A Concise Synthesis of (−)-Hispidospermidin Guided by a Postulated Biogenesis

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In the course of a microbial screen for novel inhibitors of phospholipase C (PLC), a key enzyme in the inositol phospholipid signaling pathway,[1] scientists from the Nippon Roche Research Center elucidated the unique and complex structure of (−)-hispidospermidin (**4**).[2] This tetracyclic natural product, which comprises seven contiguous stereocenters and a trimethylspermidine chain, exhibited moderately potent inhibitory activity against PLC and instigated serious efforts in the area of organic synthesis.[3] In this communication, we describe a concise, enantiospecific synthesis of **4** by a pathway guided by our hypothesis about the origin of its structure in Nature.

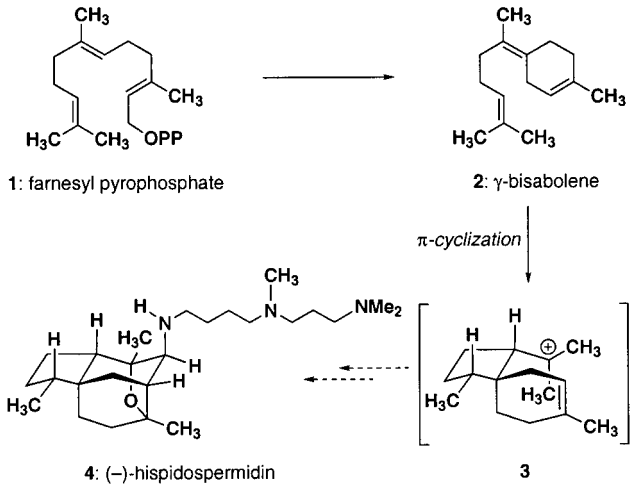
Our plan evolved from a perceived homology between the structures of **4** and spirocyclic cation **3** (Scheme 1). The transient cation **3** can be traced, via the well-known compound γ-bisabolene (**2**),[4] to farnesyl pyrophosphate (**1**),[5] the fundamental building block of sesquiterpene biogenesis.[6] *We noted that the constitution of cation **3** is quite clearly expressed in the structure of **4** and thus reasoned that this natural product might be a novel trimethylspermidine-containing sesquiterpene*.[7]

We considered the known spirocyclic ketone **6**[8] (Scheme 2) to be an ideal building block because it encompasses a significant portion of the architecture of **4**. Our hope was that a nucleophilic derivative of ketone **6** could be joined in a stereocontrolled fashion with 8-phenylmenthyl pyruvate (**7**).[9] A benefit accruing from the selection of compounds **6** and **7** as key intermediates for our synthesis is that both compounds can be created enantiospecifically from the abundant monoterpene (*R*)-(+)-pulegone (**5**).

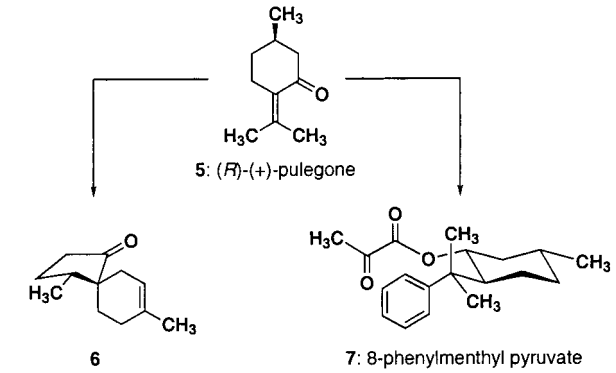
By a straightforward condensation, ketone **6** could be converted to trisylhydrazone **8** (Scheme 3). Despite its sterically congested nature, the putative vinyl Grignard reagent, produced from **8** under the conditions shown,[10] added diastereoselectively to the keto function of **7** to give hydroxy ester **9**.[11,12] After protection of the tertiary hydroxyl of **9** in the form of a 2-(trimethylsilyl)-ethoxymethyl (SEM) ether,[13] a reduction of the 8-phenylmenthyl ester to alcohol **10** was achieved with diisobutylaluminum hydride (Dibal-H). A Swern oxidation[14] of **10** gave rise to aldehyde **11**.

With an enforced proximity of functional groups with complementary reactivity, compound **11** was considered well-suited for a carbonyl ene cyclization.[15] Somewhat unexpectedly, when **11** was dissolved in acetic acid and allowed to stand at room temperature, it underwent a Prins cyclization *with participation by the tertiary ether oxygen* and afforded a mixture of tetracyclic alcohol epimers shown as **12**.[16] This intrinsically favorable bicyclization completed the tetracyclic architecture of the natural product and verified our stereochemical assignment of **9**. While cleavage of the SEM ether of **11** could conceivably precede the Prins ring closure, we found that the SEM ether of compound **10** was impervious to acetic acid at room temperature. We propose

Scheme 1



Scheme 2



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(3) For total syntheses of hispidospermidin, see: (a) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 6686. (b) Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039. (c) Frontier, A. J.; Raghavan, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6151.

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(5) Cyclization of *trans,trans*-farnesyl pyrophosphate (**1**) to γ-bisabolene (**2**) presupposes an initial isomerization of **1** to nerolidyl pyrophosphate or alternatively to *cis,trans*-farnesyl pyrophosphate. For discussions, see: (a) Cane, D. E. *Acc. Chem. Res.* **1985**, *18*, 220. (b) Andersen, N. H.; Syrdal, D. D. *Tetrahedron Lett.* **1972**, 2455.

(6) Ruzicka, L.; Eschenmoser, A.; Heusser, H. *Experientia* **1953**, *9*, 362.

(7) The biosynthesis of (−)-hispidospermidin has not yet been described.

(8) We achieved a 5-step synthesis of ketone **6** from (*R*)-(+)-pulegone (**5**) and isoprene by a modification of the 7-step sequence described by Marx and Norman (see: *J. Org. Chem.* **1975**, *40*, 1602).

(9) 8-Phenylmenthyl pyruvate (**7**) was prepared by the reaction of (−)-8-phenylmenthol with pyruvic acid in the presence of *p*-toluenesulfonic acid in refluxing benzene. For a convenient synthesis of 8-phenylmenthol from pulegone, see: (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Ort, O. *Organic Syntheses*; John Wiley & Sons: New York, 1993; Collect. Vol. 8, p 522.

(10) (a) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147. (b) Chamberlin, A. R.; Bloom, S. H. *Org. React. (N.Y.)* **1991**, *39*, 1.

(11) For diastereoselective additions of Grignard reagents to the pyruvate ester of (−)-8-phenylmenthol, see: (a) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802. (b) Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443.

(12) We isolated a single tertiary alcohol diastereomer and tentatively assigned its stereochemistry as shown in **9** by analogy to the stereochemical outcomes reported by Whitesell et al. (see refs 11a,b).

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(16) We could not isolate the anticipated carbonyl ene product, although it may be a transient intermediate in this process. This transformation even occurs to some extent on silica gel. We do not yet know if the outcome of this reaction is dependent on the identity of the protecting group in **11**.

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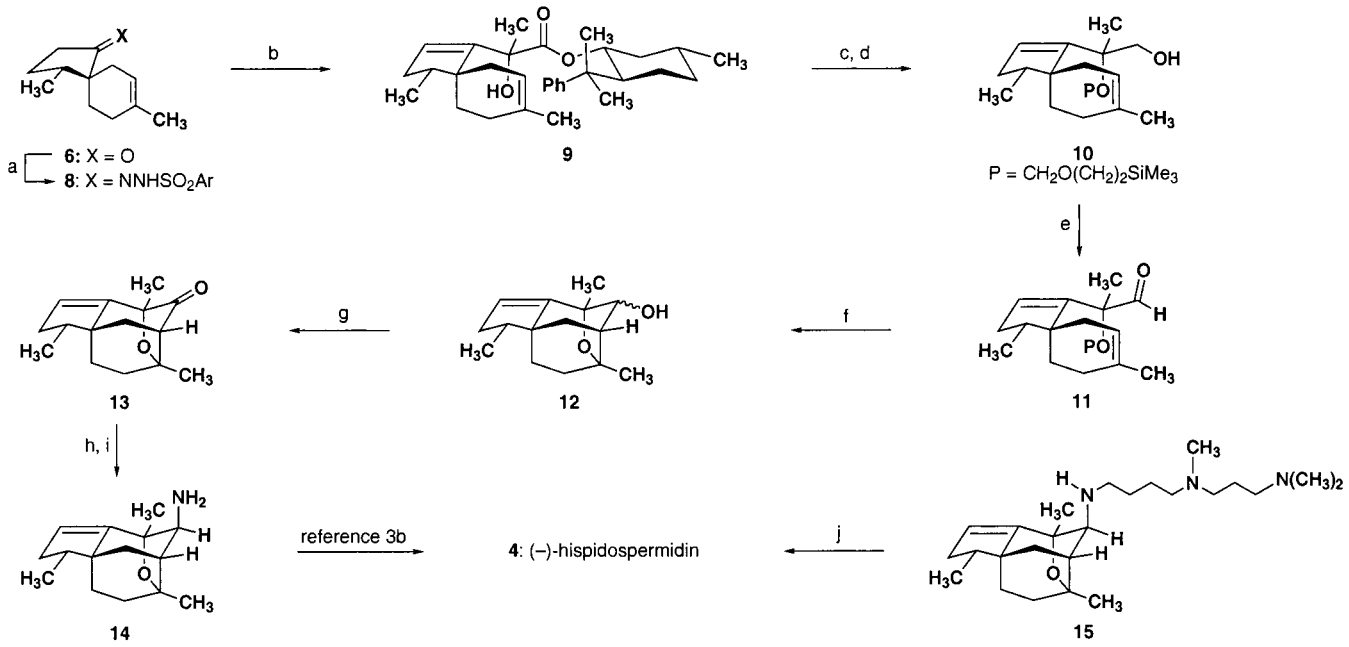
Scheme 3[a]



[a] Reagents and conditions: (a) 2,4,6-triisopropylbenzenesulfonyl hydrazide, HCl (1.2 equiv), CH_3CN, room temperature, 75%. (b) *n*-BuLi (2.05 equiv), Et_2O/THF, −78 to −20 °C; then $MgBr_2 \cdot OEt_2$, −78 °C; then **7**, −78 °C to room temperature, 55% from **8**. (c) SEMCl, *n*-Bu_4NI, *i*-Pr_2NEt, CH_2Cl_2, 50 °C, ca. 100%. (d) Dibal-H, toluene, −78 °C, 93%. (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then *i*-Pr_2NEt, −78 °C to room temperature, ca. 100%. (f) AcOH, room temperature, 2 d, 83% or AcOH, 80 °C, 3 h, 87%. (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then *i*-Pr_2NEt, −78 °C to room temperature, ca. 100%. (h) $HONH_2 \cdot HCl$, $NaOAc \cdot 3H_2O$, EtOH, room temperature, ca. 100%. (i) $LiAlH_4$, $NiCl_2$, Et_2O, room temperature, 97%. (j) Rh/C (2 equiv), EtOAc, H_2, 1100 psi, (70% yield of a 3:1 mixture of epimers favoring **4**). Ar = 2,4,6-triisopropylbenzene.

that the tertiary ether oxygen of **11** intercepts a transient tertiary carbocation in the course of the conversion of **11** to **12**. Interestingly, heating a mixture of **11** and trimethylspermidine in toluene followed by exposure of the crude imine to acetic acid afforded an equimolar mixture of **15** and its equatorial side chain diastereomer, ostensibly through an aza-Prins cyclization with ether oxygen participation.

A Swern oxidation[14] of the diastereomeric mixture of alcohols afforded tetracyclic ketone **13**, a substance that was advanced to $\Delta^{8,9}$-dehydrohispidospermidin (**15**) by a reductive amination with trimethylspermidine.[3c] The high haptophilicity of amines[17] and close spatial relationship between the trimethylspermidine moiety and the ring alkene in **15** were expected to favor the formation of **4** under the conditions of a hydrogenation. After considerable experimentation, we found that **4** could be obtained as the major component of a 3:1 mixture of diastereomers via a high-pressure hydrogenation of **15** in the presence of rhodium on carbon.[18] We also converted ketone **13** to the corresponding oxime and thence to the known unsaturated primary amine **14**[3b] by reduction under the conditions shown.[19] In their instructive synthesis, Overman and Tomasi showed that **14** could be converted to **4** in a completely diastereoselective fashion.[3b] By this known three-step sequence, we also transformed **14** to **4** and established the identity of our sample of synthetic (−)-hispidospermidin by comparison with an authentic sample.

Following a strategy guided by our biogenetic postulate, we achieved a concise, enantiospecific synthesis of the novel PLC inhibitor (−)-hispidospermidin (**4**) from known compounds **6** and **7**. A facile, acid-induced bicyclization of compound **11** is a noteworthy stage of this synthesis.

Acknowledgment. This paper is dedicated with respect and affection to our mentor Professor Albert Eschenmoser on the occasion of his 75th birthday. Financial support from The Skaggs Institute for Chemical Biology at TSRI, a Graduate Research Fellowship to J.T. (Abbott Laboratories), a grant from the Merck Research Laboratories, and a Beckman Young Investigator Award to E.J.S. are gratefully appreciated. We thank Prof. Larry Overman and Dr. Adam Tomasi for samples of natural and synthetic (−)-hispidospermidin and helpful discussions.

Supporting Information Available: Characterization data and experimental procedures for compounds **9**, **10**, **11**, **12**, **13**, **14**, **15**, and **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) We could not resolve this 3:1 mixture of stereoisomers by SiO_2 chromatography or HPLC.

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