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A Short Synthesis of the C1-C7 Fragment of Methymycin by Ring-Closing Olefin Metathesis

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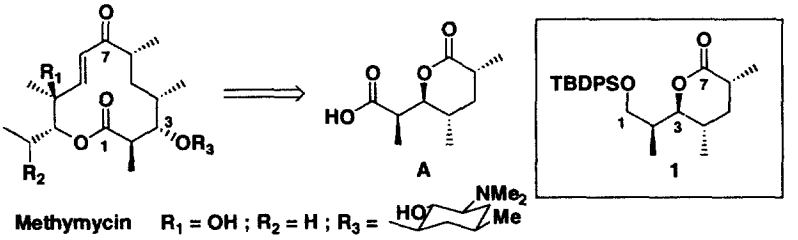
Abstract : The synthesis of the C1-C7 fragment of methymycin was achieved via a ring-closing olefin metathesis employing Grubb's catalyst in the presence of $Ti(OiPr)_4$.

The Prelog-Djerassi lactonic acid **A**[1] was first isolated as an oxidative degradation product of several macrolide antibiotics such as methymycin, neomethymycin, narbomycin and picromycin. It has emerged as a key building block in several total syntheses of these macrolides and related polypropionate antibiotics[1].



We wish to describe a new synthesis of the C1-C7 fragment of methymycin in the form of the protected Prelog-Djerassi lactone alcohol **1**, by using Grubbs catalyst in the presence of $Ti(OiPr)_4$, a binary catalyst system[2] that has already been successfully applied to the preparation of α,β-unsaturated γ- and δ-lactones by ring-closing metathesis[3].

Treatment of the Roush crotylboration product **2**[4] with acryloyl chloride (iPr_2NEt, DMAP, CH_2Cl_2, -78°C) provided the acrylate ester **3** that was exposed to Grubb's catalyst (10 mol%) in the presence of $Ti(OiPr_4)$ (0.3 equiv). These conditions afforded the δ-lactone **4**, which was hydrogenated (H_2, $Pd(OH)_2$, AcOEt) into **5** with an overall yield of 70% (two steps)[5]. Alkylation of lactone **5** by methyl iodide (LDA, HMPA, THF, -78°C) provided a 1:1 mixture of the desired alkylated lactone **1** and of its 2-epimer **6**. Equilibration of this mixture

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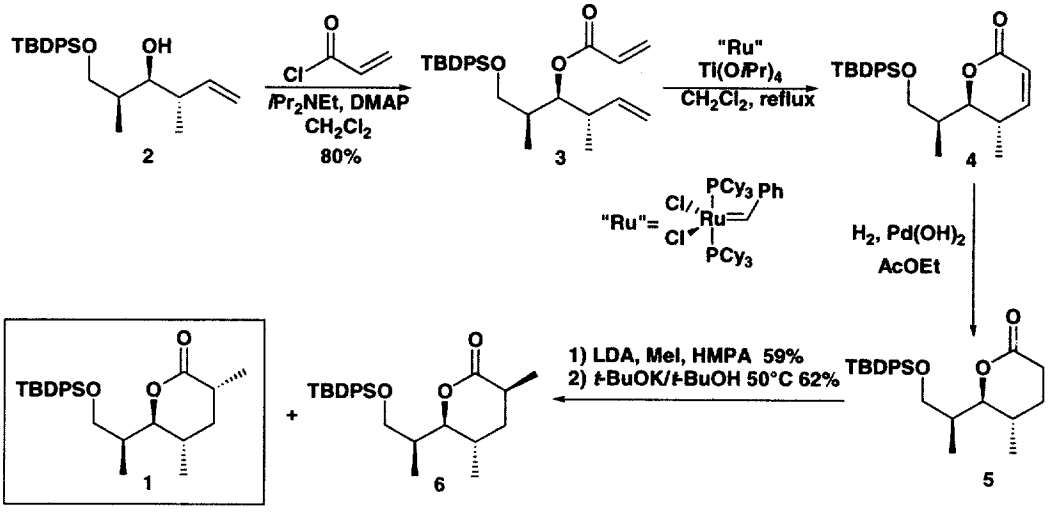
(*t*BuOK, *t*BuOH, 50°C, 16h)[6] gave a 4:1 ratio of **1** and **6** (62% yield) that were separable by chromatography (Scheme).

The protected Prelog-Djerassi lactone-alcohol **1** was obtained in 5 steps from compound **2** with an overall yield of 20%.



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References and Notes

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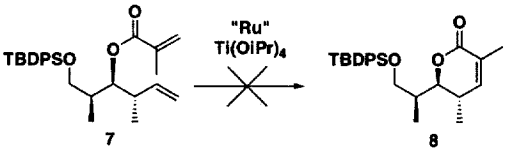
[5] We have to point out that when unsaturated ester **7** was treated with Grubbs'catalyst in the presence of $Ti(OiPr_4)$, the expected unsaturated lactone **8** was not obtained :



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