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Total synthesis of octalactin A via ring-closing metathesis reaction

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Abstract—A new total synthesis of the novel lactone natural product octalactin A is described. The key step involves the facile construction of the eight-membered lactone core via ring-closing metathesis (RCM). This oxocene was elaborated to give the powerful antitumor agent octalactin A.

Medium-ring systems are found in many biologically and medicinally active natural products.[1] The octalactins[2] are the most important members of a small but fascinating class of saturated eight-membered ring lactone natural products that includes cephalosporolide D,[3] dregeanin,[4] and the putative structures of the gonioheptolides.[5] Octalactin A **1** (Fig. 1) in particular is noted for its potent toxicity against certain human colon cancer cell lines, among others, and has emerged as a highly promising new anticancer agent. This activity, combined with its interesting and challenging topology and associated architectural features, continues to generate intense interest from synthetic organic chemists.[6]

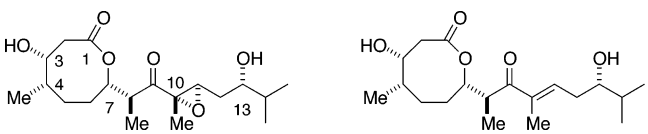
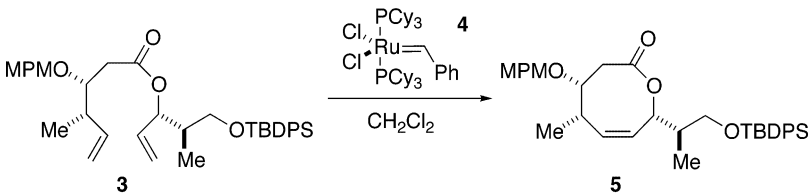


Figure 1. Structures of the octalactins.

We published the first total synthesis of the octalactins by means of an unprecedented and exceptionally facile and direct lactonization from their corresponding *seco* acids.[7,8] Although this strategy provided efficient access to many other similar lactone systems,[9] we required a more flexible entry into the octalactin scaffold. Our continuing interest in determining the molecular target and finding the mode of action of octalactin A prompted us to secure a more expeditious and practical route to this important compound and its analogues from a common intermediate.[10] The construction of an impressive number of diverse cyclic structures via the ring-closing metathesis (RCM) reaction[11] prompted us to consider this alternate approach to the eight-membered lactone systems. In connection with our early work with the octalactins, we found that the position of certain stereocenters imposed conformational constraints on the hydroxy carboxylic acids that permitted successful lactonization in high yield.[7–9] It occurred to us that these same constraints might also favor a reactive diene conformation that affords oxocenes via RCM. We now report that this is indeed the case and describe the first example of this type of ring closure in a saturated, monocyclic eight-membered lactone system (Scheme 1).



Scheme 1. RCM with an acyclic diene ester precursor.

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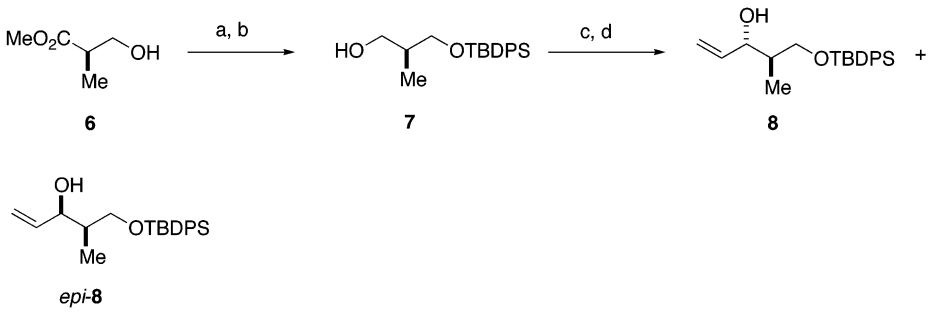
It should be noted that the oxocene **5**, which we have previously prepared by a much longer and more elaborate route,[7] also possesses significant antitumor activity.[10] We reported that this lactone partially blocks the polymerization of purified tubulin in vitro and may disrupt microtubule dynamics and therefore work as a novel mitotic spindle poison.

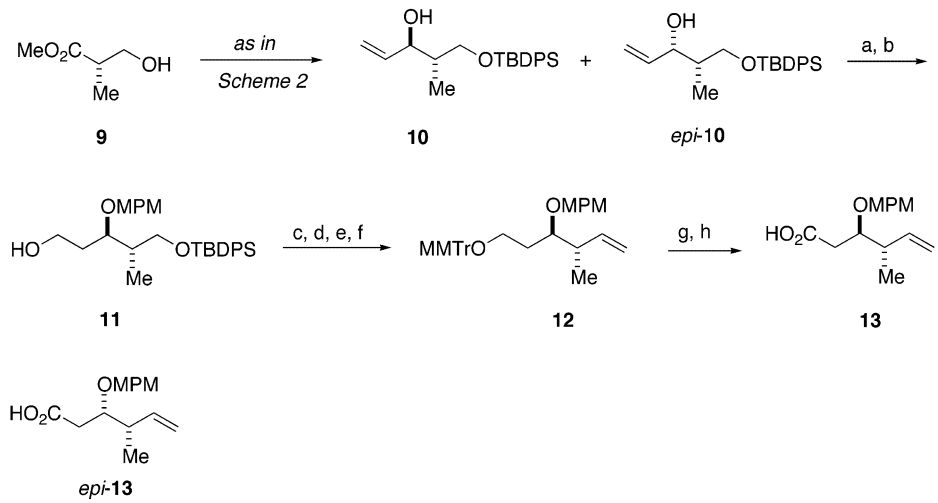
The synthesis of the alcohol and carboxylic acid components of the diene ester precursor to the oxocene **5** began with the methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates, respectively. Protection of **6** as its TBDPS ether followed by DIBAL reduction in diethyl ether at −78°C provided the alcohol **7** in 87% yield for two steps (Scheme 2).[12] Oxidation of **7** with Dess–Martin periodinane[13] was followed immediately by condensation with vinyl magnesium bromide in THF at −78°C and slow warming to room temperature to afford a 1:1 mixture of the diastereomers **8** and *epi*-**8** in 92% yield. Separation by flash chromatography (10% EtOAc: hexanes) gave the desired intermediate **8**.

The synthesis of the carboxylic acid unit began similarly with the Roche ester antipode **9**. The allylic alcohols **10** and *epi*-**10** were prepared in the same manner described above. The alcohol **10** was first protected as its MPM ether under Lewis acid catalysis conditions[14] and the olefin regioselectively hydroborated with 9-BBN and oxidized to give the desired primary alcohol **11** in 90% yield for the three steps (Scheme 3). Protection of the alcohol as its MMTr ether followed by fluoride-induced desilylation with TBAF in THF at 0°C gave the intermediate alcohol (92%), which was oxidized with Dess–Martin periodinane and the resulting crude aldehyde immediately subjected to Wittig olefination to afford the alkene **12** in 85% yield. Hydrolysis of the MMTr ether followed by Jones oxidation gave the desired carboxylic acid **13** (82%, two steps). By the same sequence *epi*-**13** was generated from *epi*-**10**.

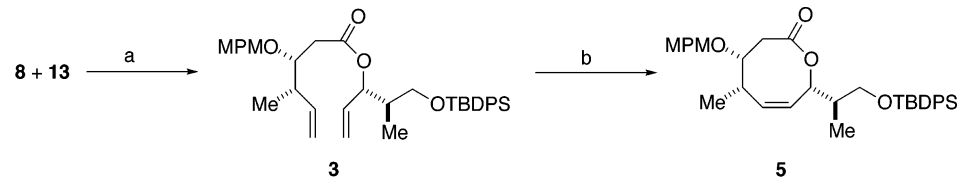
The components **8** and **13** were esterified with DCC and DMAP[15] to yield the diene ester **3** in 94% yield (Scheme 4). The stage was now set for the key ring closure. Gratifyingly, the diene underwent RCM cleanly in refluxing dichloromethane with 10–20 mol% Grubbs catalyst[16] to afford the desired oxocene **2** in 86% yield after 24 h. Eight-membered rings have long been considered the most difficult to construct from acyclic precursors.[17] It had been reported that the formation of eight-membered rings from acyclic precursors and their



Scheme 2. Synthesis of the C.6–C.9 segment. *Reagents and reaction conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h. (b) DIBAL, Et_2O, −78°C. (c) Dess–Martin periodinane, CH_2Cl_2, rt. (d) $(CH_2{=}CH)MgBr$, THF, −78°C to rt.



Scheme 3. Synthesis of the C.1–C.5 segment. *Reagents and reaction conditions*: (a) $MPMO(C{=}NH)CCl_3/BF_3{\cdot}OEt_2$/cyclohexane–$CH_2Cl_2$ (2:1)/0°C. (b) 9-BBN, THF, 65°C, then 30% H_2O_2, 15% NaOH, 0°C. (c) MMTrCl, Et_3N, CH_2Cl_2, rt. (d) TBAF, THF, rt. (e) Dess–Martin periodinane, CH_2Cl_2, rt. (f) $Ph_3P{=}CH_2$, THF, −78 to 0°C. (g) PPTS, MeOH:THF (1:1). (h) Jones reagent, acetone, 0°C.



Scheme 4. Synthesis of oxocene **5** via RCM. *Reagents and reaction conditions*: (a) DCC, DMAP, CH_2Cl_2, rt, 4 h. (b) Grubbs' catalyst, CH_2Cl_2, 40°C, 24 h.

formation via RCM was effective only with additional cyclic[18] or conformational constraints.[19] To our knowledge, the formation of **2** represents the first example of a successful RCM from a simple acyclic diene ester precursor. The stereocenters presumably restrict bond angles in a way that leads to a conformation that is favorably disposed toward RCM. The conformational effect of quaternary centers in controlling torsional angles, for example, has been reported.[20] Consistent with this view is the observation that other members of the octalactin series undergo RCM with varying degrees of difficulty. It was found for example that the lactone **14** (derived from **8** and *epi*-**13**) experienced ring closure only with difficulty, while the lactones **15** (from *epi*-**8** and **13**) and **16** (from *epi*-**8** and *epi*-**13**) formed readily via RCM (Table 1). These results are entirely consistent with that found for the same series in the lactonization reaction manifold.

As we have previously reported, reduction of the alkene in **5** could not be accomplished. This lack of reactivity presumably reflects severe non-bonded steric interactions. However, by elaborating the C.7 side chain in a manner previously described[7] to that required for octalactin (compound **17**, Scheme 5), we found that the olefin underwent smooth hydrogenation with Pearlman's catalyst and 1 atm of hydrogen. We ascribe this change in behavior to a more favorable conformation induced by intramolecular hydrogen bonding of the C.13 hydroxyl group with the lactone carbonyl. Finally, oxidative hydrolysis[21] of the MPM ether with DDQ gave (−)-octalactin A **1**, whose spectral characteristics were identical to the naturally derived material.

In conclusion, we have discovered that the synthesis of the key lactone core of the octalactins via RCM is a facile process. We believe this to be the first example of the synthesis of monocyclic eight-membered ring lactones by olefin metathesis chemistry. This method should find wide applicability to the synthesis of other medium-ring lactone systems also. The intermediate can be elaborated to give the octalactins by first extending the C.7 side chain followed by hydrogenation and removal of the remaining MPM protecting group. This novel approach is applicable to the preparation of a wide range of octalactin analogues as part of a program to elucidate the mode of action. The results of these efforts will be reported in due course.

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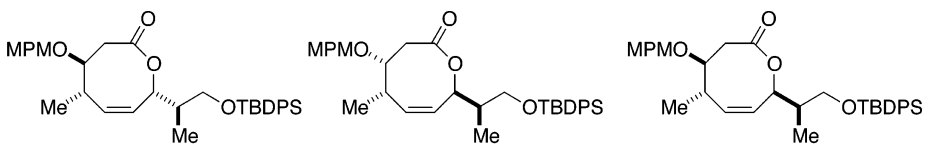
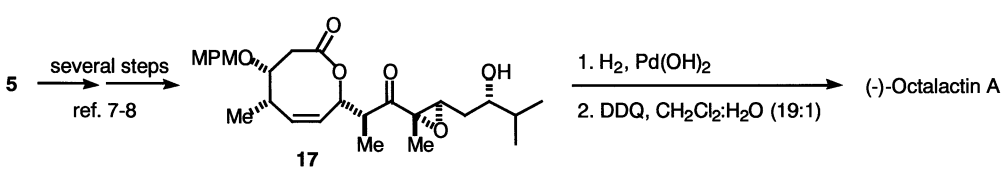
Table 1. Synthesis of octalactin epimers via RCM



Epimer	**14**	**15**	**16**
Reaction Time (h)	168	24	24
Yield (%)	20	84	90



Scheme 5. Synthesis of octalactin A.

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