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Synthesis of lupinacidins A and B via sequential cycloaddition–double elimination

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ABSTRACT

The first synthesis of lupinacidins A and B, tumor cell invasion inhibitors of microbial origin, has been achieved in four operational steps from 3-methoxy-2-methyl-2-cyclohexenone via the Diels–Alder cycloaddition of a conjugated cyclohexadiene derivative with a juglone-derived sulfinyl quinone followed by sequential elimination of a sulfenic acid and ethylene to afford protected forms of the target molecules.

In the course of screening for tumor cell invasion inhibitors of microbial origin, Igarashi and co-workers discovered two novel anthraquinones, lupinacidins A and B, from the culture broth of the endophytic actinomycete *Micromonospora lupini* Lupac 08 isolated from the root nodules of *Lupinus angustifolius* and determined their structures to be **1** and **2**, respectively, on the basis of extensive spectroscopic analyses (Fig. 1).[1] Lupinacidins A and B exhibited significant inhibitory effects on the invasion of murine colon 26-L5 carcinoma cells with IC_{50} values of 0.07 μg/mL and 0.3 μg/mL, respectively, while showing low cytotoxicity against the same cells (IC_{50} >10 μg/mL, WST-1 staining method). The selective *anti*-invasive property of **1** and **2** suggests their potential as practical carcinostatic agents with few side effects. From a structural viewpoint, **1** and **2** are characterized by the presence of a 1,3-dihydroxy-2,4-dialkyl benzene unit embedded in the anthraquinone nucleus, which is unprecedented as a structural motif found in naturally occurring anthraquinones excluding anthraquinone dimmers (bianthraquinones).[2,3] The unique substitution pattern and the medicinally important biological activity of **1** and **2** prompted our synthetic efforts toward lupinacidins A and B. We describe herein the first total synthesis of lupinacidins A (**1**) and B (**2**) through a concise cycloaddition–double elimination sequence.

Our retrosynthetic analysis of **1** and **2** is shown in Scheme 1. We envisaged that the anthraquinone derivatives **1** and **2** would be obtainable by the Diels–Alder cycloaddition reaction between a properly substituted naphthoquinone derivative **4** and a conju-

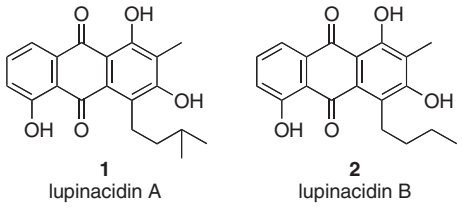
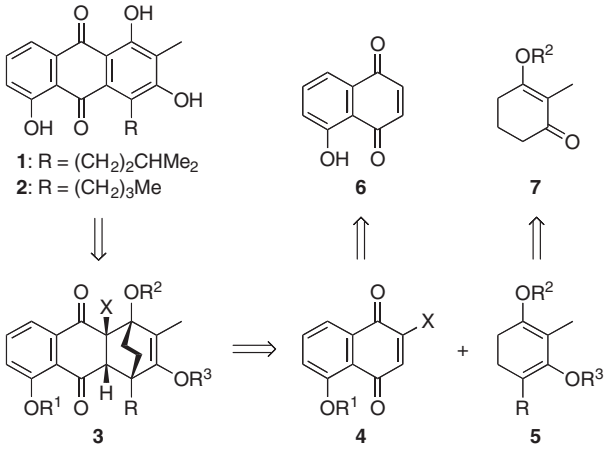


Figure 1. Structures of lupinacidins A (**1**) and B (**2**).



Scheme 1. Retrosynthetic analysis of **1** and **2**.

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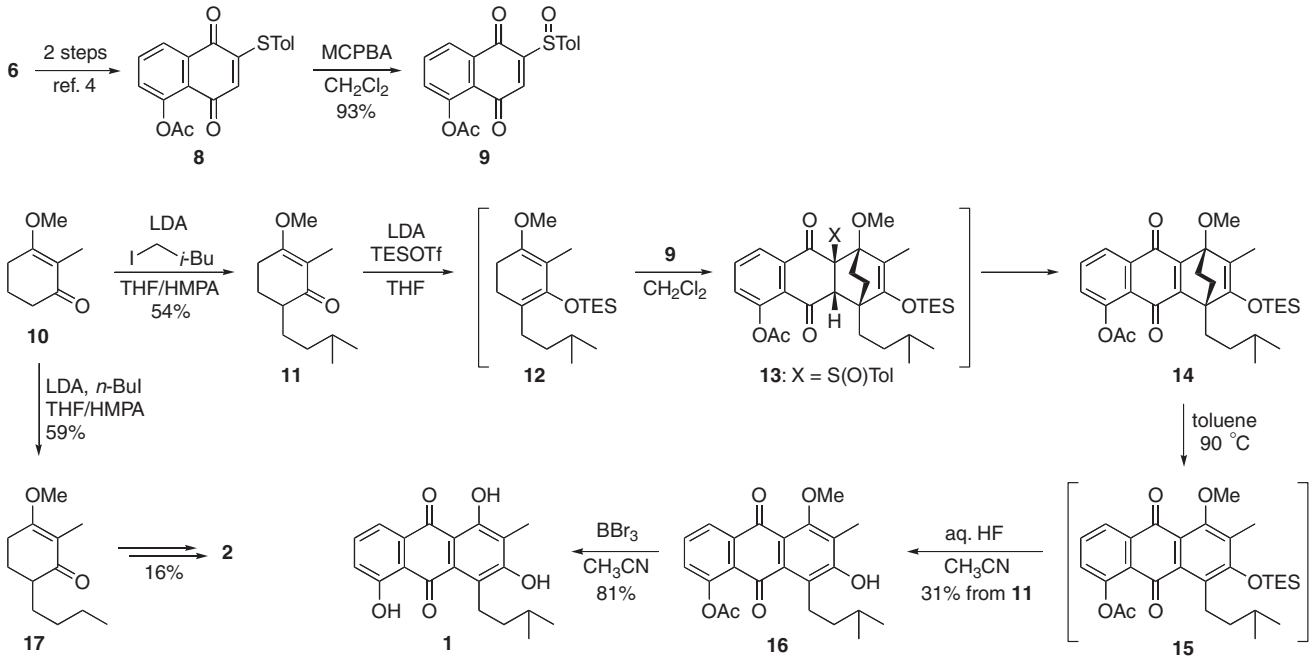

Scheme 2. Synthesis of **1** and **2**.

gated cyclohexadiene **5** followed by *syn*-elimination of HX from the resulting cycloadduct **3** and a subsequent retro-Diels–Alder reaction of the elimination product which would release ethylene to form the fully substituted benzene ring. The dienophile **4** in the Diels–Alder reaction should be prepared from a commercially available compound **6** (juglone) by regioselective installation of an appropriate leaving group (X), while the enophile **5** would be readily accessible from substituted cyclohexenone **7** via its alkylation followed by enol etherification.

According to the synthetic plan, a known juglone derivative **8**, prepared in two steps from **6** by acetylation and regioselective installation of a tolylthio group,[4] was oxidized with MCPBA to afford dienophile **9**. The *p*-toluenesulfinyl group of **9** was chosen to effect the Diels–Alder reaction in a regioselective manner and also as a leaving group in the following elimination step (Scheme 2).[5] The enophile (**12**) for the synthesis of lupinacidin A (**1**) was prepared by alkylation of the known cyclohexenone derivative **10** with 1-iodo-3-methylbutane and by subsequent TES enol etherification of the resulting alkylation product **11**.[6] Due to its instability, the diene **12** was subjected in situ to the Diels–Alder reaction with **9** to give cycloadduct **13**, which spontaneously liberated *p*-toluenesulfenic acid under the reaction conditions via a *syn*-elimination reaction, affording tetracyclic intermediate **14** as the only detectable regioisomer.[5d] After being roughly purified by silica gel column chromatography,[7] **14** was heated in toluene to give anthraquinone **15** with the evolution of ethylene.[5d,6] The TES group of **15** was then removed by directly treating the reaction mixture containing **15** with a solution of aqueous hydrofluoric acid in acetonitrile to furnish **16** in a two-pot operation and 31% overall yield from **11**. Finally, the treatment of **16** with BBr_3 in acetonitrile and subsequent workup with aqueous $NaHCO_3$ brought about the deprotection of the methoxy and acetoxy groups, giving lupinacidin A (**1**) (mp 235–237 °C, lit.[1] mp 234–238 °C) in 81% yield. The other target molecule **2** (mp 201–203 °C, lit.[1] mp 201–203 °C) was also synthesized in the same manner as described for **1** except that the initial alkylation of **10** was conducted with 1-iodobutane instead of 1-iodo-3-methylbutane. The ^1H and ^{13}C NMR spectra of **1** and **2** were identical with those of natural lupinacidins A and B, respectively.

In conclusion, the four-step syntheses of lupinacidins A and B, featuring the Diels–Alder reaction of the suitably substituted diene **12** with the quinone dienophile **9** possessing a *p*-tolylsulfinyl group as a regiochemistry-controlling auxiliary followed by the sequential elimination of *p*-tolylsulfenic and ethylene, were achieved from the readily available starting material **10** in 14% and 9% overall yields, respectively. Synthesis of a variety of analogs of **1** and **2** as well as their structure–activity relationship studies is now underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization data, and NMR spectra for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.121.

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