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Stereoselective synthesis of the decahydrofluorene core of the hirsutellones

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ABSTRACT

A stereoselective synthesis of the decahydrofluorene core of the hirsutellones was accomplished in eight steps and in 43% overall yield. The key step of the synthesis is the highly stereoselective intramolecular Diels–Alder cyclization of the siloxacyclopentene-constrained tetraene **1**.

The hirsutellones are a family of polyketides isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594 that display potent antitubercular activity, with minimum inhibitory concentrations against *Mycobacterium tuberculosis* $H_{37}H_{37}Ra$ ranging from 0.78 to 3.125 μg/mL.[1,2] The interesting polycyclic structures consisting of a decahydrofluorene core with a 12- or 13-membered *para*-cyclophane, as well as the antitubercular activity make the hirsutellones intriguing synthetic targets (Fig. 1).[3]

We reasoned that the tricyclic core common to the hirsutellones could be assembled by an intramolecular Diels–Alder (IMDA) cycloaddition[4] of tetraene **1**, utilizing a siloxacyclopentene-constrained dienophile to ensure proper stereochemical control of the *trans*-fused C(14) ring juncture relative to the C(13)-hydroxyl group in **2** (Fig. 2).[5,6] Control of the hydroxyl stereochemistry at this position is often difficult to achieve in IMDA reactions.[4,7] Thus, implementation of this strategy would enable us to control all of the stereocenters present in the decahydrofluorene core while simultaneously introducing functionality at C(13) and C(15) that could be used to append the macrocycle en route to the natural products.

The synthesis of the common hirsutellone core **2** commenced with the synthesis of triene aldehyde **9** as presented in Scheme 1. The enantioselective Diels–Alder reaction of commercially available (*E*,*E*)-hexa-2,4-dien-1-ol (**3**) with methyl acrylate was performed in the presence of the reagent generated from (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL), Me_2Zn, and MeMgBr as described by Ward.[8] This reaction provided lactone **4** in 95% yield and with 96% ee. Hydrogenation of **4** over 10% Pd/C gave the saturated lactone **5** (99% yield), which was then reduced to lactol **6** using diisobutylaluminum hydride (DIBAL) in CH_2Cl_2 at −78 °C. Wittig olefination of lactol **6** using the ylide generated by treatment of trimethylphosphonium salt **7**[9] with potassium hexamethyldisilazide in THF at 0 °C then gave trienol **8a** with no detectable (*Z*)-olefin at the newly formed double bond, but with approximately 15% of the *E*,*Z* isomer **8b** which could not be separated from **8a**.[9,10] Trienol **8a** was then oxidized under Parikh–Doering conditions,[11] followed by treatment with potassium carbonate in methanol, which led to smooth epimerization of the aldehyde and provided exclusively **9** with the desired equatorial carboxaldehyde stereochemistry.

Aldehyde **9** was further elaborated to triene **1** as summarized in Scheme 2. Addition of the lithium acetylide generated by treatment of propiolaldehyde acetal **10**[12] with *n*-BuLi to a solution of **9** in 1:1 THF and *tert*-butyl methyl ether (TBME) at 0 °C, with

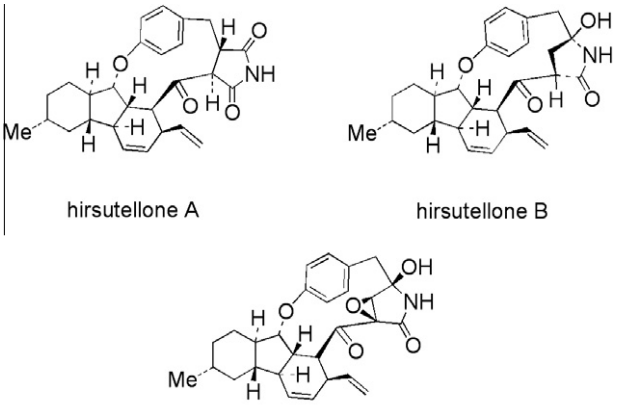

Figure 1. Structures of hirsutellones A–C.

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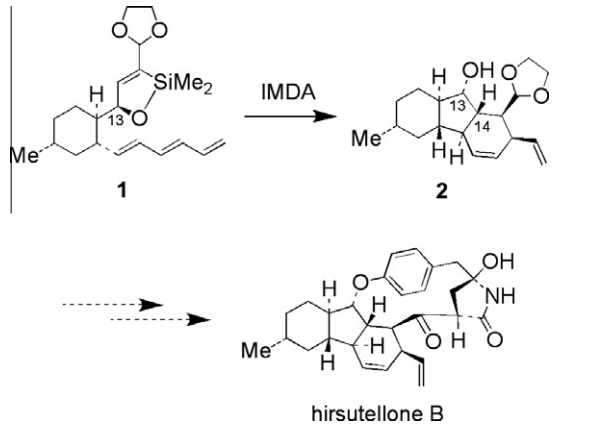
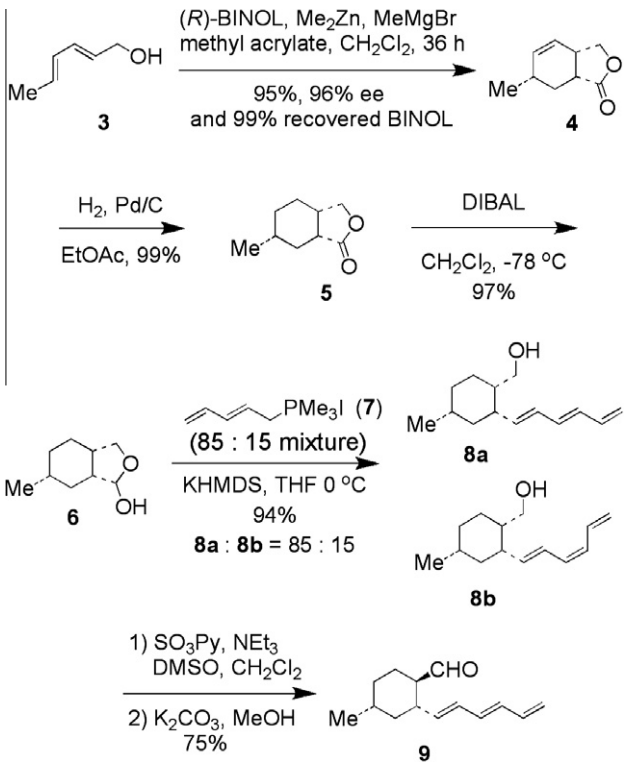
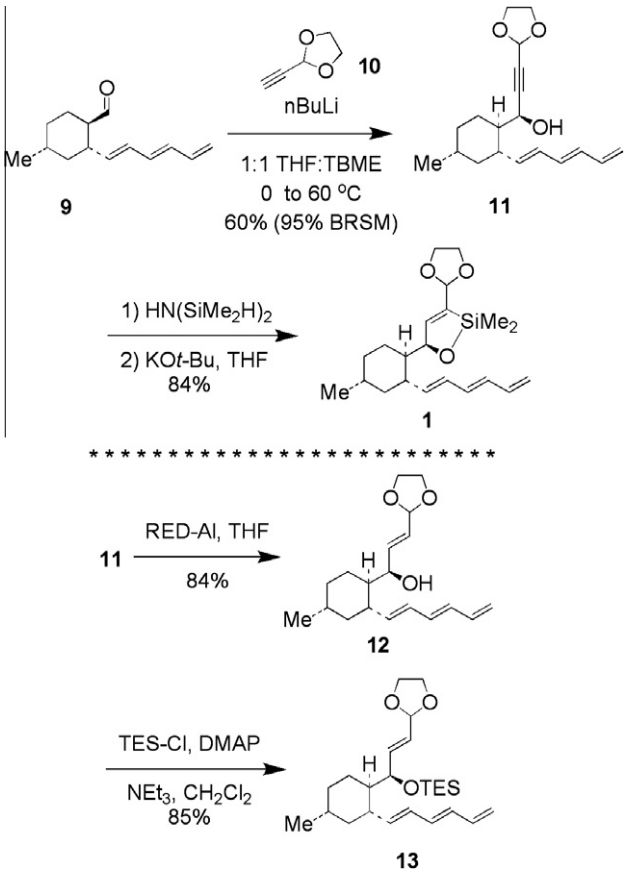


Figure 2. IMDA cycloaddition strategy for synthesis of the hirsutellone core.



Scheme 1. Synthesis of triene aldehyde **9**.



Scheme 2. Synthesis of tetraenes **1** and **13**.

warming to 60 °C, provided propargyl alcohol **11** in 60% yield with excellent Felkin-Anh diastereoselectivity (>95:5 dr). Hydrosilylation of propargyl alcohol **11** was accomplished using the procedure developed by Lee.[13] Thus, treatment of **11** with tetramethyldisilizane to give the silyl ether followed by addition of potassium *tert*-butoxide in THF gave siloxacyclopentene **1** in 84% yield. Because we had anticipated at the outset that the diastereoselectivity of the key IMDA reaction might be poor if the siloxacyclopentene strategy was not utilized,[4,7] we also synthesized the non-constrained triene **13** for use in comparative IMDA reactions. Therefore, hydroalumination of propargyl alcohol **11** with sodium bis-(2-methoxyethoxy)-aluminumhydride (RED-Al®) followed by standard workup gave allylic alcohol **12** (84%) which was then protected as the triethylsilyl ether teraene **13** (Scheme 2).

Cycloaddition reactions of **1** and **13** were performed by treatment of a solution of the triene in CH_2Cl_2 at −78 °C with trimethylsilyltriflate followed by warming to −20 °C.[14] These reactions undoubtedly proceed via oxonium ion activated dienophiles, generated by TMS-OTf promoted ring opening of the cyclic acetals.[14] After the cycloadditions were complete, the crude reaction mixtures were immediately subjected to desilylation conditions (TBAF in THF) to facilitate product isolation and purification.[15,16]

The cycloaddition of **1** and subsequent proteodesilylation of the crude cycloadduct gave decahydrofluorene **2** in excellent yield and as a single diastereomer as determined by ^{1}H NMR analysis of the crude reaction mixture. The stereochemistry of **2** was assigned by using a combination of coupling constant analysis and NOE studies, as summarized in Scheme 3.

In contrast, the Lewis acid promoted cyclization of the unconstrained tetraene **13** was less selective, giving an inseparable 85:15 mixture of cycloadduct diastereomers, among which **2** predominated, following deprotection of the silyl ether (Scheme 3). Analysis of the key coupling constants identified for **14** enabled us to identify the minor diastereomer in this reaction as decahydrofluorene **14**, which is epimeric to **2** at the vinyl substituent (in particular $J_{f,g}$ = 11.8 Hz in **14** vs 6 Hz in **2**; see Scheme 3). This compound presumably arose from the IMDA cyclization of the minor (*E*,*Z*)-tetraene present in triene **13** (see Scheme 4). This raises the question, why was the analogous cycloadduct not realized in the IMDA cyclization of (*Z*)-**1** (triene **1** used in Scheme 3 was also an 85:15 mixture of *E* and *Z* olefin isomers, deriving from **7**).[9]

Examination of transition states available for the IMDA reactions of **1** and **13** are presented in Schemes 4 and 5. Examination of **TS13A** and **TS13B** in Scheme 5 for the IMDA cyclization of the (*E*)- and (*Z*)-isomers of **13** indicates that the (*Z*)-isomer can readily cyclize via transition state **TS13B**. In contrast, **TS1B** in Scheme 5 for