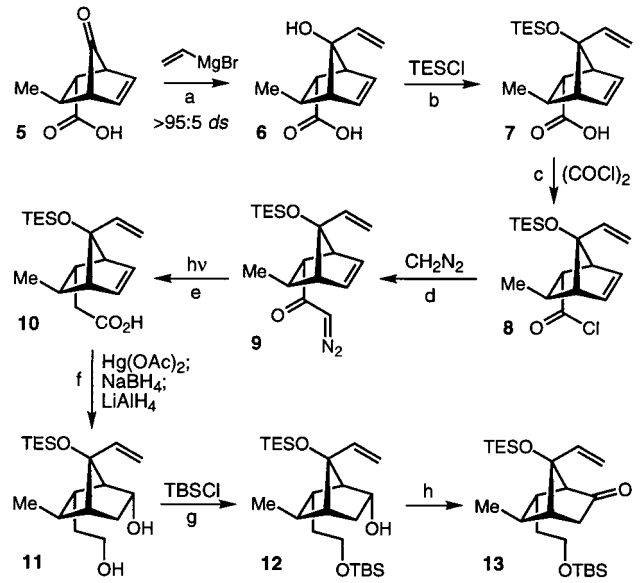
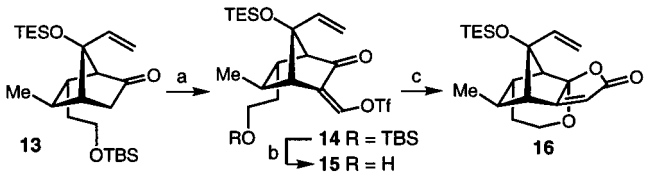
Scheme 1



[a](a) THF, -78 to 0 °C. (b) Imidazole, CH_2Cl_2, 61% from **5**. (c) LiOH; DMF, CH_2Cl_2. (d) Et_3N, CH_2Cl_2, 64% from **7**. (e) H_2O, dioxane. (f) THF, 50%. (g) Imidazole, CH_2Cl_2, 85%. (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 23 °C, 92%.

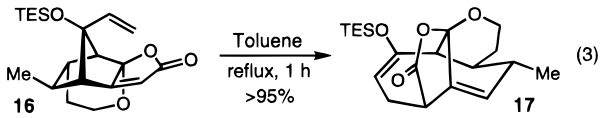
Scheme 2



[a](a) KHMDS, HCO_2Me; 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, 48% + 41% **13**. (b) Camphorsulfonic acid, MeOH, 74%. (c) $Pd(PPh_3)_3$, Et_3N, 600 psi CO, THF, 60 °C, 19% + 11% **15**.

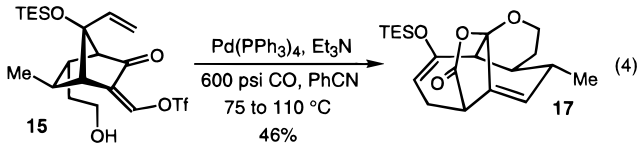
an alcohol and a ketone, thus forming two rings in a single step. To test this reaction, the synthesis of an enol triflate α to the ketone was required. Thus, ketone **13** was subjected to a Claisen condensation with methyl formate and the product was trapped in situ with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[12,13] (Scheme 2). This one-pot procedure provided vinyl triflate **14** in 48% yield as a >10:1 *Z:E* mixture of olefin isomers along with 41% recovered **13**. Selective methanolysis of the TBS group then gave the required hydroxyenol triflate **15** in 74% yield. Treatment of **15** with $Pd(PPh_3)_4$ (10 mol %) and Et_3N under 600 psi CO at 60 °C did indeed proceed to give the desired lactone spiroketal **16** in modest yield (19%, plus 11% recovered enol triflate **15**). With the desired system **16** in hand, we elected to investigate the Cope rearrangement prior to optimization of this crucial carbonylation reaction.

With recourse to the anionic variant of the oxy-Cope rearrangement as a potential alternative, the direct silyloxy-Cope rearrangement of **16** was examined first. Heating a toluene solution of **16** at reflux for 1 h led to smooth conversion to a single compound, identified as silyl enol ether **17**, in near quantitative yield (eq 3).[14] That this reaction proceeds at 110 °C



in 1 h, while the Clive anionic oxy-Cope experiment required 100 °C for 20 h is remarkable. The rate acceleration due to the anion effect has been estimated at $10^{10}-10^{17}$, and we may thus conclude that qualitatively, the strain we have built into lactone spiroketal **16** results in a similar acceleration. In addition, this reaction is in principle an equilibrium process, and it is noteworthy that the equilibrium overwhelmingly favors the desired bridgehead[15] double bond.

With the ease and efficiency of this rearrangement established, we recognized that isolation of **16** may be unnecessary. Indeed, it was discovered that simply by repeating the carbonylation experiment described above (**15** → **16**, Scheme 2) and raising the temperature to 110 °C that **15** could be converted into **17** in a single step. We then set about optimizing the efficiency of the carbonylation process, and quickly discovered that the proper choice of solvent was critical. Thus, carbonylation of **15** in benzonitrile at 75 °C, and then simply raising the temperature of the reaction to 110 °C, led to the isolation of **17** in 46% yield (eq 4).



With the synthetically powerful single step conversion of **15** to **17**, we have thus developed an 11-step synthesis of CP-263,-114 core fragment **17** from ketoacid **5**. While many issues remain to be resolved for a total synthesis of CP-263,114, we believe a viable route has been demonstrated. Our current efforts are focused on the total synthesis.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds as well as details of structural proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a review of the preparation and uses of enol triflates, see: Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47−54.
(14) The structure of silyl enol ether **17** was determined spectroscopically including COSY and nOe experiments. All data are in full accord with the assigned structure. See the Supporting Information for details.
(15) For a recent review on bridgehead or "anti-Bredt" double bonds, see: Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067−1093.