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An Acid-Catalyzed Macrolactonization Protocol

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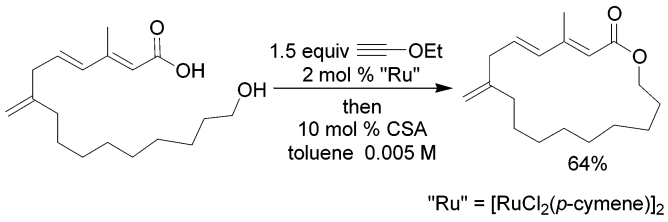
ABSTRACT



An efficient macrolactonization protocol devoid of any base was developed derived from the use of vinyl esters in transesterification. Subjecting a hydroxy acid and ethoxyacetylene to 2 mol % $[RuCl_2(p\text{-cymene})]_2$ in toluene followed by addition of camphorsulfonic acid or inverse addition provided macrolactones in good yields.

With the advent of modern isolation techniques, numerous large-ring lactones that possess interesting biological activity have been isolated. The need for dependable methods of forming such lactones in the presence of sensitive functionality has led to the development of numerous methods.[1] The most recognized of these is the Yamaguchi[2] cyclization, where the ester is activated as a mixed anhydride and esterification is facilitated by a high concentration of the acylation promoter 4-(dimethylamino)pyridine (DMAP). While effective, this can often lead to side reactions with base-sensitive substrates such as unsaturated acids.[3] Exposure of the activated carboxylic acid derivative in any of these protocols to base is normally responsible for the undesired side reactions.

During the course of another investigation, this problem showed itself to be substantive. To combat its effects, we attempted to adapt intermolecular esterification methods that did not require basic conditions to model substrates in the hope of solving this problem. Our most successful approach is based upon the work of Dixneuf and Kita.

Dixneuf had shown that acetylenes and carboxylic acids will react in the presence of certain ruthenium catalysts to form the corresponding vinyl ethers.[4] Kita saw this as an opportunity to activate the carboxylic acid as the ethoxyvinyl ester, an activating group originally explored by Wasserman.[5] Wasserman had used stoichiometric mercury to synthesize his vinyl esters instead of catalytic ruthenium, and this likely led to their lack of preparative use.[6] In any event, the ethoxyvinyl esters perform admirably in intermolecular esterification reactions under acid-catalyzed conditions.

To adapt this method to intramolecular lactone formation, two questions had to be answered. First, can the ethoxyvinyl ester be formed in the presence of an alcohol? Second, can the esterification be performed with catalytic acid under the high dilution conditions necessary to form large rings?

To address the first question, hydroxycarboxylic acid **1**, which forms a 16-membered macrolactone, also new, was examined. Initial experiments showed that the activated ester could be formed under both high dilution conditions (0.005 M) and at higher concentration (0.1 M) without any ester or macrolactone formation occurring. Evidently, without the presence of an acid catalyst, the ethoxyvinyl ester is not a

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(2) Inanaga, J.; Hirata, H.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(3) Hartmann, B.; Kanazawa, A. M.; Depres, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077.
(4) Ruppin, C.; Dixneuf, P. H. *Tetrahedron Lett.* **1986**, *27*, 6323.
(5) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *Synlett* **1993**, 273.
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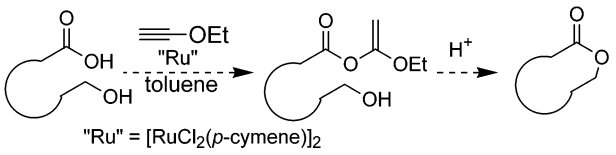
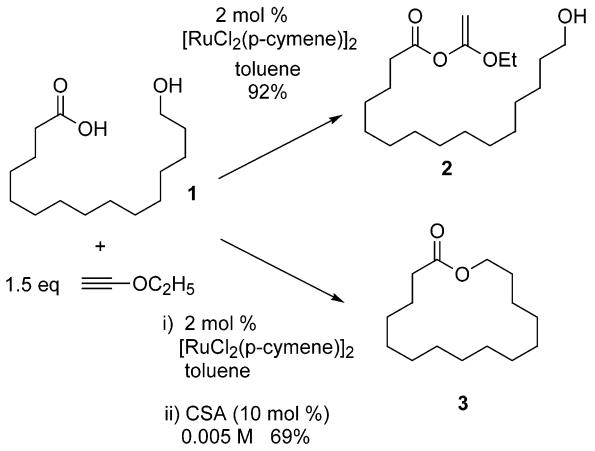
Scheme 1. Concept



Scheme 2. Initial Experiments



good electrophile for the alcohol. The ethoxyvinyl ester could be obtained in relatively pure form by silica gel chromatography, but this was accompanied by significant hydrolysis of the ester. Keeping the TLC R_f fairly high (~0.6) and performing the chromatography quickly allowed the hydrolysis to be controlled and the activated ester to be isolated in excellent yield if desired. Synthetically, the enol ester was not isolated. Instead, the reaction mixture was used directly for cyclization.

With the activated ester in hand, cyclization was attempted. Heating the activated ester to reflux in toluene at relatively high dilution (0.005 M) led to a disappointing 22% yield of the lactone. However, addition of 10 mol % of camphorsulfonic acid (CSA) to the dilute solution at room temperature led to a gratifying 60% yield, along with 11% of the dimeric product. Other acids such as PPTS and TFA were less effective in this cyclization. As a standard macrolactonization protocol starting from the hydroxycarboxylic acid, formation of the enol ester was followed by either direct addition of CSA to the reaction mixture or, preferably, slow addition of the reaction mixture from the enol ester formation to a toluene solution of CSA.

With conditions for cyclization in hand, a study of substrate generality was undertaken. Toward this purpose, a number of other hydroxy acid substrates were synthesized. To add some variety to these substrates, some were synthesized using the ruthenium-catalyzed alkene−alkyne coupling reaction currently under development in our group.[7−9] These provided hydroxy acids as mixtures of branched and linear olefin isomers, as shown in Scheme 3.

The use of the Fmoc ester for the synthesis of hydroxy acid **8** was required because of the facile isomerization of the triene under basic hydrolysis conditions. Even under the mild conditions used for the removal of the Fmoc ester, if the reaction was allowed to proceed for long periods of time (>3 h), some isomerization was observed. Unsaturated hydroxy acid **8** would, therefore, provide the most strenuous test of our methodology.[10] The hydroxy acid **15** was synthesized from the 13-membered ketone following the literature procedure.[11]

A summary of the cyclization results are presented in Table 1. The 12-membered hydroxy acid gave almost all dimeric product, and the 13-membered lactone also gave a poor result, with about half of the isolated product being dimer. The lack of any conformational constraint present on these

Scheme 3. Synthesis of Substrates by Alkene−Alkyne Coupling

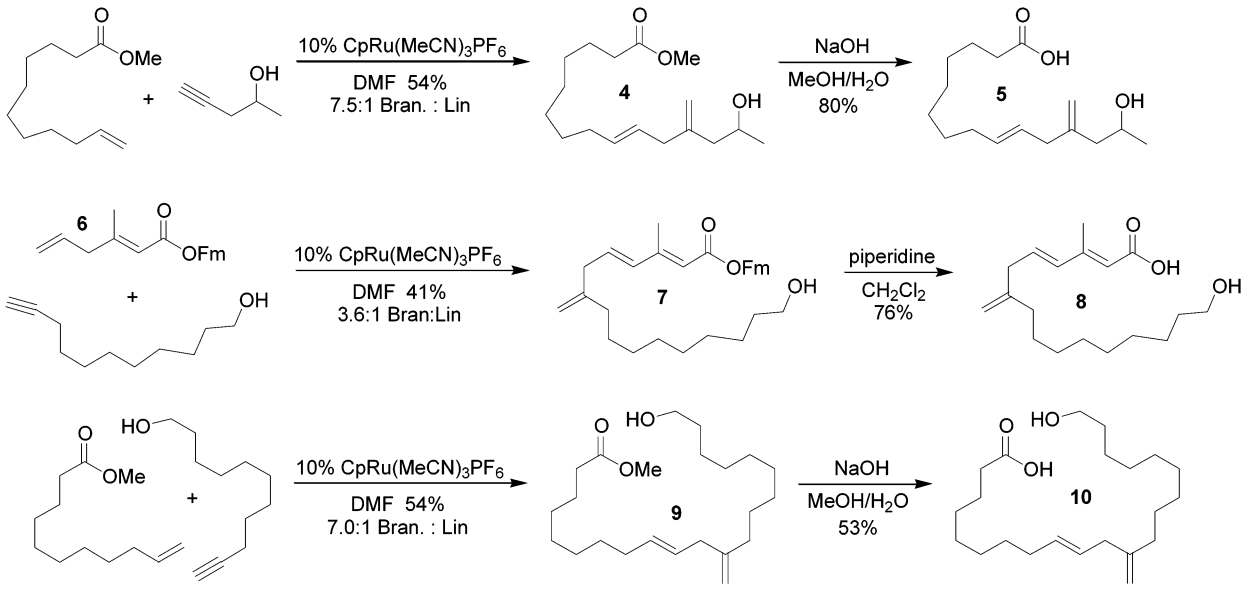
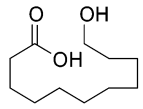
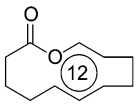
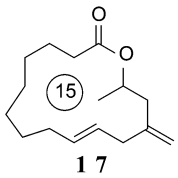
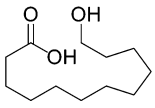
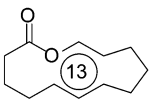
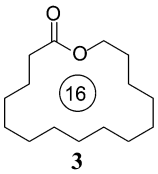
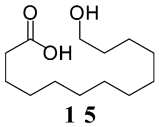
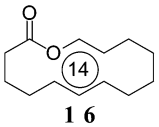
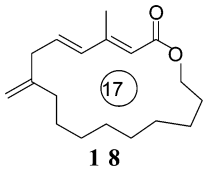
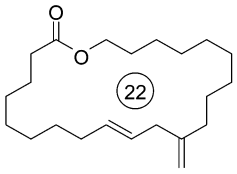


Table 1. Macrolactonization Examples

hydroxy-acid	lactone	yield	hydroxy-acid	lactone	yield
 **11**	 **12**	4% (38% dimer)	**5**	 **17**	69%
 **13**	 **14**	22% (24% dimer)	**1**	 **3**	60% (11% dimer)
 **15**	 **16**	49% (18% dimer)	**8**	 **18**	64%
			10	 **19**	70%

rings may have contributed to this excessive formation of dimer. On the other hand, all lactones of 14 or greater members gave satisfactory results. Both primary and secondary alcohols were good substrates for the reaction. Of note is the unsaturated ester, **18**, which underwent no isomerization of the sensitive triene. This is in contrast to the Yamaguchi protocol with DMAP, which resulted in isomerization of approximately 50% of the product (the yields of the two reactions are comparable). The yield of macrolactone **17** from hydroxy acid **5** via the Yamaguchi cyclization was also comparable to the method used here when performed at the same concentration.

Thus, the ruthenium−proton two stage esterification protocol constitutes an effective macrolactonization method for rings of 14 members or more. In contrast to other macrolactonization protocols, which frequently require base (even stoichiometric or larger amounts), this method requires only a catalytic amount of acids (Lewis and Bronsted). The excellent chemoselectivity of the process is highlighted by formation of lactone **18** in 64% yield. Application of this method to the synthesis of biologically relevant natural products will be reported in due course

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Supporting Information Available: Procedures for Ru-catalyzed alkene−alkyne coupling and macrolactonization and characterization data for **2**, **4**−**10**, and **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Cf.: Hartmann, B.; Kanazawa, A. M.; Depres, J. P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077.
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