Natural Product Synthesis

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Total Synthesis of Hopeahainol A and Hopeanol**

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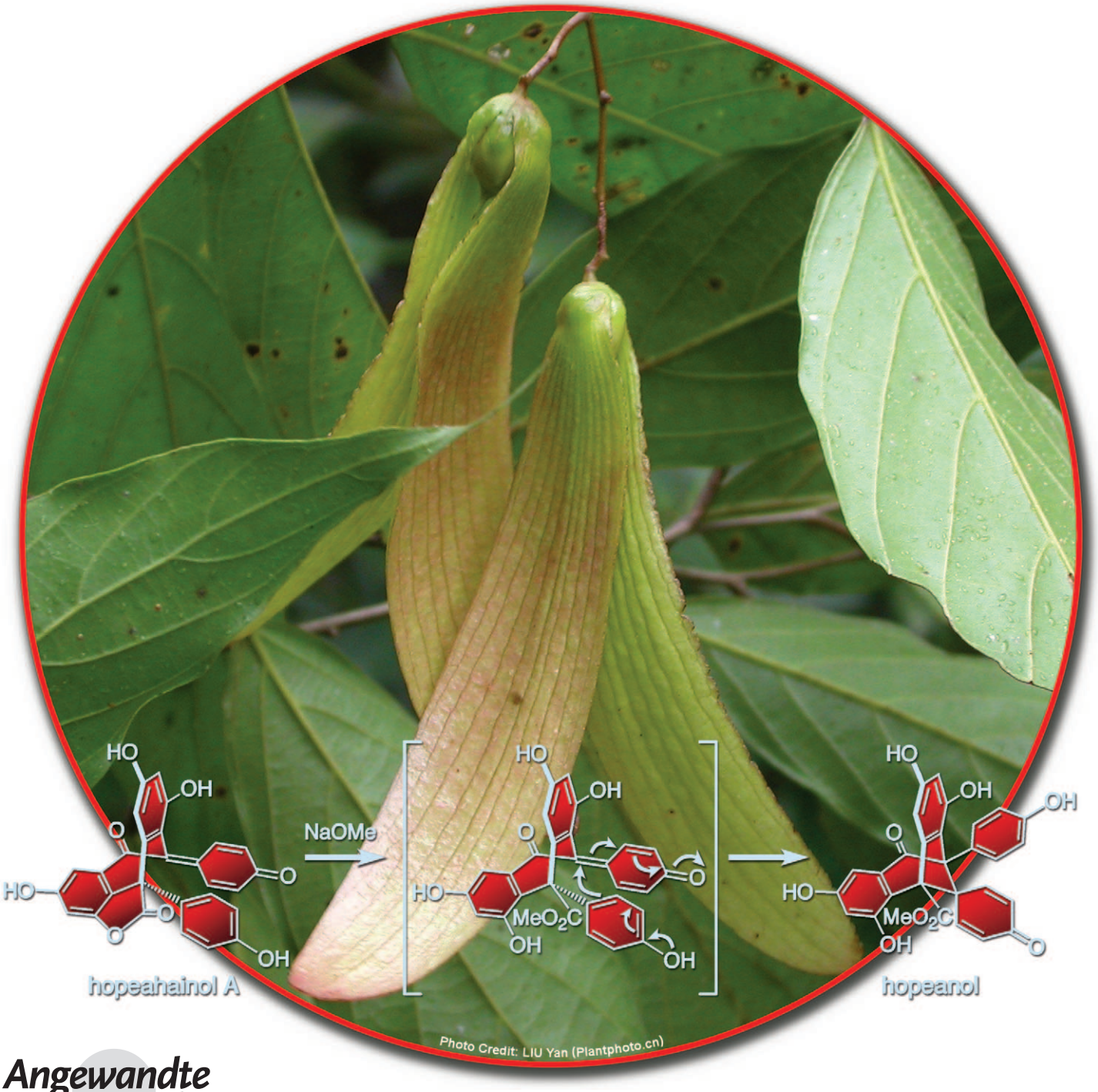
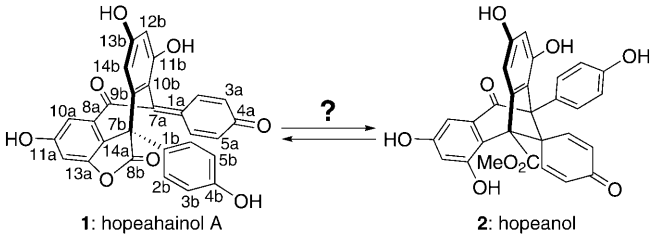


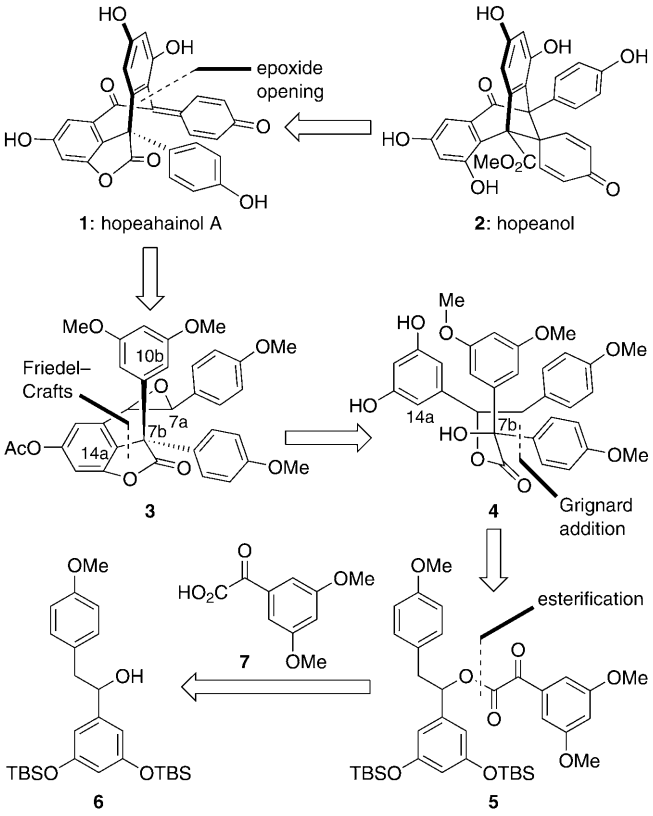
The polyphenols are a large and growing class of secondary metabolites with diverse molecular structures and biological activities.[1] Resveratrol and its oligomeric descendents are particularly interesting owing to their unique structures and important physiological properties as evidenced by the recent surge of research on their chemistry and biology.[2] Hopeahainol A[3] (**1**, Scheme 1) and hopeanol[3,4] (**2**, Scheme 1) are



Scheme 1. Molecular structures of hopeahainol A (**1**) and hopeanol (**2**).

two recently disclosed molecules, each thought to be biosynthetically derived from two molecules of resveratrol. Although closely related in structure and biosynthetic origin, their promising biological properties are diverse. Originally isolated from *Hopea exalata*[4] and subsequently from *Hopea hainanensis*,[3] hopeanol (**2**) is a cytotoxic agent which is active against a variety of tumor cells, including KB cells ($IC_{50} = 0.52$ μM). Hopeahainol A (**1**), on the other hand, was isolated from *Hopea hainanensis*[3] and exhibited inhibitory activity against acetylcholinesterase ($IC_{50} = 4.33$ μM), an enzyme implicated and exploited for the treatment of Alzheimer's disease. The novel molecular architecture of these natural products, coupled with their impressive biological properties, prompted us to undertake their synthesis. Herein we report their first total synthesis, in racemic form, through a short and efficient strategy that involves a series of cascade reactions and a number of unusual skeletal rearrangements.

Scheme 2 shows the retrosynthetic analysis that led to the design of the synthetic strategy toward both hopeahainol A (**1**) and hopeanol (**2**), in that order. Despite a hypothesis that



Scheme 2. Retrosynthetic analysis of hopeahainol A (**1**) and hopeanol (**2**). TBS = *tert*-butyldimethylsilyl, Ac = acetyl.

defined hopeanol (**2**) as the biosynthetic precursor to hopeahainol A (**1**),[3] we envisioned this transformation to be reversible under suitable conditions. With this expectation, we targeted hopeahainol A (**1**) first through precursors **3** (epoxide ring-opening and formation of C7a–C10b, hopeahainol A numbering) and then **4** (Friedel–Crafts-type reaction to link C14a and C7b). Hydroxy ester precursor **4** was traced back to simple building blocks through the indicated disconnections (Grignard reaction and esterification) as shown in Scheme 2.

Scheme 3 summarizes the assembly of epoxide **3** and its conversion into hydroxy γ-lactone **15**. Thus, benzylic alcohol **6** (prepared by the reaction of 3,5-bis(OTBS)phenyl lithium[5] and *p*-methoxyphenylacetaldehyde) was esterified with 3,5-dimethoxy-α-oxophenylacetic acid (**7**)[6] (DCC, DMAP, 95% yield) and afforded keto ester **5**. Reaction of the latter with *p*-methoxyphenylmagnesium bromide furnished the bis-TBS derivative **8** (mixture of diastereoisomers, ca. 1:1 d.r.), whose silyl ethers were cleaved through the action of TBAF, and led to hydroxy ester **4** (mixture of diastereoisomers, ca. 1:1 d.r.) in 79% overall yield. Exposure of the tetracyclic substrate **4** to

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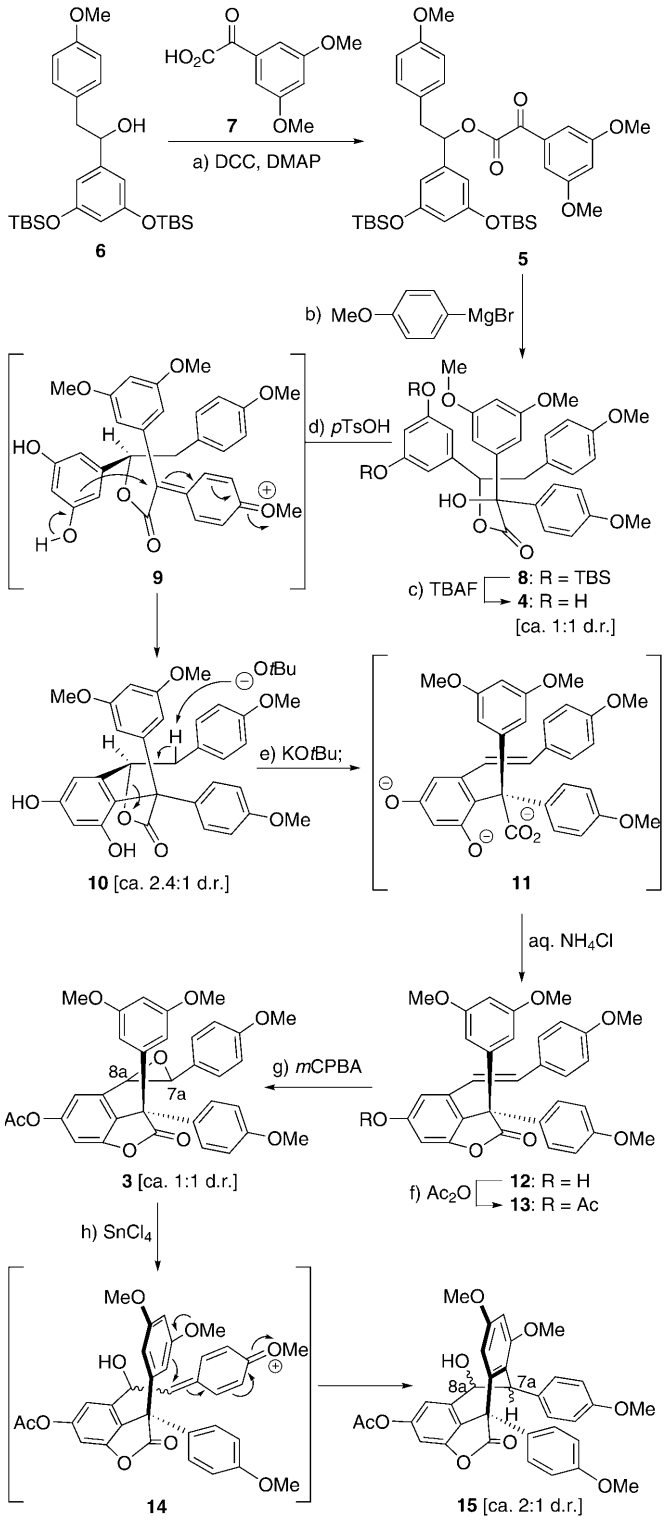
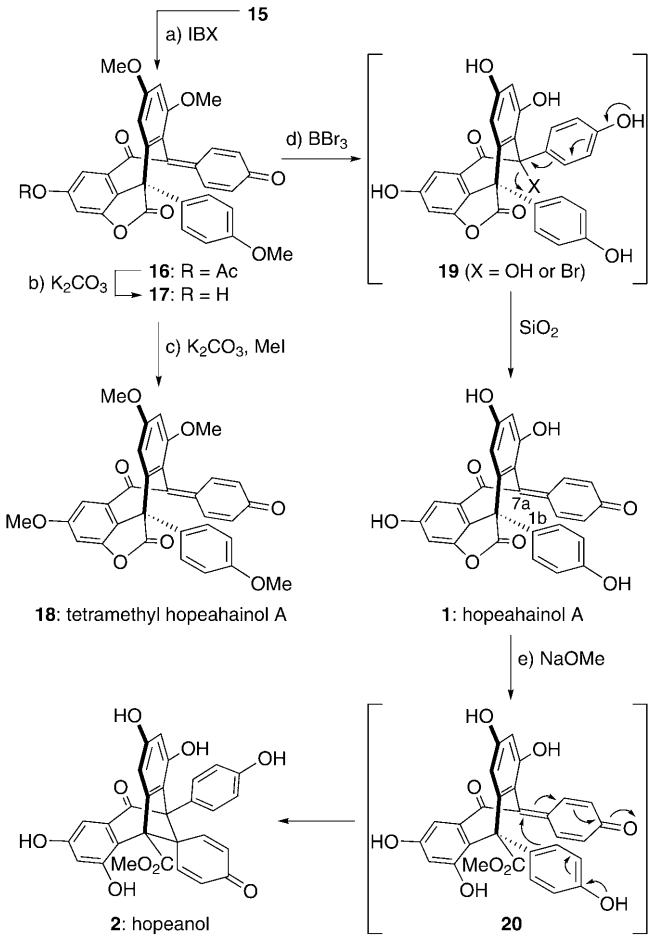


Scheme 3. Construction of epoxide **3** and hexacyclic intermediate **15**. Reagents and conditions: a) **7** (1.5 equiv), DCC (2.3 equiv), DMAP (0.3 equiv), CH_2Cl_2, 25 °C, 12 h, 95%; b) 4-methoxyphenylmagnesium bromide (0.2 M in THF, 1.3 equiv), THF, −10 °C, 10 min; c) TBAF (1.0 M in THF, 2.0 equiv), THF, 0 °C, 30 min, 79% for two steps (ca. 1:1 mixture of diastereoisomers); d) *p*TsOH (3.0 equiv), CH_2Cl_2, 25 °C, 48 h, 65% (ca. 2.4:1 mixture of diastereoisomers); e) KO*t*Bu (1.0 M in THF, 5.0 equiv), THF, 0→25 °C, 4 h, then sat. aq NH_4Cl, 76%; f) Ac_2O (1.5 equiv), DMAP (0.1 equiv), pyridine, 0→25 °C, 1 h, quant.; g) *m*CPBA (77% wt/wt, 4.0 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, 0 °C, 30 min, (ca. 1:1 mixture of diastereoisomers); h) $SnCl_4$ (1.0 M in CH_2Cl_2, 1.5 equiv), CH_2Cl_2, −40→−20 °C, 20 min, 62% for two steps (ca. 2:1 mixture of diastereoisomers). DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, *m*CPBA = *meta*-chloroperoxybenzoic acid, *p*TsOH = *para*-toluenesulfonic acid, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

*p*TsOH in CH_2Cl_2 at ambient temperature then led to pentacyclic product **10** (65% yield, mixture of diastereoisomers, ca. 2.4:1 d.r.). The observed difference of the diastereomeric ratios in going from starting material to product (**4**→**10**) in this carbon–carbon bond-forming reaction suggests the intermediacy of reactive species **9**. The stereochemical outcome of this reaction, however, is inconsequential since one of the stereocenters is erased in the subsequent step. Indeed, exposure of δ-lactone **10** to KO*t*Bu in THF at 0→25 °C led, upon quenching with aqueous NH_4Cl solution, to olefinic γ-lactone **12**, which was obtained through anion formation, β-elimination, and ring closure, as a single isomer (76% yield; Scheme 3). The remaining phenolic group was then protected as an acetate (**13**, Ac_2O, DMAP, quantitative yield), and the resulting olefinic product was subjected to epoxidation with *m*CPBA to afford epoxide **3** as a mixture of diastereoisomers (ca. 1:1 d.r.). This mixture was treated with $SnCl_4$ in CH_2Cl_2 at −40→−20 °C to give hydroxy γ-lactone **15** in 62% overall yield (mixture of diastereoisomers, ca. 2:1 d.r.), presumably through epoxide ring-opening and carbon–carbon bond formation.[7] The fact that the d.r. of product **15** does not reflect exactly the d.r. of the starting material **3** may be explained by the different reactivities of the two epoxide isomers.

With the entire hexacyclic framework of hopeahainol A (**1**) in place, the stage was now set for the final drive towards the target molecule. Scheme 4 depicts the devised steps through which this task was completed, and that allowed our second target molecule, hopeanol (**2**), to be reached as well through a single step thereafter. Thus, oxidation of hydroxy compound **15**[8] (mixture of two diastereoisomers at C7a and C8a) with IBX furnished keto quinoid compound **16** in 66% yield, which was deacetylated with $NaHCO_3$ in MeOH (quantitative yield) to yield phenol **17**. Methylation of this compound (K_2CO_3, MeI) afforded tetramethyl hopeahainol A (**18**, 90% yield), whose spectroscopic data (^{1}H NMR) matched those reported for this known derivative,[3] thus supporting the close resemblance and skeletal identity of structure **17** to that of hopeahainol A (**1**) through a cascade reaction. Pleasingly, the latter was prepared from **17** by treatment with BBr_3 in CH_2Cl_2 (−78→−20 °C) in 84% yield. Equally pleasant was the generation of hopeanol (**2**) from hopeahainol A (**1**) in 80% yield upon exposure of the latter to one equivalent of NaOMe in MeOH at 25 °C. Synthetic racemic **1** and **2** exhibited identical physical properties (^{1}H and ^{13}C NMR, and mass spectroscopic data) to those reported in the literature.[3,4] The conversion of **17** into hopeahainol A (**1**) appears to proceed through a labile intermediate (**19**: X = OH or Br),[9] which collapses to the desired product when placed on a preparative silica gel plate and allowed to stand for a few hours. It is also interesting to speculate that hopeahainol A (**1**) is locked in its unique structure by the γ-lactone ring which pushes carbons C1b and C7a



Scheme 4. Total synthesis of tetramethyl hopeahainol A (**18**), hopeahainol A (**1**), and hopeanol (**2**). Reagents and conditions: a) IBX (10 equiv), DMSO, 25 °C, 24 h, 66%; b) sat. aq $NaHCO_3$, MeOH, 25 °C, 1 h, quant.; c) MeI (20 equiv), K_2CO_3 (5.0 equiv), acetone, 80 °C, 1 h, 90%; d) BBr_3 (1.0 M in CH_2Cl_2, 18 equiv), CH_2Cl_2, −78→−20 °C, 24 h, 84%; e) NaOMe (1.0 equiv), MeOH, 25 °C, 60 h, 80%. DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid.

too far apart for interaction, and that it is its rupture with NaOMe (**1**→**20**) that allows the skeletal rearrangement (**20**→**2**) to occur, thus allowing the emergence of hopeanol (**2**), as shown in Scheme 4.

The described chemistry opens a path to the construction of hopeahainol A (**1**) and hopeanol (**2**) and their analogues for biological investigations, and further demonstrates the power of cascade reactions in total synthesis.[10]

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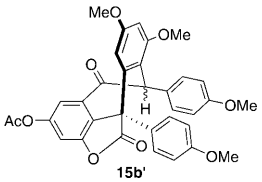
[8] It is interesting to note that, while the major diastereoisomer of **15** (unassigned) undergoes oxidation to **16** smoothly at 25 °C, its minor diastereoisomer resisted complete oxidation under the same reaction conditions, and led instead to partially oxidized ketone **15b′**.



[9] Intermediate **19** was observed by TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Owing to its lability the nature of X is still uncertain (most likely Br or OH).

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