Enantioselective Total Synthesis of Hispidospermidin

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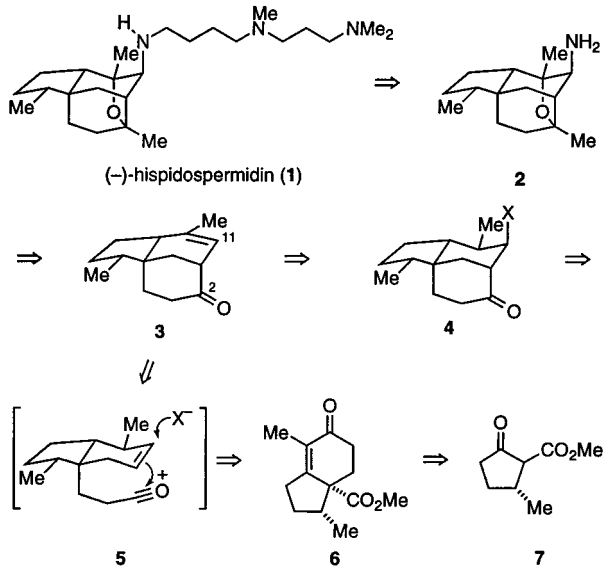
Signal-transduction therapy is drawing increasing attention for its potential to combat ailments resulting from deviations in normal cell signaling pathways.[1−4] Studies conducted in the early 1980s showed that phosphoinositol is metabolized in response to extracellular peptide growth factors with phospholipase C (PLC) being a key enzyme.[5,6] PLC catalyzes the hydrolysis of phosphatidylinositol diphosphate to produce diacylglyceride (DAG) and myoinositol triphosphate (IP_3). DAG in turn activates protein kinase C (PKC) which initiates phosphorylation of proteins, while IP_3 stimulates the release of intracellular Ca^{2+} effecting many cellular processes.[7] Because of its key role in the cell growth signaling pathway, inhibition of PLC could provide a novel means to manage certain proliferative diseases.[8] In this paper, we report the first enantioselective total synthesis of (−)-hispidospermidin (**1**), a recently discovered inhibitor of PLC.

The tetracyclic spermidine alkaloid (−)-hispidospermidin (**1**) was isolated in 1994 from a fungal culture broth by Nippon Roche scientists.[9] While **1** is a micromolar inhibitor of PLC,[10] amine **2** shows little activity, suggesting that both the hydrophobic tetracyclic core and polyamine side chain are required for inhibitory activity.[10,11] Stimulated by the unique skeleton of **1** and the opportunity to further probe structure−activity relationships for this novel PLC inhibitor, we initiated efforts to access (−)-hispidospermidin (**1**) by total synthesis. During the course of our investigations, the Danishefsky group recorded the first total synthesis in this area, an incisive construction of (±)-hispidospermidin.[12]

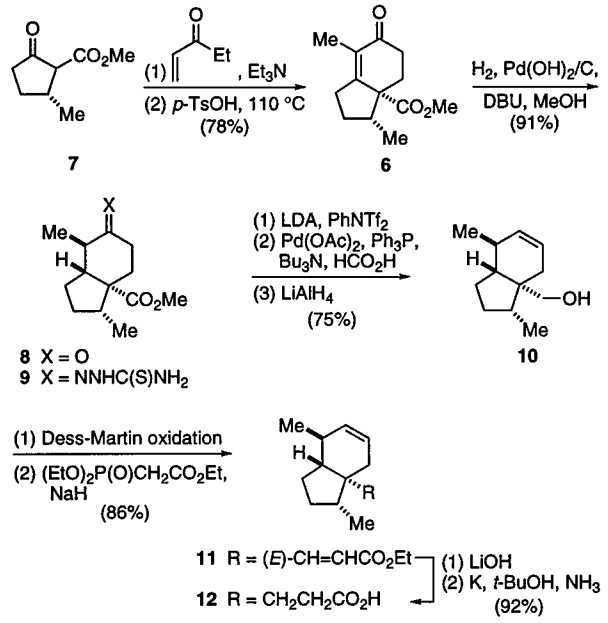
Tricyclic ketone **3** was targeted as an attractive platform for assembling **2**, since the rigid geometry of this intermediate should regulate stereochemistry in subsequent elaboration of the heteroatom substituents at C2 and C11 (Scheme 1). We envisaged **3** as arising from an intramolecular Friedel−Crafts acylation, **5** → **3**. Although direct cyclization to **3** was ultimately subverted by an unexpectedly facile hydride shift (vide infra), construction of **3** was realized as suggested in Scheme 1 by engaging an external nucleophile in the pivotal cyclization step.[13] The acid precursor of **5** was seen as arising from hydrindenone **6** and ultimately enantiopure β-ketoester **7**, the latter being readily available from (*R*)-pulegone.[14]

The construction of hydrindene acid **12** is summarized in Scheme 2. Base-catalyzed condensation of **7** with ethyl vinyl ketone (1.5 equiv, 60 °C, 28 h), followed by cyclization of the resulting Michael adduct in refluxing toluene in the presence of *p*-TsOH (0.5 equiv) provided hydrindenone **6** in 78% yield. Hydrogenation of **6** under carefully optimized conditions (20% $Pd(OH)_2/C$, 0.2 equiv of DBU, 32:1 MeOH−H_2O, rt) afforded a single hydrindanone **8** (91%),[15−17] whose trans ring fusion stereochemistry was confirmed by single-crystal X-ray analysis of thiosemicarbazide derivative **9**.[18] The presence of DBU during hydrogenation was critical and served to epimerize the initially formed axial methyl group and suppress competing reduction of

Scheme 1



Scheme 2



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(15) Exclusive formation of **8** is noteworthy, since hydrogenation of a related hydrindenone lacking the α-methyl substituent yielded only the cis-fused hydrindanone.[16] That the α-methyl group would enhance trans stereoselection has precedent.[17]
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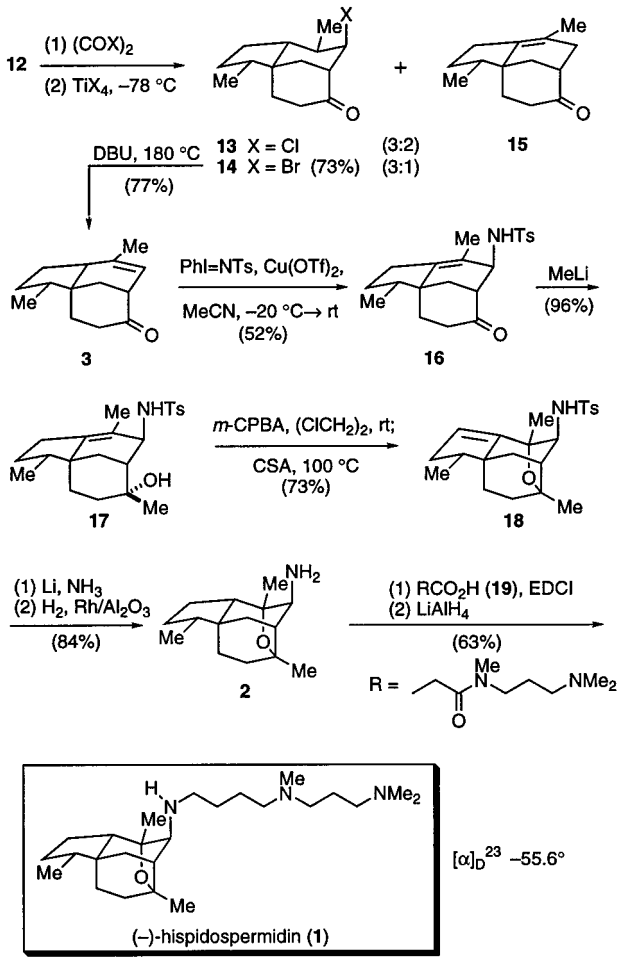
Scheme 3



the ketone.[19] To create the nucleophilic partner for the Friedel−Crafts cyclization, the ketone carbonyl of **8** was converted to an alkene. This was accomplished in two steps,[20] and after reduction of the hindered ester with $LiAlH_4$, alcohol **10** was obtained in 75% overall yield. Oxidation of **10** to the corresponding aldehyde and Horner−Wadsworth−Emmons olefination produced enoate **11** (86% yield). Saturation of the double bond of this intermediate was not straightforward, since the substantial steric hindrance at the β-carbon resulted in partial (or exclusive) 1,2-reduction when **11** was treated with many standard reducing agents.[21] This problem was solved by hydrolysis of **11** to the carboxylate, which reduced cleanly with potassium in *t*-BuOH−NH_3[22] to give cyclization precursor **12** in 92% yield.

Attempts to cyclize the acid chloride derivative of **12** with various Lewis acids did not yield **3**, but rather a mixture of **15** and tricyclic chloride **13** (Scheme 3). Apparently the initially formed secondary tricyclic carbenium ion does not suffer direct proton loss to form **3**, but rather is partitioned between 1,2 hydride shift to form a tertiary carbenium ion (and ultimately **15**) and halide capture to form **13**. Fortunately, increasing the nucleophilicity of the halide counterion partially suppressed this deleterious hydride migration. Thus, exposure of the acyl bromide derivative of **12** to 1.0 equiv of $TiBr_4$ in CH_2Cl_2 at −78 °C provided tricyclic bromide **14** in yields as high as 73%.

With the carbocyclic framework established, there remained the challenge of introducing the trans diaxial nitrogen and oxygen functionality. To accomplish this elaboration, bromide **12** was first dehydrobrominated under forcing conditions to form **3** (77%). We were delighted to discover that reaction of **3** with (*N*-(*p*-tolysulfonyl)imino)phenyliodinane and 5 mol % of $Cu(OTf)_2$ at −20 °C → rt for 2 h in MeCN, conditions generally used to aziridinate alkenes,[23] produced allyl sulfonamide **16** as the predominant product. The Cu(II) salt plays a critical role in this transformation, since **3** is recovered unchanged after 24 h at room temperature when exposed to (*N*-(*p*-tolysulfonyl)imino)phenyliodinane in the absence of $Cu(OTf)_2$.[24,25] Addition of methyllithium to **16** then provided **17** in near quantitative yield. Despite some precedent,[26] attempts to close the final tetrahydrofuran ring by reaction of **17** with protic acids, $Hg(OAc)_2$, or $Hg(OCOCF_3)_2$ were uniformly unsuccessful. However, the desired cyclization was eventually realized by treating a 1,2-dichloroethane solution of **17** with 1.1 equiv of *m*-CPBA (rt, 1 h), adding camphorsulfonic acid (CSA) (1.6 equiv), and then heating the resulting solution at 100 °C for 7 h; this sequence delivered tetracyclic ether **18** in 73% yield. The β-epoxide and tertiary alcohol that are intermediates in this conversion could be isolated by quenching the reaction at intermediate stages.

To complete the synthesis **1**, the double bond and tosyl protecting group must be removed and the spermidine side chain appended. The order in which the first two operations is carried out proved critical. Hydrogenation of **18** using several catalysts (Pd, Pt, and Rh) resulted in predominant hydrogen delivery from the face opposite the axial sulfonamide substituent to generate the undesired cis hydrindane unit. However, hydrogenation of the corresponding primary amine over 5% Rh/Al_2O_3 at 1300 psi provided **2** as the only detectable stereoisomer in 84% yield. This dramatic change in stereoselectivity could result from a decrease in steric hindrance of the exo face upon removal of the tosyl group or from a directing effect of the primary amine.[27] The synthesis of (−)-hispidospermidin (**1**) was then completed by acylation of **2** with amido acid **19**[28] followed by reduction of the resulting diamide with $LiAlH_4$. Synthetic (−)-hispidospermidin (**1**) was identical in all respects, including optical rotation $[\alpha]^{23}_D$ −55.6°,[9] with an authentic sample.

In conclusion, the first enantioselective total synthesis of natural (−)-hispidospermidin was completed in 20 steps. This synthesis defines a new strategy for assembling the tetracyclic core of hispidospermidin and highlights the propitious role that external nucleophiles can play in Friedel−Crafts cyclizations.

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Supporting Information Available: Characterization data and preliminary experimental procedures for new compounds described in Schemes 2 and 3 and ^{13}C NMR spectra of synthetic and natural (−)-hispidospermidin (21 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(18) The authors have deposited atomic coordinates for this compound with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(19) When this hydrogenation was carried out in the absence of DBU, the epimer of **8** having an axial methyl group was isolated.

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(28) Amido acid **19** was prepared by reaction of succinic anhydride with *N*,*N*-dimethyl-3-(methylamino)propylamine. An excess of the crude product from this reaction was employed in the coupling reaction.