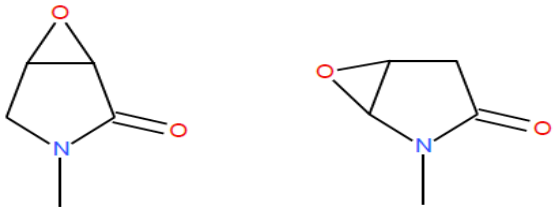
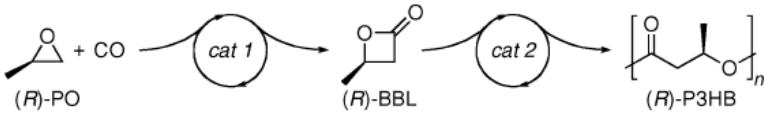
Polyester Containing Pyrrolidones

By: Robert B. Login rloginconsulting.com

My idea was to start from 3,4 or 4,5 pyrrolidone epoxide derivatives.



Scheme 1. One-Pot Carbonylative Polymerization of (*R*)-Propylene Oxide to (*R*)-Poly(3-hydroxybutyrate)



Developing a one-pot catalytic system is challenging, as the two catalysts must be compatible not only with each other but also with the solvent, substrate, and reaction side products in order to achieve high activity and selectivity.[10] We have previously reported several catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ to be highly active for the carbonylation of epoxides.[11] Furthermore, (BDI)ZnO^{i}Pr (BDI = β-diiminate) has been shown to be an active catalyst for β-lactone polymerization.[12] We anticipated that the catalysts had orthogonal reactivity and could be combined to create an efficient system for the one-pot carbonylative polymerization of PO.

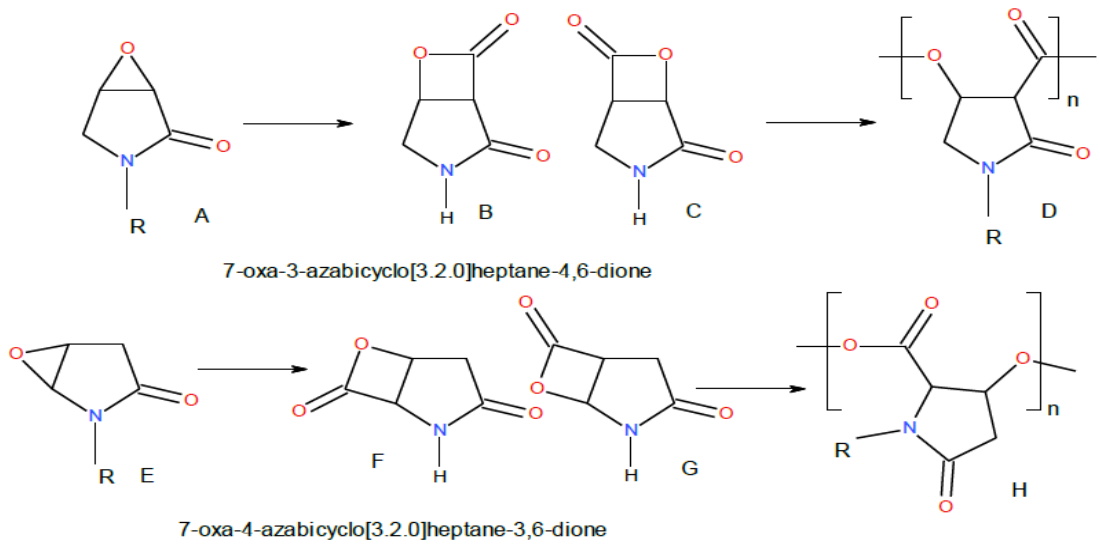
11412 ■ J. AM. CHEM. SOC. 2010, *132*, 11412–11413

Erin W. Dunn and Geoffrey W. Coates

Robert, C., & Thomas, C. M. (2013). Tandem catalysis: a new approach to polymers. *Chemical Society Reviews*,*42*(24), 9392-9402.

The above reference illustrates the conversion of an epoxide directly to the corresponding polyester. Can this procedure work with pyrrolidone epoxides? I wrote proposals describing the synthesis of pyrrolidone epoxides that you can find on my web page titled “epoxylactams” rloginconsulting.com. This proposal(s) is related to it. Please take a look.

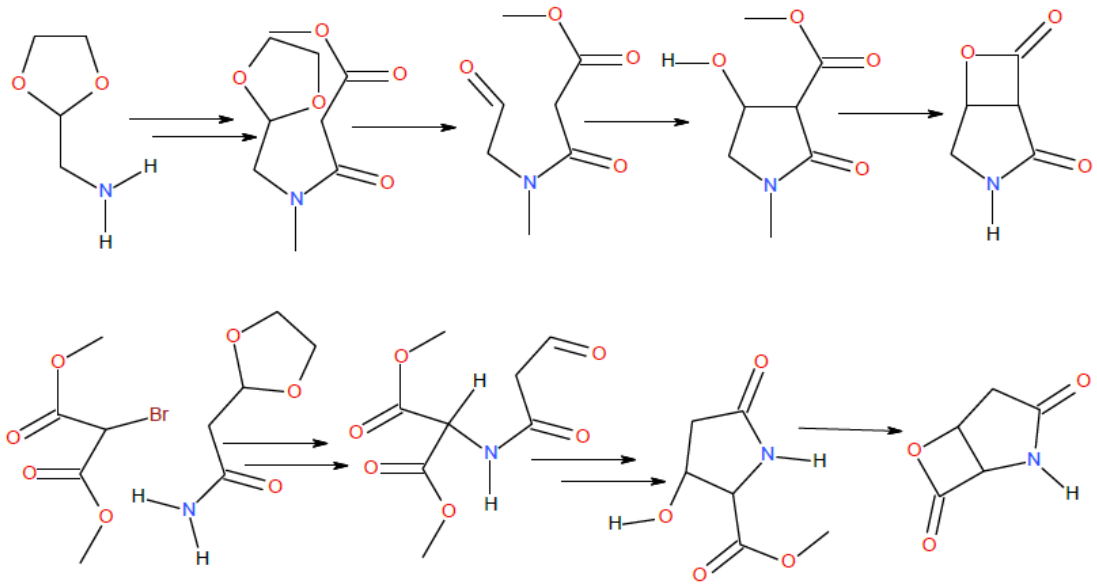
Below, using the Dunn & Coates procedure, B&C and F&G would be intermediates and not isolated.



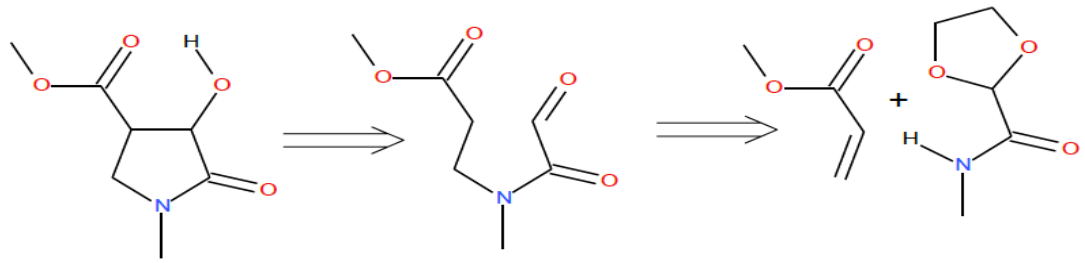
Scheme 1 : Both A&E are derived from the unsaturated precursor. I have no idea if there is a preference for B or C or F & G? Conversion to the polyester is probably straight forward(only one isomer is shown). Such polyesters would be water soluble and eventually degradable by hydrolysis. I would also think they could be copolymerized with other suitable monomers conferring water solubility and complexing with large anions like phenolics or iodine derivatives. They would not be long lasting in the environment because of eventual hydrolysis. Delivery of medicinals by hydrolizable polymers that are easy to eliminate and are nontoxic(?) would be valuable,

Mathew, A., Mathew, B., & Koshy, E. P. (2020). Polymer supported bromoderivatives of 2-pyrrolidone: an efficient reagent for the microwave assisted conversion of trans-cinnamic acid to trans-β-bromostyrene. *SN Applied Sciences*, *2*, 1-9.

Should the Dunn & Coates combined two orthogonal catalyst approach be undo-able then other synthesis routes can be considered. For example:

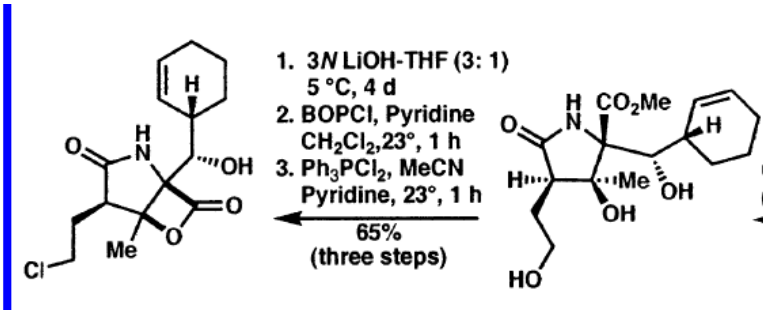


Scheme 2: If the epoxide route didn't work then other routes could be considered like the above.



Scheme 3: Alternative synthesis of the 4-carboxy derivative.

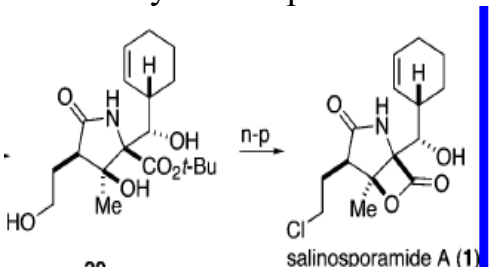
I'm sure there are other routes to these compounds. This then brings up the subject of these structures being already in the chemical literature but however not in the above underivatized form.



Reddy, L. R., Saravanan, P., & Corey, E. J. (2004). A simple stereocontrolled synthesis of salinosporamide A. *Journal of the American Chemical Society*, *126*(20), 6230-6231.

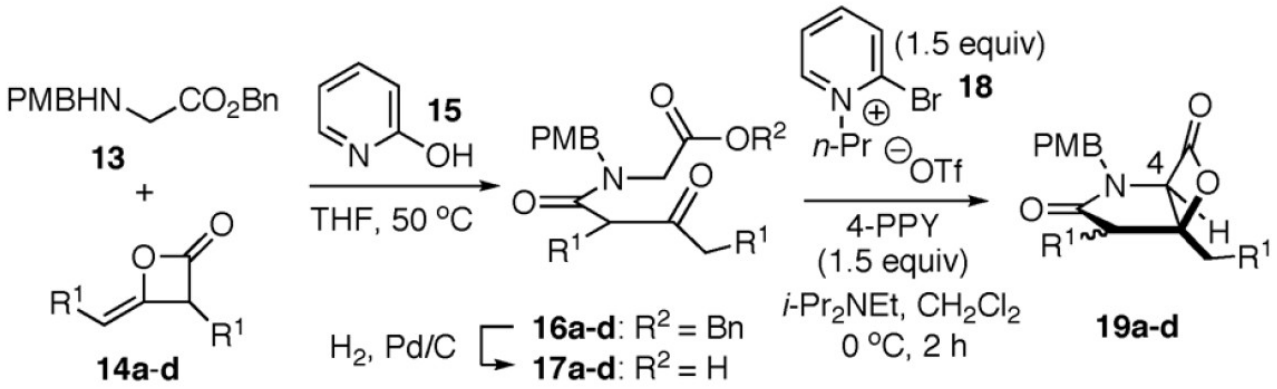
It took 11 steps to get to the final esterification. The last step is a method of forming the

lactam from the alcohol and carboxylic acid pertinent to my above schemes.

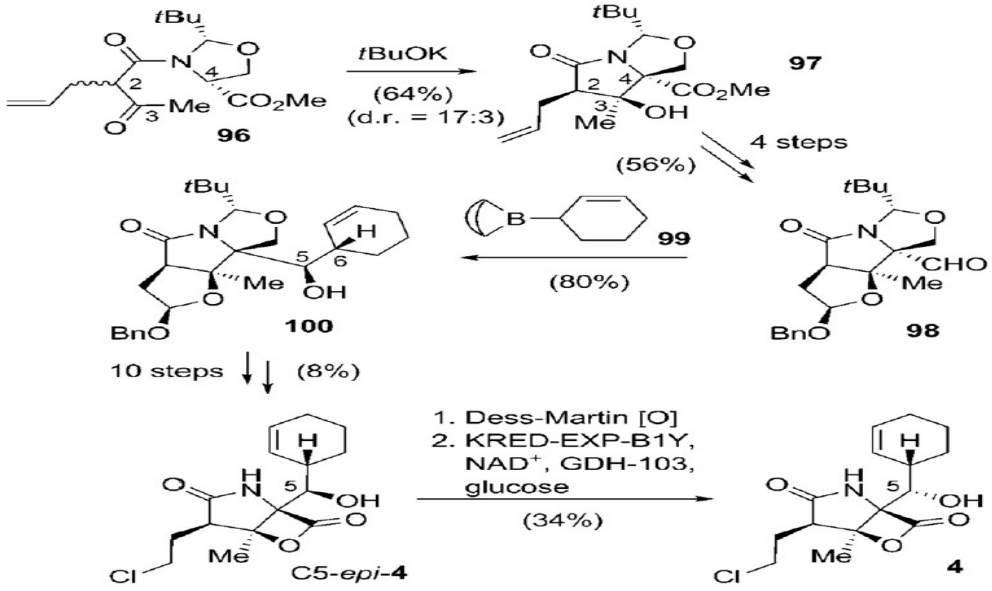


(n) BCl3, CH2Cl2, 0 °C; (o) BOPCl, TEA, CH2Cl2, rt; (p) Ph3PCl2, pyridine, CH3CN, rt (51% in three steps). It took many steps to get to the last one that shows the esterification.

Endo, A., & Danishefsky, S. J. (2005). Total synthesis of salinosporamide A. *Journal of the American Chemical Society*, *127*(23), 8298-8299.



Ma, G., Nguyen, H., & Romo, D. (2007). Concise total synthesis of (±)-salinosporamide A,(±)-cinnabaramide A, and derivatives via a bis-cyclization process: implications for a biosynthetic pathway?. *Organic letters*, *9*(11), 2143-2146.



Scheme 11.
Total synthetic pathway towards salinosporamide A (**4**) by Nereus Pharmaceuticals. NAD^+=nicotinamide adenine dinucleotide (oxidized form).

(12) **United States Patent**
Palladino et al.
(10) **Patent No.: US 8,168,803 B2**
(45) **Date of Patent: May 1, 2012**

Nereus patent with a rather complete literature review.

Scheme 11 above from this review.

Gulder, T. A., & Moore, B. S. (2010). Salinosporamide natural products: Potent 20 S proteasome inhibitors as promising cancer chemotherapeutics. *Angewandte Chemie International Edition*, *49*(49), 9346-9367.

Nguyen, H., Ma, G., Gladysheva, T., Fremgen, T., & Romo, D. (2011). Bio inspired total synthesis and human proteasome inhibitory activity of (−)-salinosporamide A,(−)-homosalinosporamide A, and derivatives obtained via organonucleophile promoted bis-cyclizations. *The Journal of organic chemistry*, *76*(1), 2-12.

Caruano, J., Muccioli, G. G., & Robiette, R. (2016). Biologically active γ-lactams: synthesis and natural sources. *Organic & biomolecular chemistry*,*14*(43), 10134-10156.

The interest in these derivatives is a result of their anti-cancer activity. This is why so much effort has gone into their synthesis, To me this is very important but I'm still amazed that you can become famous for being able to figure out how to make a compound produced by bacteria living in ocean sediments. It suggests that possibly someday we could reprogram bacteria, fungi etc to produce compounds we design since they are very able chemists.

Thanks for reading this proposal!
Dr. Robert B. Login rloginconsulting.com