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Concise Total Synthesis of (−)-Muricatacin by Tandem Ring-Closing/Cross Metathesis

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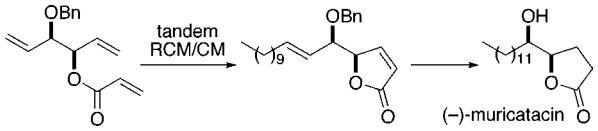
ABSTRACT

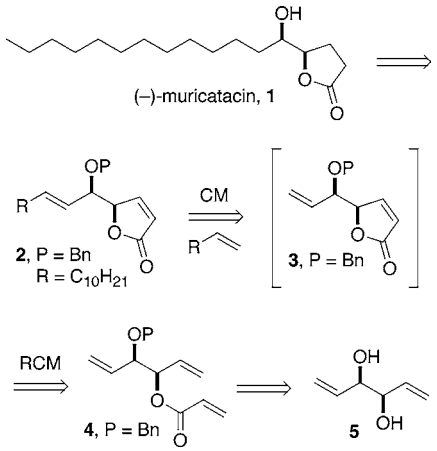


A strategy for the synthesis of chiral 5-(1-hydroxyalk-2-enyl)-5*H*-furan-2-ones and its application to the total synthesis of (−)-muricatacin, in four steps and 37% overall yield from (*R*,*R*)-hexa-1,5-diene-3,4-diol, are described. The key synthetic step in this approach is a highly regioselective and stereoselective tandem ring-closing/cross metathesis reaction in which both lactone formation and alkyl chain extension are accomplished in an efficient one-pot process.

The chiral 5-hydroxyalkylbutan-4-olide nucleus is an integral structural component of an ever increasing number of biologically and chemically significant natural products, including many members of the Annonaceous acetogenin family.[1] (−)-Muricatacin (**1**, Scheme 1) is a simple example. **1** is isolated as the major component of a scalemic mixture (ca. 25% ee based on optical rotation) from the seeds of *Annona muricata* and has received a great deal of attention due to its diverse biological profile.[2] Notably, both **1** and its enantiomer exhibit potent cytotoxicity toward several human tumor cell lines with SAR studies showing that activity is influenced significantly by the nature of the side chain.[3] In addition to their interesting biological properties, muricatacin and related hydroxylactones have served as precursors in syntheses of more complex acetogenins and other natural products.[4] The biological and chemical potential of muricatacin has prompted many syntheses;[5] however, development of general and flexible strategies for the preparation of more highly functionalized side chain analogues[6] and other hydroxyalkylbutanolide natural products remains a goal.

Herein, we report an approach to the synthesis of (*R*,*R*)-5-hydroxyalkylbutan-4-olides and demonstrate its utility by application to the total synthesis of (−)-muricatacin. Our retrosynthetic analysis is outlined in Scheme 1. Key to our approach is the recognition that protected 5-(1-hydroxyalk-

Scheme 1. Retrosynthetic Analysis



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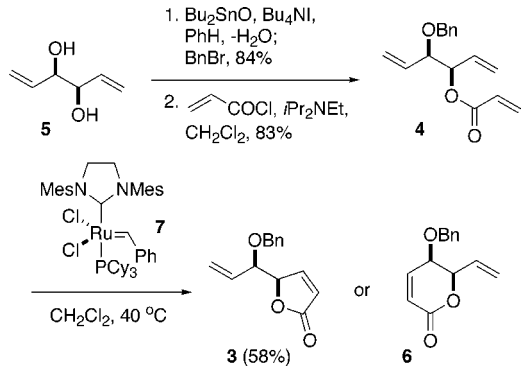
Scheme 2. Preparation and RCM of **4**



2-enyl)-5*H*-furan-2-ones, such as muricatacin precursor **2**, could be constructed directly from acyclic trienes (**4**) by a tandem process in which lactone ring formation and chain extension are achieved by olefin metathesis. Initial ring-closing metathesis[7] (RCM) of **4** would provide an intermediate butenolide **3**, in which the two olefins are clearly differentiated by their electronic environments. Intermolecular cross metathesis[8] (CM) between the terminal olefin of **3** and an alkene coupling partner ($RCH{=}CH_2$) would complete the tandem to provide an extended hydroxyalkenylbutenolide (**2**).[9] Specific to our proposed muricatacin synthesis, benzyl-protected acrylate ester **4**, available from C_2-symmetric dienediol **5**, and 1-dodecene would serve as substrates for the RCM/CM tandem.

Preparation of metathesis substrate **4** began with (*R*,*R*)-hexa-1,5-diene-3,4-diol **5**, which is conveniently prepared in multigram quantities from D-mannitol (Scheme 2).[10] Desymmetrization was achieved by monobenzylation of the stannylene acetal of **5**.[11] Subsequent acylation of the remaining hydroxyl with acryloyl chloride provided easy access to triene **4** in 70% yield over two steps and set the stage for examination of the proposed metathesis reaction.

To establish the feasibility of our approach, we first needed to determine the regiochemical outcome of ring-closing metathesis of **4**. Two modes of closure, metathesis between the acrylate group and either the proximal olefin to give **3** or the distal olefin to give **6**, are possible (Scheme 2). At the outset, it was unclear which pathway would be favored; however, both **3** and **6** are potentially valuable synthetic intermediates, so we felt that either outcome would be productive. In the event, we found that treatment of **4** with 10 mol % of the second generation Grubbs' catalyst **7**[12] in either refluxing PhH or CH_2Cl_2 resulted in the formation of **3** as the only isolable product in 52 and 58% yield, respectively. The assignment of **3** as the RCM product was based on the relatively large downfield shifts of the β proton (7.47 ppm) in the ^{1}H NMR spectrum and the carbonyl carbon (172.6 ppm) in ^{13}C NMR spectrum and later confirmed by comparison (vide infra). In a preliminary examination of the effect of the protecting group on regioselectivity, we found that RCM of the TBS-protected analogue of **4** also gave only the five-membered lactone product (55%). Efforts to manipulate the observed RCM regiochemistry to provide for complementary preparation of dihydropyranones such as **6** are in progress.

Encouraged by the yield and selectivity observed for RCM of **4**, we turned our attention to its incorporation into the proposed RCM/CM process for the preparation of the chain-extended butenolide **2**. Two procedures were examined: a sequential method in which the cross coupling partner (1-dodecene) was added after RCM of **4** was complete and a tandem method in which both 1-dodecene and triene **4** were present at the time of addition of metathesis catalyst **7**.[13] Our results are summarized in Table 1. For the sequential procedure, a 0.005 M solution of triene **4**[14] and catalyst **7** (10 mol %) in either PhH or CH_2Cl_2 was refluxed until TLC analysis indicated complete conversion of **4** to RCM product **3** at which time 5 equiv of 1-dodecene was added (entries 1 and 2). At either temperature, conversion of **4** to **3** required approximately 24 h. We were pleased to find that addition of the alkene coupling partner resulted in completion of the metathesis sequence to provide **2** in respectable overall yields. CM generated **2** with complete (*E*)-selectivity for the acyclic olefin as determined by ^{1}H NMR (J = 15.4 Hz). None of the (*Z*)-isomer was detected.

For the tandem procedure, catalyst **7** (10 mol %) was added to a 0.005 M solution of triene **4**[14] and 5 equiv of 1-dodecene in either PhH or CH_2Cl_2, and the reaction mixtures were heated to reflux. Considering the expected rate difference for intra- vs intermolecular metatheses, we

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(8) For a recent review of olefin cross metathesis, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900.

(9) For synthesis of δ-alkenyl β,γ-unsaturated δ-lactones by RCM/CM, see: Virolleaud, M. A.; Bressy, C.; Piva, O. *Tetrahedron Lett.* **2003**, *44*, 8081.

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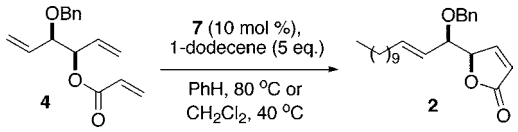
(13) For definitions of sequential and tandem reactions, see: Denmark, S. E.; Thorasen, A. *Chem. Rev.* **1996**, *96*, 137.

(14) Yields were greatly diminished if reactions were performed at higher concentration.

Table 1. RCM/CM of **4** and 1-Dodecene



entry	procedure	solvent	time (h)[a]	yield (%)
1	sequential	PhH	38	49
2	sequential	CH_2Cl_2	48	55
3	tandem	PhH	32	20
4	tandem	CH_2Cl_2	42	57
5[b]	tandem	PhH	44	55
6[c]	tandem	CH_2Cl_2	18	60
7[c,d]	tandem	CH_2Cl_2	12	65

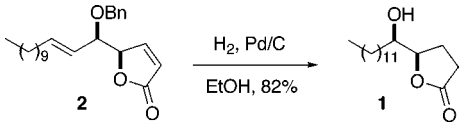
[a] Reactions were considered complete when TLC indicated that **4** and **3**, generated in situ, were no longer present. [b] Reaction performed at 40 °C. [c] Slow addition of **7** as a solution via syringe pump. [d] Concentration of 0.01 M in **4**.

anticipated that RCM would occur much faster than CM and, thus, a timing of events similar to those under sequential conditions. As such, we were surprised to find that tandem reactions run at 80 °C gave much lower yields of **2** than sequential reactions at the same temperature (entry 3). We believe this is due to deleterious CM processes prior to RCM at elevated temperature.[15] Fortunately, the yield of **2** was increased dramatically to 57% when the reaction was conducted at 40 °C (entries 4 and 5). In these cases, RCM product **3** was observed as the sole intermediate by TLC prior to the formation of **2**.

Although we were gratified by the success of tandem RCM/CM, we hoped to reduce the extended times required for completion. We felt that decomposition of catalyst **7** and/or propagating catalytic species during the course of the reaction was a possible cause. To better maintain a concentration of active catalyst, **7** was added as a 0.01 M solution over 8 h via syringe pump (entries 6 and 7). Using this modification, we observed substantial reductions in completion times and found that reactions could be run at higher concentration (0.01 M in **4**) leading to an optimal yield of 65% (entry 7).

(15) As evidenced by the observation of products of CM between **4** and 1-dodecene by ^{1}H NMR.

Scheme 3. Completion of the Synthesis of (−)-Muricatacin



Completion of the synthesis of required only reduction of the olefins and removal of the benzyl protecting group. This was accomplished smoothly by catalytic hydrogenation/hydrogenolysis of **2** to give **1** as a white solid in 82% yield (Scheme 3). (−)-Muricatacin produced in this manner displays spectral data, optical rotation, and melting point consistent with those reported the literature.[2,5] (+)-Muricatacin should also be readily available from (*S*,*S*)-hexa-1,5-diene-3,4-diol[16] by this route.

In summary, an efficient strategy for the synthesis of 5-hydroxyalkylbutan-4-olides via tandem RCM/CM has been demonstrated by application to the total synthesis of (−)-muricatacin. The flexibility inherent in this approach and the high degree of functionality present in tandem products such as **2** make it broadly applicable. Extension to the synthesis of more complex Annonaceous acetogenins and other oxygenated alkylbutyrolactone natural products is currently underway, and results will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for the monobenzyl derivative of **5** and compounds **4**, **3**, **2**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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