Cross metathesis / Tandem *N*-Acyliminium Ion Cyclization Approach toward the Synthesis of Grandisine A

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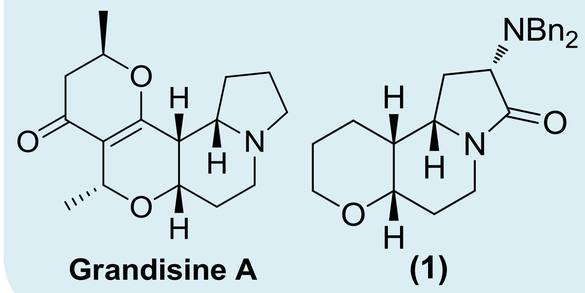
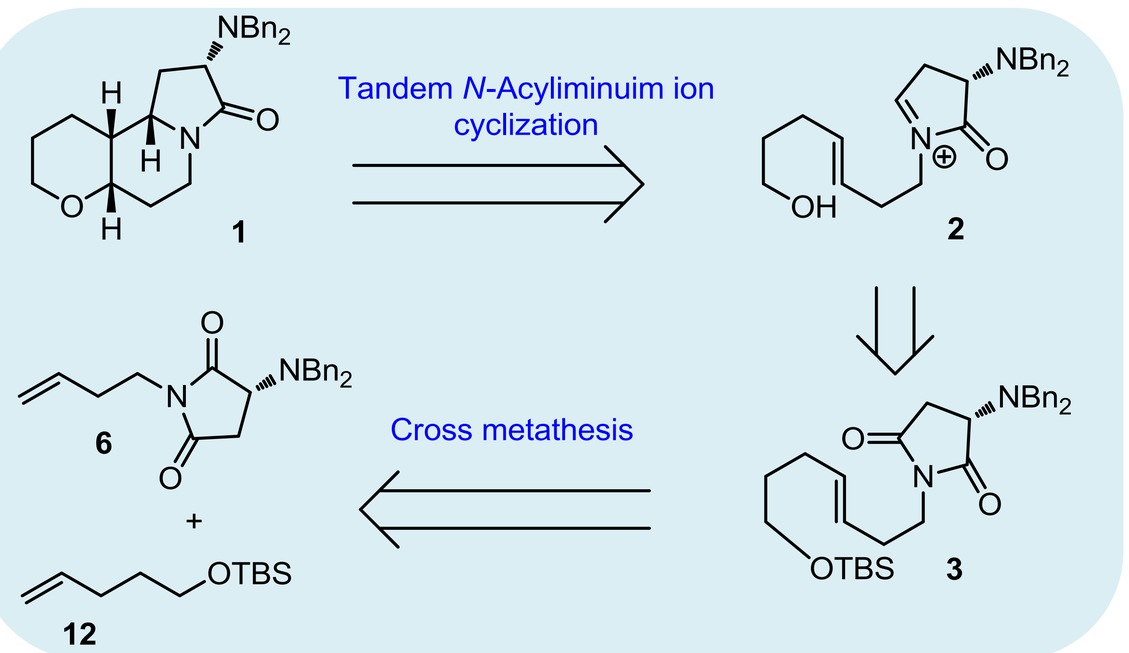
Abstract

Model studies for the synthesis of grandisine A were carried out featuring cross metathesis and tandem *N*-acyliminium ion cyclization. Cross metathesis of TBS ether of 4-penten-1-ol and an imide derived from 3-butenylamine and L-aspartic acid, and subsequent carbonyl reduction and desilylationresulted in the corresponding tethered hydroxyalkene-hydroxyl-β-lactam, which is the substrate for tandem *N*-acyliminium ion cyclization. Treatment of this lactam with TMSOTf resulted in a diastereoselective cyclization to afford the tricyclic product **(1)** with a pyranoindolizidine ring system of grandisine A. The stereogenic center bearing the protected amino group derived from L-aspartic acid served as the stereocontrol element and gave the diastereomeric products in non-racemic form.

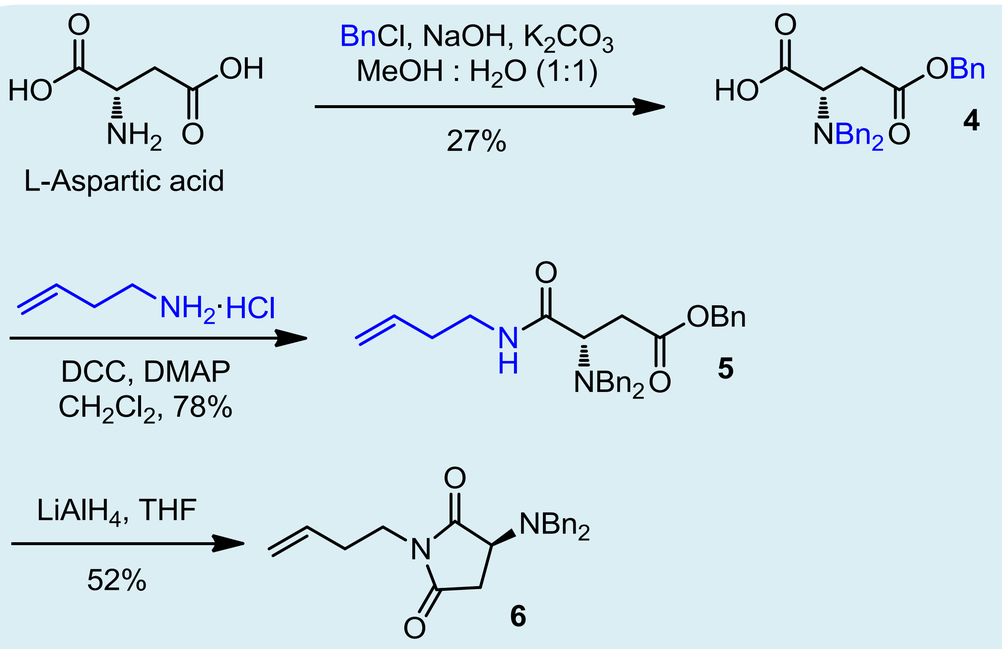


Retrosynthetic Analysis



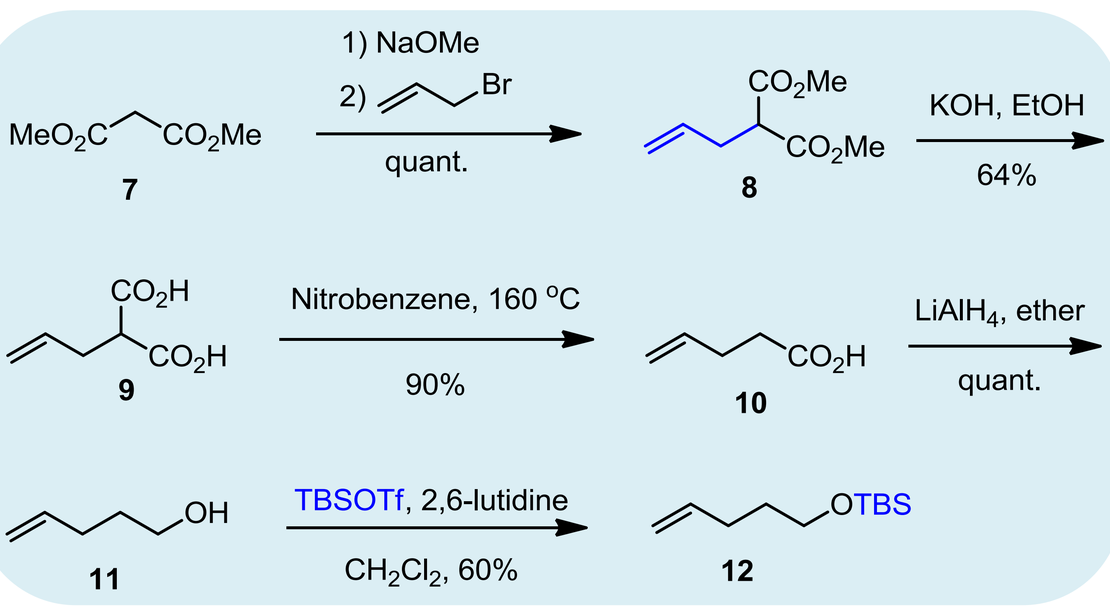
The most important key step of this work is the model study of tricyclic **1** would be derived from Tandem *N*-acyliminium ion cyclization of intermediate **2**. Another step is cross metathesis of imide **6** and TBS ether **12**.

Synthesis of imide 6



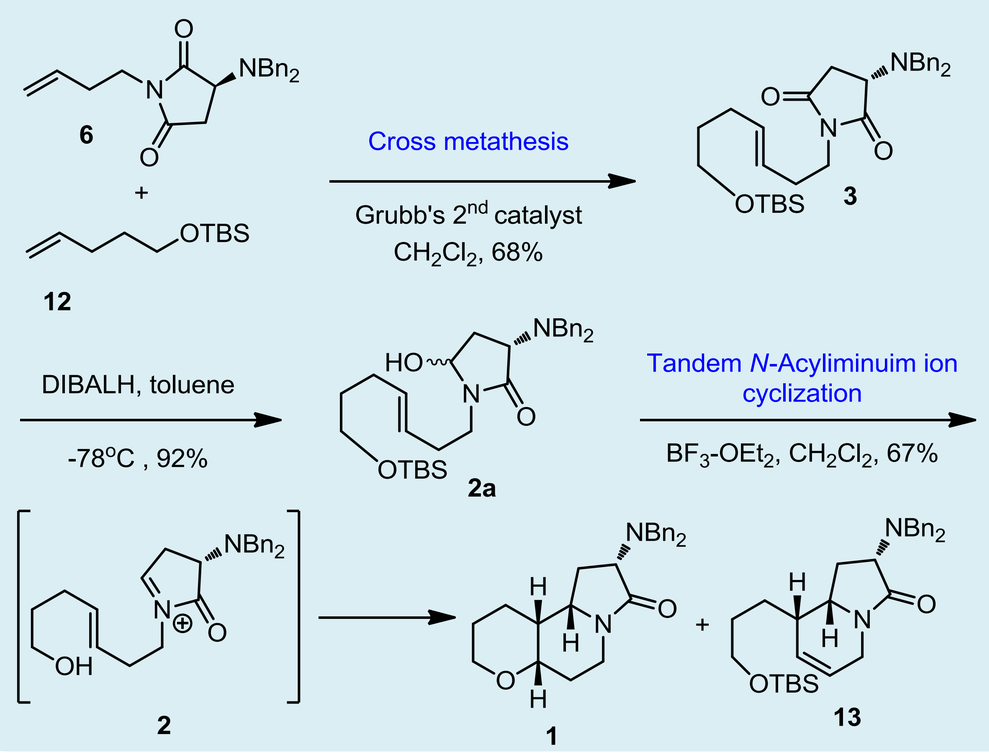
A commercially available L-aspartic acid was converted to benzyl L-aspartate **4**. Amide formation of 3-butylamine and benzyl L-aspartate **4** gave amide **5** which was converted to imide **6** upon treatment with $LiAlH_4$.

Synthesis of TBS ether 12



Dimethyl malonate **7** was converted to allyl dimethyl malonate **8**. Hydrolysis of allyl dimethyl malonate **8** gave diacid **9** which was decarboxylated to 4-pentenoic acid **10**. 4-Pentenoic acid **10** was converted to 4-pentenol **11** upon treatment with LiAlH4. 4-pentenol **11** was protected with TBS to give 4-penten-1-ol **12**.

Synthesis of tricyclic 1



Cross metathesis of imide **6** with TBS-protected 4-penten-1-ol **12** gave tethered 4-hepten-1-ol imide **3** which was selectively reduced with DIBALH to give hydroxylactam **2a**. Upon treatment of **2a** with BF_3OEt_2 gave the desired product **1** along with the bicyclic indolizidine **13**.

References

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2. Kuntiyong, P.; Piboonsrinakara, N.; Bunrod, P.; Namborisut, D.; Akkarasamiyo, S.; Songthammawat, P.; Hemmara, C.; Buaphan, A.; Kongkathip, B. *Heterocycles* **2014**, *89*, 437-452.

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