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# Ruthenium-catalyzed olefin metathesis after tetra-*n*-butylammonium fluoride-mediated desilylation

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ABSTRACT

One-pot procedures expedite organic synthesis but pose challenges in that many reagents must be compatible with each other. We discovered that the presence of $^{n}Bu_4NF$ hindered ruthenium-catalyzed olefin metathesis when $^{n}Bu_4NF$-mediated desilylation and olefin metathesis were performed in one pot. This problem could be solved by the addition of $(TMS)_2O$ to remove fluoride anions in order to facilitate the ruthenium-catalyzed olefin metathesis.



Small molecule inhibitors of pre-mRNA splicing are an emerging class of molecules that can be used as chemical probes and drug candidates.[1–9] Direct inhibitors of the spliceosome known to date are pladienolides,[4,10–12] herboxidiene,[13–15] and FR901464[2,16–18] and its analogs.[3,19,20] While many of these splicing inhibitors are widely used in biochemical studies,[1–5,21–23] their drug development lags behind. A pladienolide analog was advanced to phase I studies,[6] but none of the FR901464 analogs advanced to the same level. In our laboratory, we reported an in vivo study of meayamycins; these FR901464 analogs, despite high potency in vitro, showed poor pharmacokinetics in mice.[8] In order to design meayamycin analogs that are active in vivo, the absorption, distribution, metabolism, and excretion (ADME) of meayamycins must be elucidated.

A classic approach to the ADME studies of small molecules requires a highly sensitive method to detect the parent compound and its derivatives. The most common method is to label the parent compound with a radioisotope. However, organic synthesis of radioactive compounds imposes a challenge in that purification steps must be minimized.

Our previously reported synthetic scheme for meayamycin B is shown in Scheme 1a.[19,20] Briefly, alkene **1** was subjected to oxymercuration-reduction conditions to form tetrahydrofuran **4** in 76% yield. The subsequent deprotection of the triethylsilyl (TES) group using tetra-*n*-butylammonium fluoride (TBAF) provided alcohol **5** in 97% yield. Finally, the cross-olefin metathesis of this alcohol with diene **6** in the presence of nitro-Grela reagent **Ru-1** yielded meayamycin B in 44% yield.

We reasoned that the replacement of the hydrogen atom in the conversion of **2** into **3** with tritium should allow us to incorporate the radioactive atom in **4** and eventually in meayamycin B. In order to develop a one-pot procedure for the conversion of alkene **1** into meayamycin B to minimize purification steps, the alkene was treated with $Hg(OAc)_2$ and $NaBH_4$ (Scheme 1b). *para*-Nitrobenzaldehyde was added to the resulting mixture to trap excess hydride. Subsequently, TBAF was added to furnish alcohol **5** without complications. Finally, diene **6** and **Ru-1** were added in this order in the same flask; however, the final cross-coupling reaction did not take place.

This problem raised a question about whether the presence of any of the preexisting molecules could interfere with the final step. Previously, Caulton and co-workers reported that treatment of a ruthenium dimer $[Ru(P^{i}Pr_3)_2HCl]_2$ with $Me_4NF$ yields $[Ru(P^{i}Pr_3)_2HF]_2$.[24] We hypothesized that fluoride ions from the use of TBAF in excess might interfere with the metathesis reaction through the possible displacement of chloride of **Ru-1** with fluoride. To test our hypothesis, we compared the ring closing metathesis of the model substrate **7**[25] in the presence of **Ru-1**. Indeed, the addition of TBAF reduced the yield of **8** from 78% (Table 1, entry 1) to 15% (entry 2), supporting our hypothesis. Previous investigation of the effects of halogens in the olefin metathesis suggested that the catalyst's activities decrease as the halogens are changed from Cl to Br to I, due to the increase in *trans* influence and the size of halogens.[26] Based on these results we would expect that fluorine on the ruthenium-based catalyst would have an increase in the

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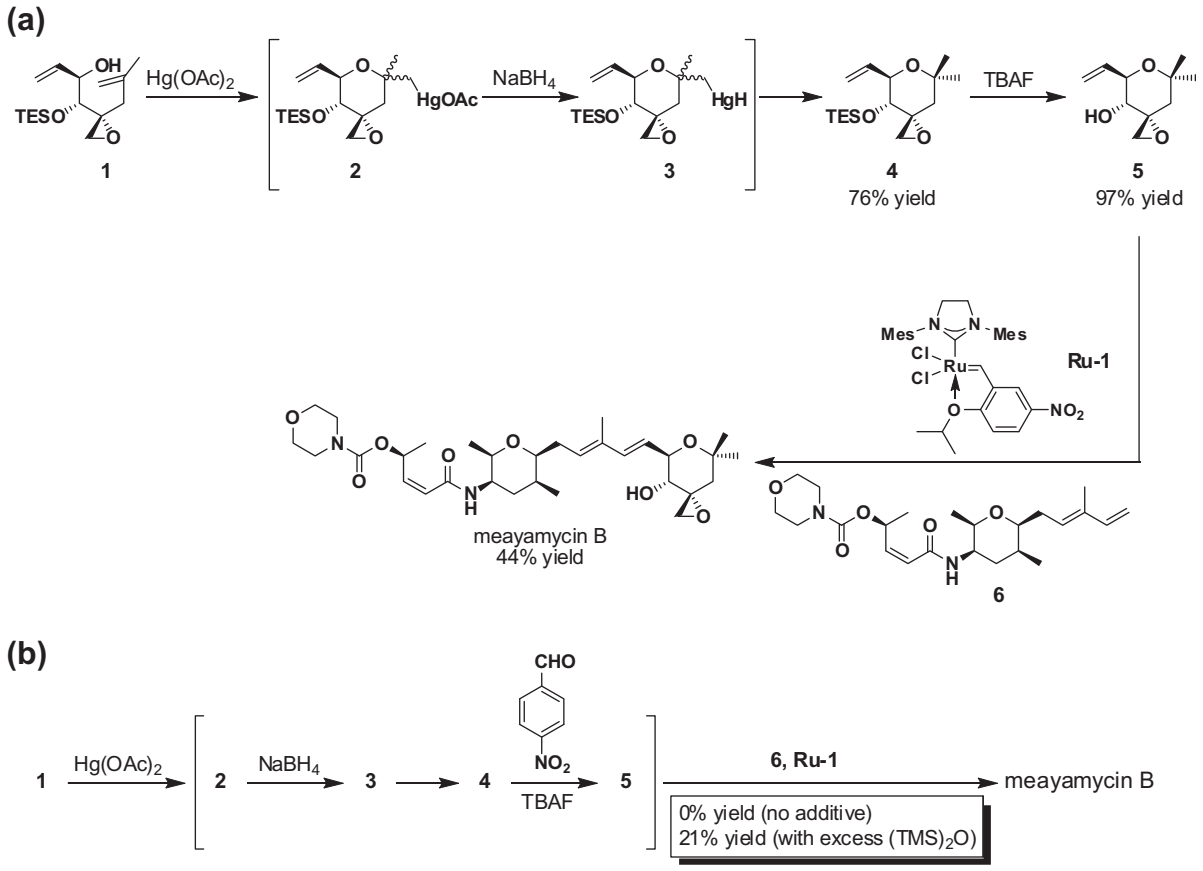
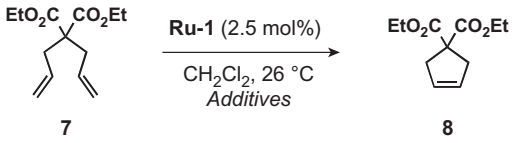



**Scheme 1.** (a) Original protocol to prepare meayamycin B. (b) Preparation of meayamycin B from **1** using the one-pot procedure.

**Table 1**
Ring closing metathesis of the model substrate **7**




| Entry | Additives | | Yield[a] |
|---|---|---|---|
| | TBAF (equiv) | $(TMS)_2O$ (equiv) | |
| 1 | 0 | 0 | 78%[b] |
| 2 | 1 | 0 | 15%[c] |
| 3 | 1 | 1.2 | quant. |

[a] Yields were determined by $^1H$ NMR spectroscopic analysis of the reaction mixture that contained PhCHO as an internal standard.
[b] Yield taken from Ref. 25.
[c] **7** was the remaining 85%.

catalyst's activity; however, this was not the case in our experiment. Meanwhile, recent theoretical investigations suggested that a σ-withdrawing group would decrease the catalyst's activity.[27] Since fluorine atoms are highly electronegative, our results are in agreement with this suggestion.

In order to couple alcohol **5** and diene **6** after the TBAF-promoted deprotection of the TES group in one pot, it became necessary to remove fluoride ions. To this end, we treated the mixture of TBAF and the model substrate **7** with ditrimethylsilyl ether $(TMS)_2O$[28–31] with the anticipation that the fluoride ions would be trapped as fluorotrimethysilane (bp 16 °C), which can be readily removed due to its high volatility. As anticipated, the ring-closing metathesis proceeded to form cyclopentene **8** in quantitative yield (entry 3). With this protocol in hand, we were able to convert alkene **1** into meayamycin B in one pot by adding $(TMS)_2O$ in the final step as determined by HPLC and $^1H$ NMR spectroscopic analyses (Scheme 1b and Fig. 1).

In conclusion, we discovered that fluoride anions interfere with ruthenium-catalyzed olefin metathesis reactions. Subsequently, we developed a protocol to effect the ruthenium-catalyzed olefin cross-metathesis after TBAF was used in the same flask. This study allowed us to establish potential access to tritium-labeled meayamycin B with one purification step. The use of $(TMS)_2O$ may find other applications in which olefin metathesis is carried out immediately after the use of TBAF.

## Protocol to prepare meayamycin B from alcohol 1

Alcohol **1** (10 mg, 34 μmol) and THF (0.3 mL) were placed in a 10-mL round-bottomed flask. The flask was cooled to 0 °C, and $Hg(OAc)_2$ (13 mg, 41 μmol) was added. The resulting solution was stirred under a nitrogen atmosphere and slowly warmed to 26 °C over 5 h. The mixture was then cooled to −78 °C, then $NaBH_4$ (1.3 mg, 34 μmol) and $Et_3B$ (1.0 M in THF, 37 μL, 37 μmol) were added. The mixture was stirred while warming to −40 °C over 3.5 h, followed by the addition of *para*-nitrobenzaldehyde (51 mg, 340 μmol). After this step, all of the experiments were carried out in an air atmosphere. The mixture was warmed to 26 °C and stirred at the same temperature for 2.5 h. The mixture was then cooled to 0 °C, and TBAF (1.0 M in THF, 60 μL, 60 μmol) was added at the same temperature, followed by warming to 26 °C over 4 h. Afterward, $(TMS)_2O$ (110 mg, 860 μmol) was added, and the mixture was stirred at the same temperature for 11 h. The mixture was then treated with a pH 7 buffer (1.23 M potassium phosphate,

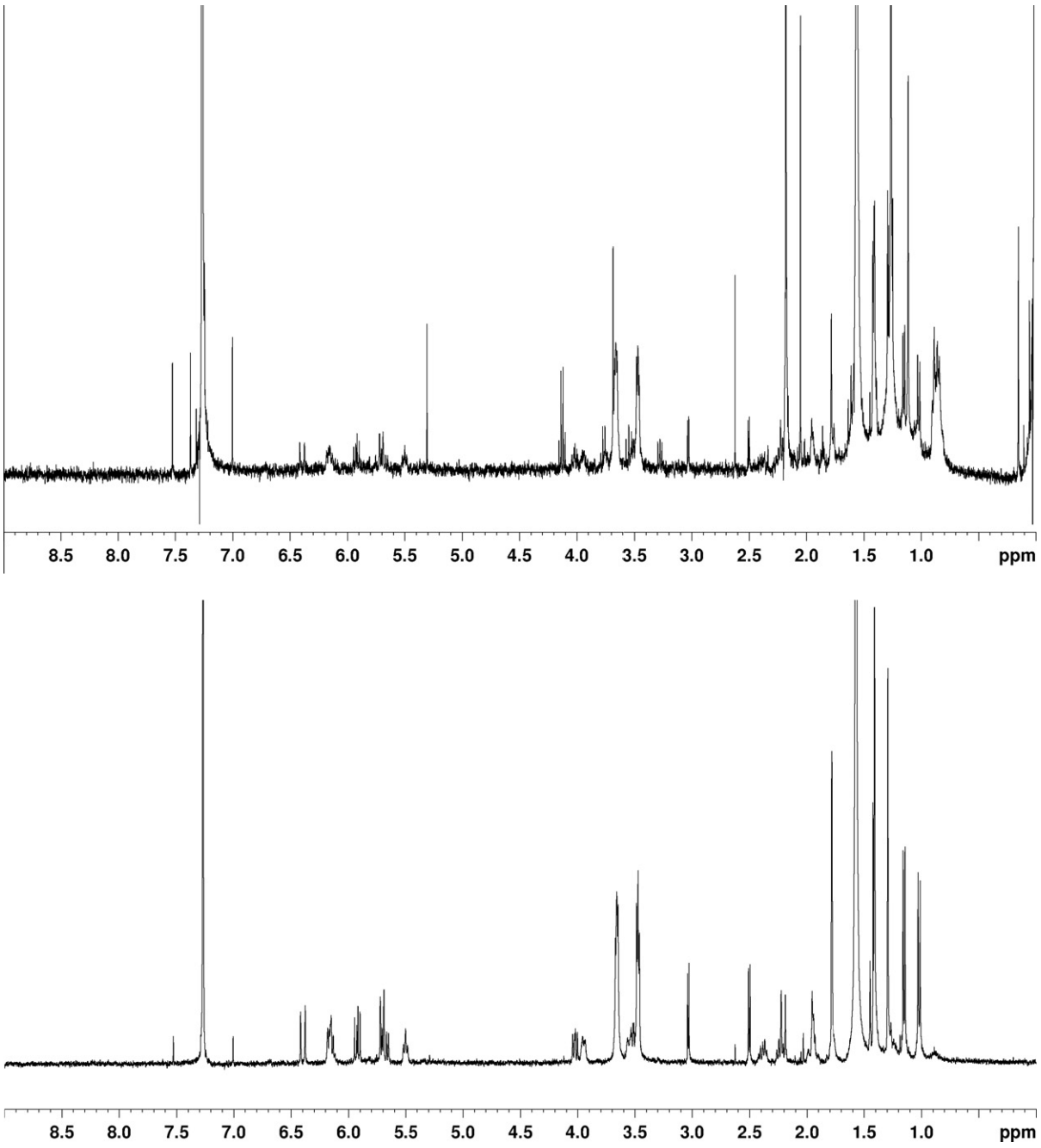



**Figure 1.** $^{1}$H NMR spectrum of meayamycin B from the one-pot protocol (top) and authentic meayamycin B (bottom).

0.25 mL), a solution of diene **6** (5 mg, 10 μmol) in 1,2-dichloroethane (0.1 mL), and **Ru-1** (4 mg, 6 μmol). The mixture was stirred in a 45 °C oil bath for 27 h, then passed through a short plug of silica gel. The filtrate was concentrated in vacuo, and the resulting residue was initially purified by preparative TLC (80% EtOAc in hexanes), then preparative HPLC (absorption at 232 nm. Elution conditions: flow rate = 10.0 mL/min, gradient: 60 → 100% MeCN in water over 15 min, then 10 min with 100% MeCN. Column: Agilent Prep-C18 column 21.2 × 150 mm, 5 μm. Retention time = 12.9 min) to furnish meayamycin B (1.2 mg, 21% yield).

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