Communications

Natural Product Synthesis

Total Synthesis of Hopeahainol A and Hopeanol**

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3440 InterScience

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Angew. Chem. Int. Ed. 2009, 48, 3440-3443

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] Hope-ahainol $A^{[3]}$ (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 (IC₅₀ = $0.52 \,\mu\text{M}$). Hopeahainol A (1), on the other hand, was isolated from Hopea hainanensis^[3] and exhibited inhibitory activity against acetylcholinesterase ($IC_{50} = 4.33 \mu M$), 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

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[**]	We thank Ms. Doris Tan (ICES) for assistance with high resolution mass spectroscopy (HRMS) measurements. Financial support for

this work was provided by A*STAR, Singapore. Supporting information for this article is available on the WWW

under http://dx.doi.org/10.1002/anie.200900438

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

Communications



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 м in THF, 1.3 equiv), THF, -10 °C, 10 min; c) TBAF (1.0 м 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) KOtBu (1.0 м in THF, 5.0 equiv), THF, $0 \rightarrow 25$ °C, 4 h, then sat. aq NH₄Cl, 76%; f) Ac₂O (1.5 equiv), DMAP (0.1 equiv), pyridine, $0 \rightarrow 25$ °C, 1 h, quant.; g) *m*CPBA (77% wt/wt, 4.0 equiv), NaHCO₃ (6.0 equiv), CH_2Cl_2 , 0 °C, 30 min, (ca. 1:1 mixture of diastereoisomers); h) SnCl₄ (1.0 м in CH₂Cl₂, 1.5 equiv), CH_2Cl_2 , $-40 \rightarrow -20$ °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*-tolue ensulfonic acid, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

pTsOH in CH₂Cl₂ 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 $(4\rightarrow 10)$ 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 KOtBu in THF at $0 \rightarrow$ 25°C led, upon quenching with aqueous NH₄Cl solution, to olefinic y-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, Ac₂O, DMAP, quantitative yield), and the resulting olefinic product was subjected to epoxidation with mCPBA to afford epoxide 3 as a mixture of diastereoisomers (ca. 1:1 d.r.). This mixture was treated with SnCl₄ in CH₂Cl₂ at $-40 \rightarrow -20$ °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 NaHCO3 in MeOH (quantitative yield) to yield phenol 17. Methylation of this compound (K₂CO₃, MeI) afforded tetramethyl hopeahainol A (18, 90% yield), whose spectroscopic data (¹H NMR) matched those reported for this known derivative,^[3] thus supporting the close resemblance and skeletal identity of structure 17 to that of hopenhainol A (1) through a cascade reaction. Pleasingly, the latter was prepared from 17 by treatment with BBr₃ in CH₂Cl₂ ($-78 \rightarrow -20$ °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 (¹H and ¹³C 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 NaHCO₃, MeOH, 25 °C, 1 h, quant.; c) MeI (20 equiv), K₂CO₃ (5.0 equiv), acetone, 80 °C, 1 h, 90%; d) BBr₃ (1.0 m in CH₂Cl₂, 18 equiv), CH₂Cl₂, $-78 \rightarrow -20$ °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 $(1\rightarrow 20)$ that allows the skeletal rearrangement $(20\rightarrow 2)$ 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]

Received: January 22, 2009 Published online: March 11, 2009 **Keywords:** cascade reactions · natural products · polyphenols · total synthesis

- For representative reviews on the chemical and biological studies of natural polyphenols, see: a) C. S. Yang, J. D. Lambert, S. Sang, Arch. Toxicol. 2009, 83, 11-21; b) L. Bonfili, V. Cecarini, M. Amici, M. Cuccioloni, M. Angeletti, J. N. Keller, A. M. Eleuteri, FEBS J. 2008, 275, 5512-5526; c) V. Habauzit, M.-N. Horcajada, Phytochem. Rev. 2008, 7, 313-344; d) S. Lafay, A. Gil-Izquierdo, Phytochem. Rev. 2008, 7, 301-311; e) B. Halliwell, Arch. Biochem. Biophys. 2008, 476, 107-112; f) L. G. Korkina, S. Pastore, C. De Luca, V. A. Kostyuk, Curr. Drug Metab. 2008, 9, 710-729, and reference therein.
- [2] For resveratrol-derived natural products and synthetic studies thereof, see: a) S. A. Snyder, S. P. Breazzano, A. G. Ross, Y. Lin, A. L. Zografos, J. Am. Chem. Soc. 2009, 131, 1753-1765; b) S. A. Snyder, L. Zografos, Y. Lin, Angew. Chem. 2007, 119, 8334-8339; Angew. Chem. Int. Ed. 2007, 46, 8186-8191, and references therein.
- [3] H. M. Ge, C. H. Zhu, D. H. Shi, L. D. Zhang, D. Q. Xie, J. Yang, S. W. Ng, R. X. Tan, *Chem. Eur. J.* 2008, *14*, 376–381.
- [4] H. M. Ge, C. Xu, X. T. Wang, B. Huang, R. X. Tan, Eur. J. Org. Chem. 2006, 5551–5554.
- [5] D. R. Vutukuri, S. Basu, S. Thayumanavan, J. Am. Chem. Soc. 2004, 126, 15636-15637.
- [6] R. A. Hudack Jr., N. S. Barta, C. Guo, J. Deal, L. Dong, L. K. Fay, B. Caprathe, A. Chatterjee, D. Vanderpool, C. Bigge, R. Showalter, S. Bender, C. E. Augelli-Szafran, E. Lunney, X. Hou, J. Med. Chem. 2006, 49, 1202–1206.
- [7] G. A. Kraus, I. Kim, Org. Lett. 2003, 5, 1191–1192.
- [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 ¹H NMR spectroscopic analysis of the crude reaction mixture. Owing to its lability the nature of X is still uncertain (most likely Br or OH).
- [10] a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* 2003, 551–564; b) L. F. Tietze, G. Brasche, K. M. Gericke *Domino Reactions in Organic Synthesis* Wiley-VCH, Weinheim, 2006, p. 617; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* 2006, 118, 7292–7344; *Angew. Chem. Int. Ed.* 2006, 45, 7134–7186.