Stereocontrolled Total Synthesis of Hispidospermidin

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In a key cellular event, the enzyme phospholipase C (PLC) mediates the hydrolysis of phosphatidylinositol diphosphate to produce two critical molecular messengers, diacylglycerol (DAG) and myoinositol 1,4,5-triphosphate (IP_3).[1,2] DAG is a stimulatory factor that governs the activity of protein kinase C (PKC), while IP_3 levels control the release of intracellular calcium, effecting many cellular processes including the action of calcium-dependent enzymes.[3] These pathways have a profound effect on cell growth, differentiation, and proliferation; productive intervention could lead to clinical advances of considerable import.

It was in this context that the discovery of the naturally occurring PLC inhibitor hispidospermidin (**1**) engaged our interests.[4,5] We found the molecule's novel caged system an architectural challenge, and preliminary biological data indicated the possibility of probing its mode of action through synthetic endeavors. A variant of **1** bearing a primary amine in place of the spermidine side chain was virtually inactive,[5] suggesting that the polyamine domain of **1** is responsible for inhibition. A total synthesis venture could establish the basis for generating a range of analogs (possibly combinatorially) to pin down delicate SAR profiles.

We came to favor a hydrindenone of the genre **2** as a subgoal of the total synthesis. This intermediate would provide a platform structure for evaluating possibilities for stereochemical governance. It would be necessary to introduce a β-hydrogen at C9,[6] a β-methyl at C10,[6] and a β-disposed polyamine at C11.[6] Placement of an α-oxygen at C10 to bridge C10 and C2 and formation of a bond to connect C12 and C2 would complete the cage (Figure 1). Globally, these transformations constitute a unique construction in which the carbons of an alkyne emerge as a quaternary carbon adjacent to the saturated carbon of a methyl group.

Critical to the success of this prospectus would be the optimal phasing of these individual steps to achieve the desired stereodirectionality. We took note that exercise of control at C9 and C10 of hydrindenone **2** could be problematic. An alternative matrix to be evaluated with respect to the required reactions would be **3**, possibly derivable from **2**, wherein X and Y are left unspecified. The more pronounced cuplike character of the bicyclo[3.3.1]nonane domain could perhaps be exploited to provide more predictable stereochemical control. We now describe the total synthesis of hispidospermidin.

Addition of Grignard reagent **4**[7] to aldehyde **5**[8] was followed by oxidation, producing ketal carbinol **6** (Scheme 1). Hydrolysis of the acetonide linkage was followed by cyclization of the crude ketoaldehyde[9] **7** with concomitant desilylation to produce

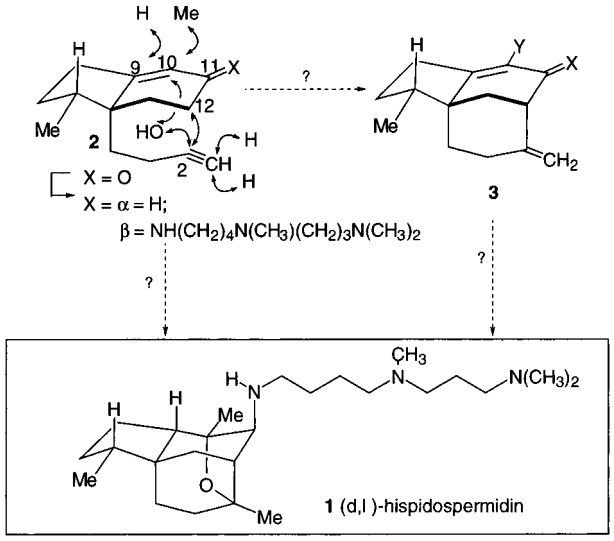
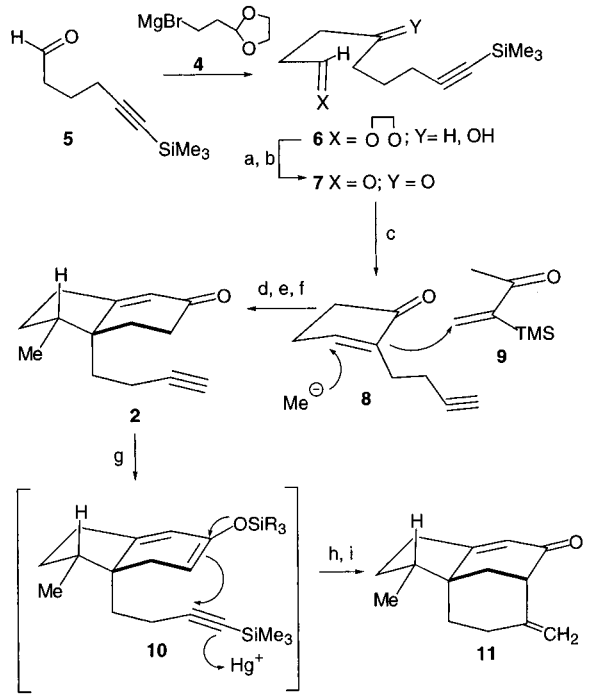


Figure 1

Scheme 1



[a] Reagents: (a) pyridinium dichromate (PDC) (77% from **5**); (b) 1:1 THF/3 N HCl; (c) Et_2O/1% NaOH (3:1), room temperature (rt), 3 days (50% from **6**); (d) Me_2CuLi, −78 °C; (e) **9** (2 equiv), −35 °C; (f) MeOH/4% KOH (4:1), reflux, 18 h (55% from **8**); (g) lithium hexamethyldisilizane (LHMDS), NEt_3, TMSCl, −78 °C; (h) $HgCl_2$, HMDS; (i) NaI, 5.0 N HCl (87% from **2**).

cyclopentenone **8**. Addition of lithium dimethylcuprate to **8**, in the fashion indicated, was followed by trapping of the metalloenolate with the methyl vinyl ketone equivalent **9**.[10] This highly stereoselective reaction gave rise to an adduct, which upon treatment with KOH and methanol was converted to the desired hydrindenone **2**.[11] Enol silylation of **2** under the specified conditions also led to incorporation of a trimethylsilyl group on the acetylene (see compound **10**). Intramolecular carbomercuration (joining C2 and C12) was triggered by the

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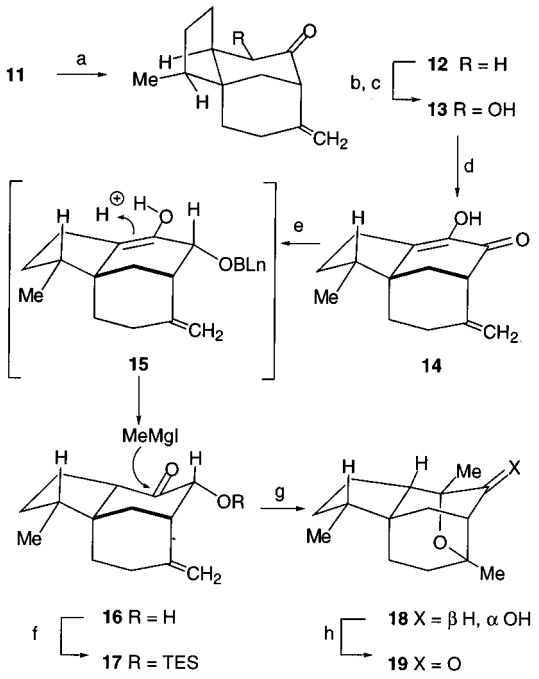
Scheme 2



[a] Reagents: (a) Li/NH_3 (85%); (b) triethylsilyl triflate (TESOTf), NEt_3; (c) *m*-chloroperoxybenzoic acid (*m*-CPBA), $NaHCO_3$ (79% from **12**); (d) trifluoroacetic anhydride (TFAA), DMSO, NEt_3 (80%); (e) $NaBH_4$, 30 s (84% based on recovered **14**); (f) TESOTf, NEt_3 (93%); (g) MeMgI, then 1.0 N HCl in Et_2O, then 5 N aqueous HCl (56%); (h) Jones reagent (85%).

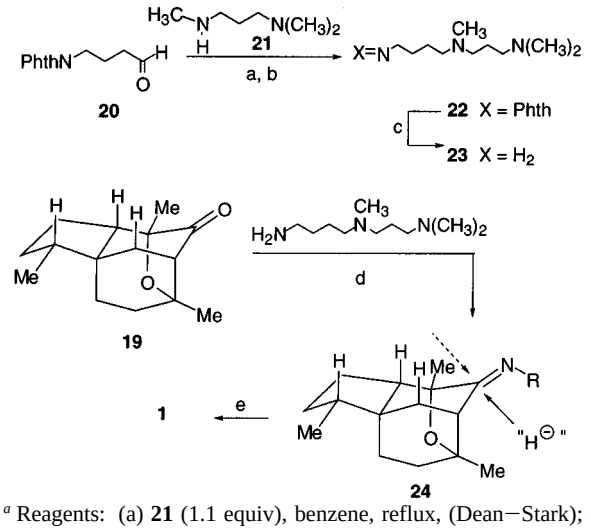
action of mercuric chloride, as shown.[12,13] Reductive cleavage of the vinyl mercurial and deprotection of the vinylsilane were accomplished in the manner indicated to afford **11** (*cf.* hypothetical construct **3** where Y = H and X = O).

Birch-like reduction of the enone linkage afforded the cis-fused dihydro product **12** (Scheme 2). This result presumably reflects substantial early rehybridization at C9 in the direction of a conformer in which the emerging hydrindanone is precisoid.[14] In general, metal−ammonia reductions of non-octalone ring systems tend to afford the thermodynamic product.[15] Hydroxylation at C10 was accomplished via Rubottom[16] oxidation of the silyl enol ether derived from **12** (see compound **13**).

Oxidation[17] of the C10 alcohol of **13** resulted in the formation of diosphenol **14** (*cf.* **3** X = O; Y = OH). Fortunately, the required β-stereochemistry at C9 could be constituted by treatment of this compound with sodium borohydride. Reduction occurred by hydride delivery from the β-face (see proposed intermediate **15**). *Most importantly, disruption of the diosphenol connectivity triggered ketonization of the C9−C10 enol with protonation at C9 occurring strictly from the β-face (see compound **16**).* We note that this sense of protonation is in contrast to the α-mode encountered in the Birch reduction step (*cf.* **11** → **12**). For the enol linkage of **15**, the sense of protonation is governed by steric accessibility factors that would certainly favor reactions from the exo face of the bicyclo[3.3.1]-moiety.

At this point, the C11 hydroxyl group of **16** was protected in the form of its triethylsilyl ether (see compound **17**). Not unexpectedly, reaction of the keto function of **17** with methylmagnesium iodide resulted in introduction of the methyl group from the β-face and appearance of an α-disposed hydroxyl group. Treatment of the crude Grignard product with ethereal HCl brought about formation of the caged ether structure. Subsequent addition of aqueous HCl effected desilylation (see compound **18**). We attribute the particularly facile cyclic ether formation to the enforced proximity of the tertiary hydroxyl disposed on the endo face of the bridged system with the exocyclic methylene at C12. Jones oxidation[18] of **18** produced ketone **19**.

Scheme 3



[a] Reagents: (a) **21** (1.1 equiv), benzene, reflux, (Dean−Stark); (b) $NaCNBH_3$, 1:1 THF/MeOH, pH 4 (50% from **20**); (c) $MeOH/NH_2NH_2$, 4:1 (55%); (d) **23** (6.0 equiv), toluene, pyridinium *p*-toluenesulfonate (PPTS) (cat.), powdered sieves, reflux, 3 days; (e) $NaCNBH_3$, MeOH, pH 4 (82% from **19**).

Aldehyde **20**[19] was utilized to reductively alkylate commercially available diamine **21** under the protocols described by Borch (Scheme 3).[20] Dephthaloylation of the resultant **22** afforded **23**. Condensation of ketone **19** with triamine **23**, as shown, led to **24**. Finally, reduction of **24** with sodium cyanoborohydride afforded (*dl*)-hispidospermidin (**1**). It will be noted that in this reduction, the hydride equivalent was delivered from the α-face of C11. This result need occasion little surprise since attack at the C11 imine is occurring through a trajectory which does not involve incursion into the concave face of the cagelike-domain. Unlike the hypothetical trajectory associated with axial delivery of hydride to C11 (which must pass through potentially deflecting axial hydrogens at C9 and C13, as well as the equatorial β-methyl at C10), the pathway for equatorial face reduction of the imine is relatively unencumbered. Furthermore, the bridging oxygen may well be exerting a directive effect.

The structure of the hispidospermidin generated by total synthesis follows from its 400 MHz NMR spectrum in conjunction with the high-field spectra of its precursors. Moreover, the 400 MHz NMR spectrum of an authentic sample of hispidospermidin was identical with that of synthetic racemate. Clearly, ketone **19** provides easy access for introduction of a variety of basic side chains at C11 using the stereochemical model established in the total synthesis.

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Supporting Information Available: Selected experimentals (for compounds **11**, **16**, and **18**) and structural information (for compounds **13** and **16**) (4 pages). See any current masthead page for ordering and Internet access instructions.

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