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# Examination of the olefin–olefin ring closing metathesis to prepare Latrunculin B

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ABSTRACT

Three subunits of the potent actin polymerization inhibitor Latrunculin B were synthesized and assembled using olefin–olefin ring closing metathesis chemistry to close the 14-membered macrocycle. Metathesis reactions of substrates with various remote protecting group patterns were examined and gave 6,7-*E*-lactones as the preferred products.



Elegant work reported by Kashman[1] in the late 1970's and early 1980's documenting the isolation and characterization of Latrunculin A (**1**) and Latrunculin B (**2**) led to a body of synthetic work[2,3] to address this family's interesting chemical architecture as well as an effort to understand their unique biological mechanism (Fig. 1). The initial wave of synthetic work was dedicated to understanding the unique challenges that the new array of functional diversity embedded in this family of natural products might present in a total synthesis campaign; specifically (using Latrunculin B as an example), (1) construction of the 14-membered macrocyclic lactone with its specific set of olefin geometries; (2) control of the configuration (both relative and absolute) of the C8/C11 stereogenic centers; (3) control of the formation of the C15 stereogenic center; (4) conservation of the stereochemical integrity of the C16 stereogenic center throughout the creation of the C14/C15 bond and protection/deprotection strategies for the 2-thiazolidinone ring; and (5) formation of the tetrahydropyran ring system. These pioneering efforts of Kashman, White, and Smith led to the total synthesis of Latrunculins A and B and relied on the basic strategy of initial C13/14 bond formation using aldol reactions, ketalization to form the tetrahydropyran (THP), and macrocycle formation (Fig. 2). The combined efforts of these research groups were able to expertly define some of the synthetic limitations of these systems and paved the way to synthetic improvements and/or alternative construction strategies. The advent of ring closing metathesis technology has invited the application of this powerful new tool to the synthesis of many complex ring systems.[4] Accordingly, Fürstner[5] has successfully applied an alkyne/alkyne ring closing metathesis/semi-hydrogenation strategy to the total synthesis of Latrunculins A and B. Our interest in this family of natural

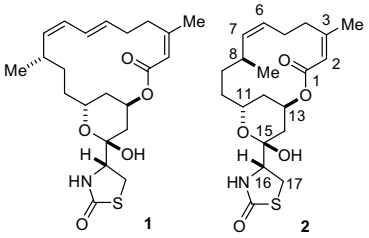


**Figure 1.** Latrunculins A and B.

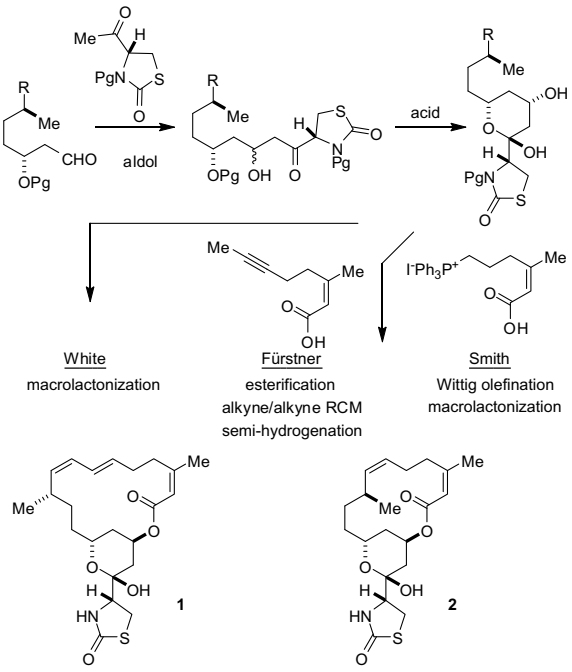


**Figure 2**

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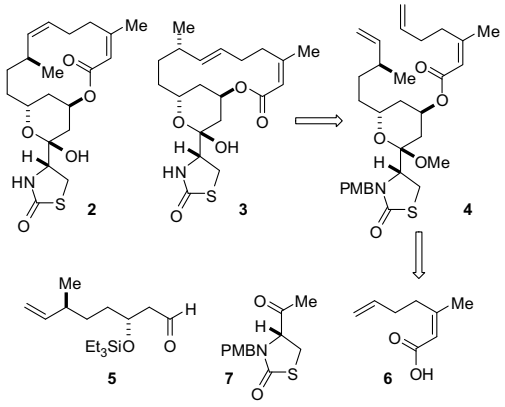


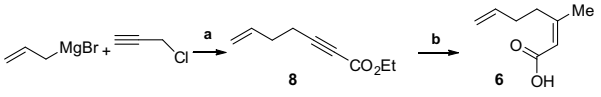
**Figure 3**

products was the discovery[6] that in addition to their extensive application as biochemical probes, Latrunculins A and B have also shown potential therapeutic value by exhibiting the ability to increase the aqueous humor outflow facility in normal tensive monkeys and may be useful for the treatment of glaucoma. As part of a program to evaluate the latrunculins as potential clinical candidates, we wanted to develop dependable methods to prepare gram quantities of Latrunculins A and B. Encouraged by the work of Fürstner, which demonstrated that a strained latrunculin macrocycle could be formed containing a C6/C7 acetylenic bond and that this bond could be reduced to the *Z*-olefin, we were interested in establishing what the stereochemical outcome would be for the direct olefin–olefin metathesis reaction of compound **4** (Fig. 3). A positive (*Z*-selective) outcome to the olefin–olefin metathesis reaction would allow for direct access to the C8 stereogenic center from the citronellene chiral pool and would avoid the unnecessary use of low molecular weight alkynes as intermediates. This report describes the preliminary results of this metathesis study and the total synthesis of Latrunculin B (**2**) and its 6,7-*E*-isomer (**3**).

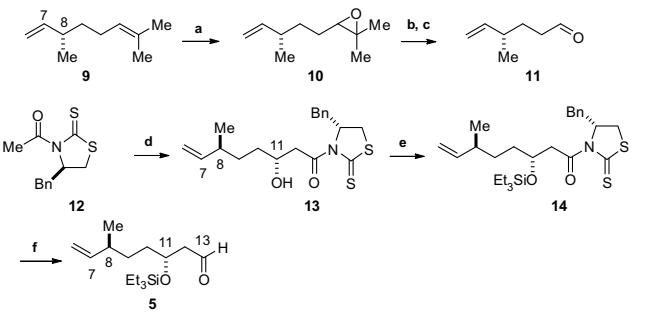
The retrosynthetic plan for the construction of metathesis precursor **4** (aldol condensation, THP ring formation, and intermolecular ester formation, Fig. 3) required the assembly of three subunits (**5**, **6**, and **7**) of fairly equal complexity. For the execution of this study, thiazolidinone ketone **7** was obtained using the published procedure of Smith.[2a] This decision obligated us to use the PMB protecting group for the thiazolidinone nitrogen and to accept the published challenges of removing this group late in the synthesis with less than ideal yields.

The dienic acid **6**, ultimately the C1/C6 portion of the macrocycle, was readily prepared as shown in Scheme 1. A one-pot substitution/deprotonation sequence with propargyl chloride and two equivalents of allyl magnesium bromide provided the magnesium acetylide intermediate,[7] which cleanly produced ynoic ester **8** upon addition to ethyl-chloroformate. Stereoselective addition of dimethyl cuprate followed by saponification of the resulting ester afforded acid **6** (see Scheme 1).

Critical to the synthesis of the C7/C13 aldehyde **5** was establishing the (*S*)-configuration for the C11-hydroxyl group. As in all other syntheses of the latrunculins, the configuration of the C11 stereo-



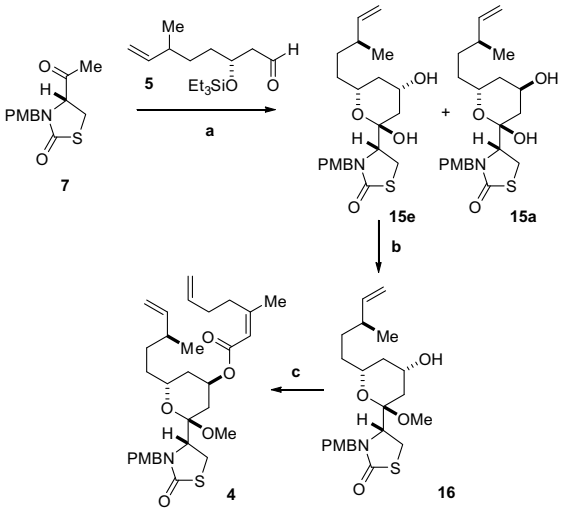
**Scheme 1.** Reagents and conditions: (a) $Et_2O$, −10 °C then $EtO_2CCl$, 40%; (b) $Me_2CuLi$, THF, −78 °C; LiOH, MeOH, $H_2O$, 92%.



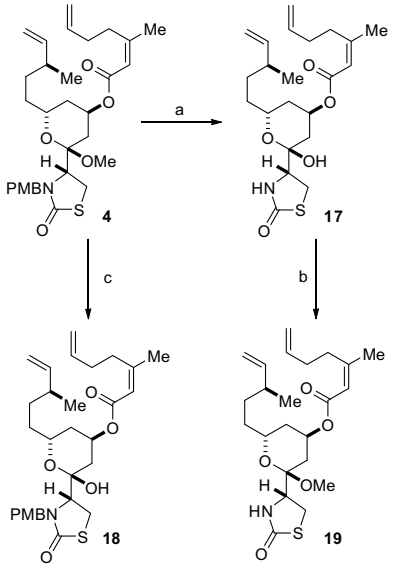
**Scheme 2.** Reagents and conditions: (a) $CH_2Cl_2$, $NaHCO_3$, $CH_3CO_3H$, 0 °C; (b) *p*-TSA, THF, $H_2O$, rt; (c) $NaHCO_3$, $H_2O$, $CH_2Cl_2$, $NaIO_4$, rt, 54% for 3 steps; (d) **12**, $TiCl_4$, $(i\text{-Pr})_2NEt$, $CH_2Cl_2$, −78 °C then **11**, 76%; (e) DMF, $Et_3SiCl$, $(i\text{-Pr})_2NEt$ , 0 °C, 98%; (f) $(i\text{-Bu})_2AlH$, toluene, −78 °C, 92%.

genic center is used to establish the relative and absolute configurations of the C13 and C15 tetrahydropyran centers. Our plan was to control this C11 configuration using an auxiliary-mediated acetate aldol of aldehyde **11** with thiazolidinethione **12.**[8] Aldehyde **11** could conveniently be produced from readily available citronellene (see Scheme 2). Selective epoxidation of (*S*)-citronellene with peracetic acid followed by hydrolysis of crude epoxide **10** and oxidative cleavage provided aldehyde **11**.[9] Thiazolidinethione **12**, readily available from D-phenylalanine[10] or commercially available in kilogram quantities, was treated with titanium tetrachloride (1.05 equiv) and diisopropyl-ethylamine (1.10 equiv) at −78 °C for 1 h to generate the corresponding enolate. Addition of aldehyde **11** (1.00 equiv) delivered alcohol **13** in 76% isolated yield. The diastereomeric ratio generated in this sequence was typically >7:1 and the minor isomer could easily be removed by flash chromatography. Protection of the secondary alcohol as its triethylsilyl ether and reductive removal of the chiral thiazolidinethione auxiliary afforded aldehyde **5** directly.

With the three required fragments in hand, their assembly into metathesis precursor **4** was undertaken (Scheme 3). Following the established precedent of Fürstner and Smith, it was anticipated that a reaction sequence entailing a Lewis acid mediated-aldol addition followed by an acid catalyzed deprotection/cyclization/equilibration step would lead to hemiketal **15e** enriched in **15e**. Fortuitously, formation of the chlorotitanium enolate of ketone **7**



**Scheme 3.** Reagents and conditions: (a) $TiCl_4$, $(i\text{-Pr})_2NEt$, $CH_2Cl_2$, −20 °C then **5**, 60% for **15a** and **15e**; (b) CSA, MeOH, toluene, 88%; (c) 2,6-lutidine, $(CF_3SO_2)_2O$, $CH_2Cl_2$, −15 °C; **6**, NaH, 15-Crown-5, THF, rt, 61% for 2 steps.




**Scheme 4.** Reagents and conditions: (a) CAN, $CH_3CN$, $H_2O$, 64%; (b) PTSA, $CH_3OH$, 91%; (c) 1 N HCl, $CH_3CN$, 57%.

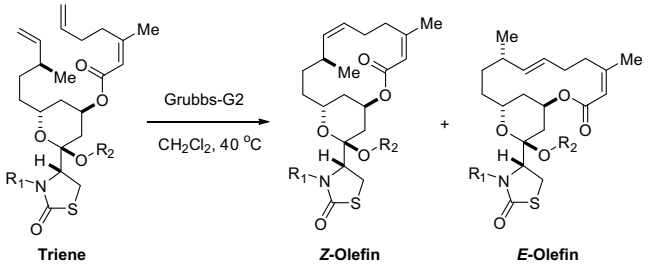



**Figure 4**

(1.05 equiv $TiCl_4$, 1.00 equiv DIPEA, $CH_2Cl_2$) at −20 °C followed by the addition of aldehyde **5** resulted in the direct production of a 1:1 mixture of **15a** and **15e** in 60% overall yield. Use of the slightly less stable triethylsilyl protecting group led to carbon-carbon bond formation, 1,5-silyl transfer, ring closure, and subsequent loss of the protecting group. Compounds **15a** and **15e** were readily separated by flash chromatography. For the purpose of completing our investigation, equatorial alcohol **15e** was converted to methyl ketal **16** by stirring in mildly acidic methanol. Formation of the C13 equatorial triflate with its ensuing displacement with the sodium salt of acid **6** gave axial ester **4**.

As part of this study, we were also interested in examining the effects of different protecting group patterns on the results of the metathesis cyclization. Several ring closing metathesis approaches to build medium-sized macrolactones have been published in the literature.[11] These previous studies reveal that a mixture of *Z*- and *E*-isomers are often obtained using this approach. However, in certain circumstances the *E*/*Z* selectivity could often be controlled by changing the catalyst, the reaction conditions, and/or the protecting group substitution pattern. Toward this end, compound **4** could be completely deprotected by treatment with ceric ammonium nitrate (CAN) in aqueous acetonitrile to provide **17**. Subsequently, the hemiketal of **17** could be converted to the methyl ketal **19** by exposure to mild acid in methanol. Compound **4** could also be converted to the N-protected precursor **18** by extended exposure to aqueous acid (see Scheme 4).

Exposure of the completely protected olefin–olefin metathesis substrate **4** in refluxing dichloromethane to the milder first generation Grubbs catalyst led to no ring closing products. However, treatment with the stronger second generation Grubbs catalyst (G2) provided a 60% isolated yield of a 22:78 mixture of *Z*/*E* macrolactones, respectively (see Fig. 4 and Table 1). It was also observed that the *Z*/*E* ratio did not change during the complete time course of the cyclization. Cyclization of the partially protected substrates **18** (natural hemiketal functionality) and **19** (natural thiazolidinone functionality) in dichloromethane provided *E*-dienyl lactones as the major products (39:61 and 25:75 *Z*/*E* ratios, respectively). Ring closing metathesis of the 'natural' acyclic substrate **17** gave a 33:67 mixture of Latrunculin B (**2**) and its *E*-isomer (**3**), see Table 1. Analytically pure **2** and **3** were obtained by HPLC separation of the crude reaction products generated from **17**, or alternatively from pure lactone precursors **20** and **21** using the established CAN deprotection conditions published by Smith. Interestingly, when **2** and **3** were independently re-exposed to a higher loading (50 mol %) of the second generation Grubbs catalyst in dichloromethane, isomerization of the C6/C7 olefin geometry was not detected. This observation suggests that the generally accepted reversible mechanism of RCM reaction is not involved in the chemistry of substrate **17**. The lack of reactivity of **2** and **3** under ring opening metathesis conditions might be attributed to the rigid conformation of the 14-membered lactone and the steric hindrance of the neighboring methyl group. Kashman has previously observed that the C6/C7 olefin of Latrunculin B was inert to vigorous hydrogenation conditions.[1b]

**Table 1**

| $R_1$ | $R_2$ | Triene | *Z*-olefin | *E*-olefin | Ratio (*Z*:*E*) | Conversion (%) |
|---|---|---|---|---|---|---|
| PMB | Me | 4 | 20 | 21 | 22:78 | 100 |
| PMB | H | 18 | 22 | 23 | 39:61 | 100 |
| H | Me | 19 | 24 | 25 | 25:75 | 97 |
| H | H | 17 | 2 | 3 | 33:67 | 96 |

In summary, an evaluation of the potential to easily prepare Latrunculin B from a direct olefin–olefin ring closing metathesis reaction has been completed. The major product of the ring closing metathesis reaction of several substrates with various remote protecting group patterns was the 6,7-*E*-geometry. A convergent synthesis of metathesis precursor **4** has been developed from readily available starting materials. Based on the current results, the selectivity of the ring closure to form Latrunculin B is under kinetic control.

## Acknowledgments

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## Supplementary data

Experimental procedures as well as $^1H$ and $^{13}C$ NMR spectra for all new compounds and Latrunculin B. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.144.

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