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A spontaneous bicyclization facilitates a synthesis of (−)-hispidospermidin

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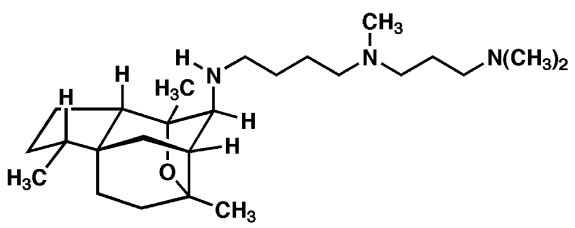
Dedicated with gratitude and admiration to Professor K. C. Nicolaou, recipient of the Tetrahedron Prize, for his mentorship and for his many outstanding contributions to organic natural product synthesis

Abstract—A concise, enantiospecific synthesis of the phospholipase C inhibitor (−)-hispidospermidin (**1**) has been achieved by approximating the architecture of a reactive intermediate that may lie on the biosynthetic pathway leading to this natural product. Two compounds derived from (*R*)-(+)-pulegone were joined by a highly diastereoselective carbonyl addition. A proximity-facilitated, acid-induced bicyclization of spiro[4.5]deca-1,7-diene **29** gave rise to the tetracyclic framework of **1** and was the key transformation in this synthesis.

1. Introduction

When R. B. Woodward wrote, 'we all know that enforced propinquity often leads on to greater intimacy…,' he was referring, in particular, to the powerful force of proximity in unimolecular chemical reactions.[1] Indeed, the benefit of a high effective molarity of complementary reacting centers is widely appreciated in chemistry.[2] 'Enforced propinquity' was the cornerstone of our approaches to the chemical problem posed by the natural product hispidospermidin (**1**) (Fig. 1). This substance was isolated from the culture broth of the fungus *Chaetosphaeronema hispidulum*, and its attractive molecular architecture and absolute stereochemistry were described by scientists from the Nippon Roche Research Center in Japan.[3] Hispidospermidin engendered interest as a potential cell growth inhibitor because it inhibits phospholipase C (PLC), a central enzyme in the inositol phospholipid signaling pathway,[4] and stimulated creative research in organic synthesis. To date, three total syntheses of this natural product[5–7] and one report describing a synthesis of an analogue of hispidospermidin[8] have been described. Herein, we provide a full account of our enantiospecific synthesis of this natural product from the monoterpene (*R*)-(+)-pulegone.[7]



1: (–)-Hispidospermidin

Figure 1. Structure of (−)-hispidospermidin (**1**).

2. Results and discussion

Although the biosynthesis of hispidospermidin (**1**) is unknown, our laboratory reasoned that the novel framework of this natural product may originate from farnesyl pyrophosphate (**2**), the fundamental building block of sesquiterpene biogenesis.[9] This proposal followed from the structural relationships shown in Scheme 1. In particular, we were drawn to the homology between the structures of hispidospermidin (**1**) and spirocyclic carbocation (**4**). All fifteen carbon atoms and the architecture of **4** are quite clearly expressed in the structure of **1**. This perception thus revealed a clear path leading back to farnesyl pyrophosphate (**2**). In Nature, compound **2** is transformed to the well-known natural product γ-bisabolene (**3**).[10] A regio- and stereoselective protonation of the tetrasubstituted olefin in **3** could instigate a π-cyclization to cation **4**, which, in principle, could be transformed to hispidospermidin (**1**) by a process that would require an

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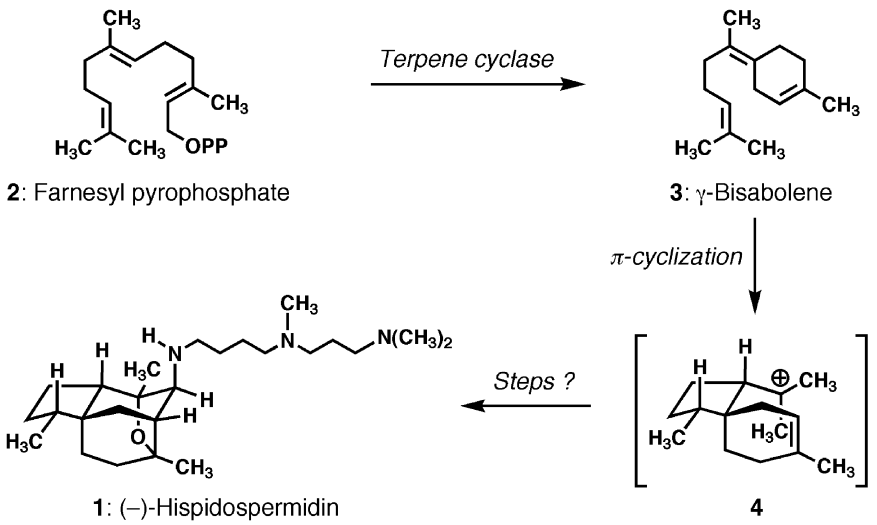
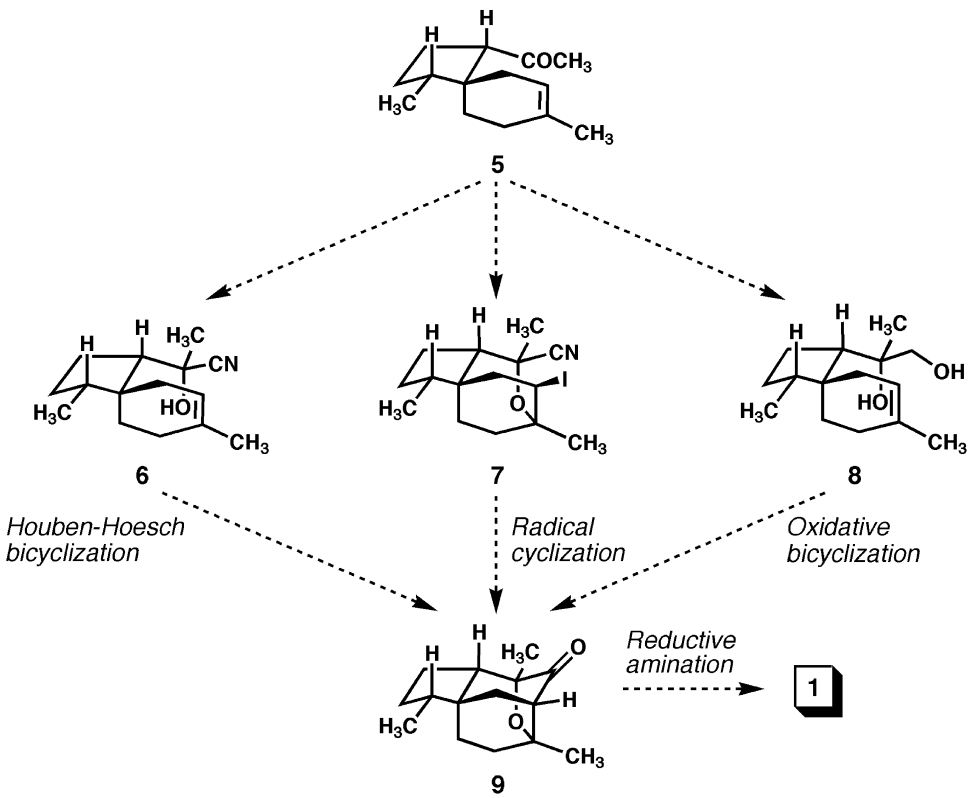


Scheme 1. Does (−)-hispidospermidin (**1**) originate from farnesyl pyrophosphate (**2**)?

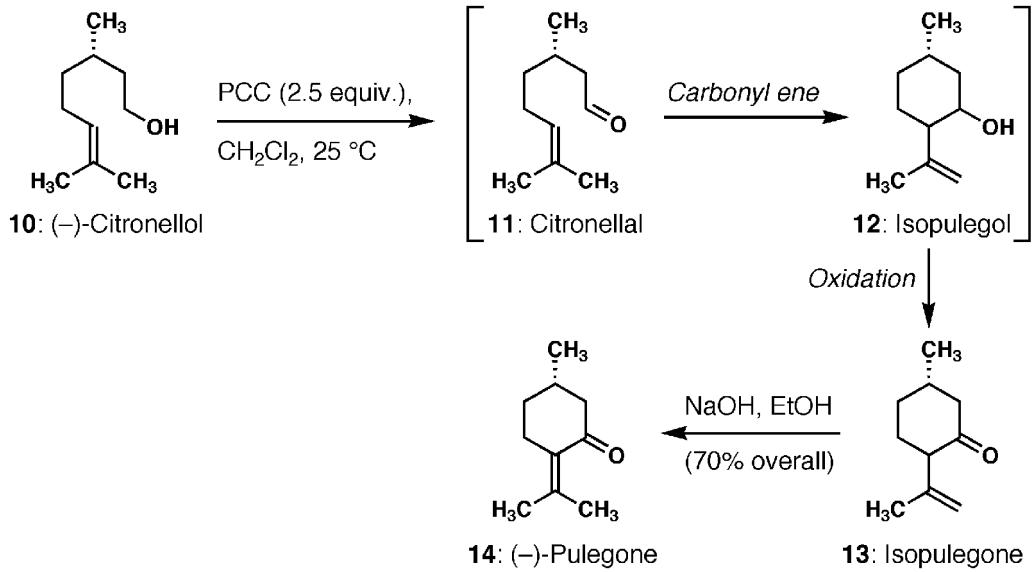
oxidation of a carbon atom and the formation two rings. The idea of transforming a functionalized spirocycle analogous to **4** to a hispidospermidin-like tetracycle followed from Scheme 1 and served as a guiding principle for our synthesis.

At the outset, spiro[4.5]decene **5** was identified as an attractive intermediate for synthesis because it seemed to bestow significant flexibility to planning. For example, nucleophilic additions to the keto group of **5** could enable syntheses of compounds **6**, **7**, **8**. Cyanohydrin **6** was desirable because a Brønsted acid-catalyzed Houben–Hoesch π-cyclization[11] with participation by the tertiary hydroxyl group could conceivably yield the desired tetracyclic ketone **9** directly. Alternatively, an iodoetherification of **6** would afford **7** and set the stage for a radical cyclization;[12] the radical addition to the nitrile function would be followed by a simple imine hydrolysis to give compound **9**.

A further opportunity for synthesis would be available if diol **8** could be elaborated from methyl ketone **5** or alternatively from cyanohydrin **6**. In 1976, Corey's laboratory described that treatment of (−)-citronellol (**10**) with 2.5 equiv. of the mildly acidic oxidant pyridinium chlorochromate (PCC) afforded isopulegone (**13**) via the



Scheme 2. Potential approaches to (−)-hispidospermidin (**1**) from a common spiro[4.5]decene intermediate.

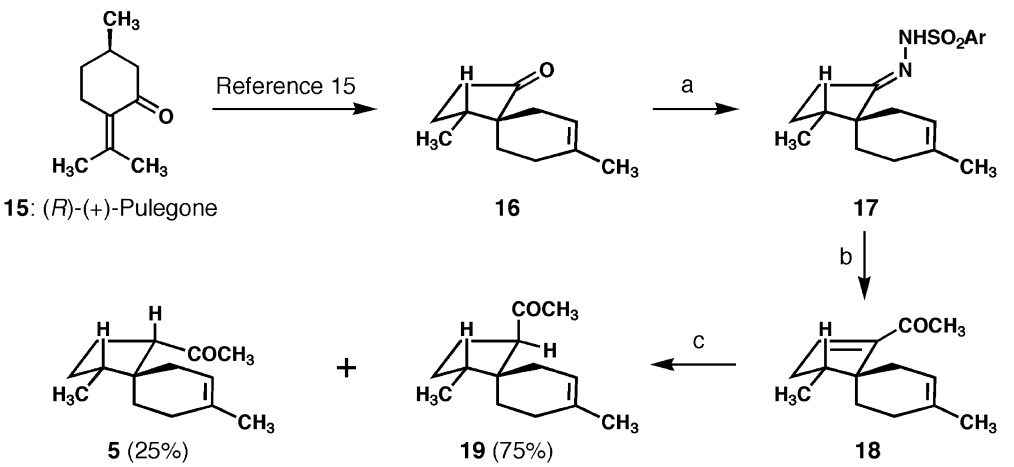


Scheme 3. Corey's short synthesis of (−)-pulegone (**14**) from (−)-citronellol (**10**).

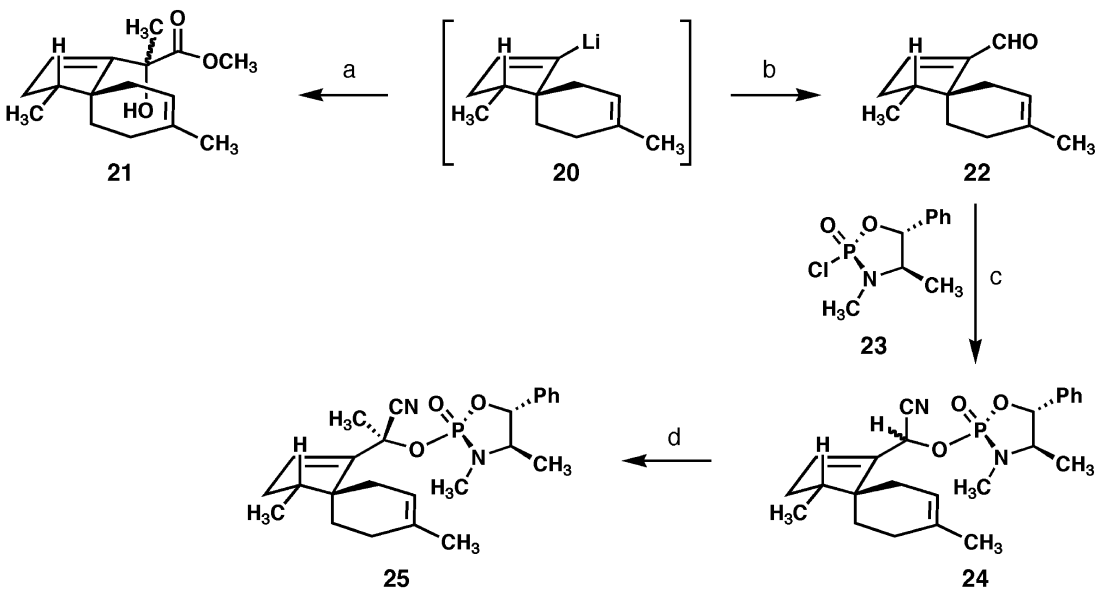
intermediates citronellal (**11**) and isopulegol (**12**) (Scheme 3).[13] A simple base-induced isomerization of **13** then afforded (−)-pulegone (**14**). Corey's novel oxidative cationic cyclization was later shown to be efficient in a range of molecular contexts,[14] and it encouraged us to contemplate the somewhat risky idea of oxidizing diol **8** to an α-hydroxy aldehyde with a mildly acidic oxidant such as PCC. If an undesired oxidative cleavage of the vicinal diol of **8** could be avoided, we reasoned that proximity between an activated aldehyde carbonyl and the nucleophilic trisubstituted alkene would facilitate a ring formation analogous to the one shown in Scheme 3.[13,14] Moreover, we hoped that the tetracyclic architecture of (−)-hispidospermidin (**1**) would arise in the wake of an intramolecular capture of a carbocation intermediate by the tertiary hydroxyl group.

An investigation of the annulation strategies outlined in Schemes 2 and 3 required an effective synthesis of bicyclic methyl ketone **5**. At the outset, we were drawn to spirocyclic ketone **16** as a precursor to **5** (Scheme 4). This known compound can be synthesized enantiospecifically from (*R*)-(+)-pulegone (**15**) in only a handful of steps[15] and already contains a substantial portion of the architecture of (−)-hispidospermidin.

When a solution of ketone **16** in acetonitrile was treated with 2,4,6-triisopropylbenzenesulfonyl hydrazide[16] and hydrochloric acid at room temperature, a condensation occurred and afforded 2,4,6-triisopropylbenzenesulfonyl-(trisyl)hydrazone **17** in 75% yield. The valuable Shapiro olefin synthesis demonstrates that sulfonylhydrazones are excellent precursors to reactive vinyllithium reagents,[17] and the subsequent studies of Bond and co-workers showed that vinyllithium reagents produced by the reaction of trisylhydrazones with *n*-butyllithium can be trapped with a range of organic and inorganic electrophiles to give functionalized alkenes.[18] Based on this solid precedent, we could advance trisylhydrazone **17** to α,β-unsaturated ketone **18**.[19] Our plan was to construct the desired ketone **5** from **18** via a



Scheme 4. *Reagents and conditions*: (a) 2,4,6-triisopropylbenzenesulfonyl hydrazide (1.2 equiv.), HCl (1.2 equiv.), CH_3CN, rt, 75%; (b) **17** (1 equiv.), *n*-BuLi (2.5 equiv.; 1.6 M in hexane), DME, −78°C, 0.25 h; then −78°C→−20°C; then *N*-methoxy-*N*-methyl acetamide (1.5 equiv.), −78°C→rt, 75%; (c) $[(Ph_3P)CuH]_6$ (30 mol%), CH_2Cl_2, rt, 90%. DME=1,2-dimethoxyethane; Ar=2,4,6-triisopropylbenzene.

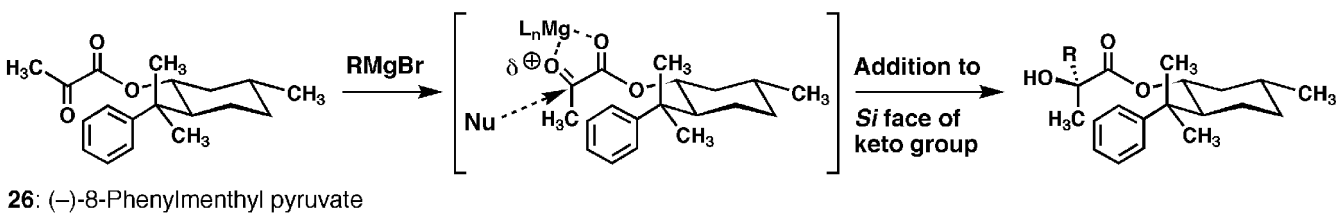


Scheme 5. *Reagents and conditions*: (a) Et_2O–THF (4:1), −78°C; then methyl pyruvate (2 equiv.), 62%; (b) DME, −78°C; then *N*,*N*′-dimethylformamide (2 equiv.), 91%; (c) LiCN (3 equiv.), (2*S*,4*R*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl 1,3,2-oxazaphospholidin-2-one (**23**) (3 equiv.), THF, rt, 95% of **24** as a mixture of diastereomers; (d) *n*-BuLi (1.1 equiv.; 1.7 M in hexane), THF, −108°C, 0.75 h; then DMPU, 0.75 h; then methyl iodide (3 equiv.), 33% **25** plus 56% recovered **24**. DME=1,2-dimethoxyethane; DMPU=*N*,*N*′-dimethylpropyleneurea.

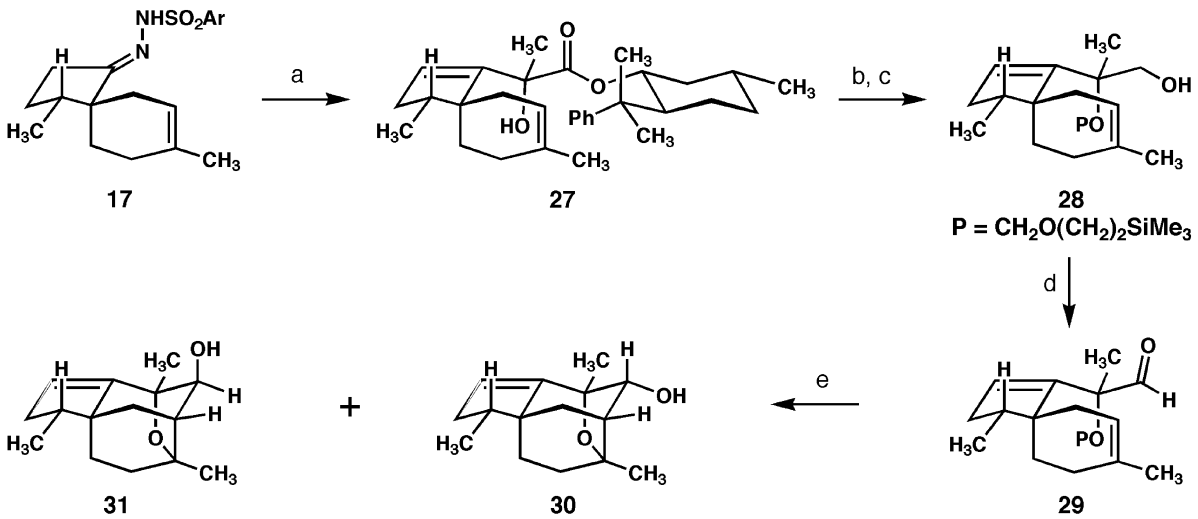
conjugate reduction of the newly formed enone moiety with Stryker's reagent.[20] In the event, compound **18** reacted efficiently and chemoselectively with Stryker's reagent, although the desired ketone **5** was the minor component of a 3:1 mixture of diastereoisomeric methyl ketones. The structure of the major diastereoisomer **19** was deduced from an X-ray crystallographic analysis of its crystalline trisylhydrazone derivative. Since attempts to epimerize **19** to **5** were unsuccessful, we elected to delay the reduction of the five membered ring double bond to a later stage in the synthesis. Our hope was that the prospects for a favorable stereochemical outcome would be brighter in more rigid molecular contexts. This idea proved to be feasible.

In the course of our studies, we also found that the putative vinyllithium reagent **20** (Scheme 5), derived from trisylhydrazone **17**, joined smoothly with methyl pyruvate to give **21** as a mixture of tertiary alcohol diastereomers and with *N*,*N*′-dimethylformamide to give enal **22**. The latter compound was considered attractive in light of Schrader's novel method for achieving diastereoselective alkylations of chiral cyanohydrin derivatives.[21] To this end, enal **22** was reacted with lithium cyanide and Schrader's (−)-pseudoephedrine-derived reagent **23**. This reaction afforded **24** as mixture of epimers, which was not resolved but instead treated sequentially with *n*-butyllithium at −108°C in THF-DMPU and methyl iodide. This alkylation process afforded the desired diastereoisomer **25** in only 33% yield together with 56% recovered starting material. The chiral auxiliary could be cleaved with excess titanium tetraisopropoxide, however this reaction proved to be capricious. Moreover, efforts to improve the yield for the key methylation step were not successful.

At this stage, we opted to build on the observation that vinyllithium reagent **20** reacts with methyl pyruvate to give compound **21** (Scheme 5) and investigate the reaction of **20** with chiral pyruvate derivatives. Nucleophilic additions of Grignard reagents to chiral pyruvate esters were studied in the early 1900's by McKenzie[22] and are among the earliest examples of asymmetric carbon–carbon bond forming reactions.[23] These pioneering studies by McKenzie and subsequent experiments by Prelog and co-workers in the early 1950's formed the basis of 'Prelog's rule' for rationalizing the stereochemical outcomes of nucleophilic additions to chiral pyruvate esters.[24] In 1975, Corey and Ensley described a convenient synthesis (−)-8-phenylmenthol from (*R*)-(+)-pulegone (**15**) and showed that this chiral alcohol is a powerful chiral auxiliary in asymmetric Diels–Alder reactions.[25,26] Our aim was to react carbon nucleophiles derived from trisylhydrazone **17** with the pyruvate ester of (−)-8-phenylmenthol (compound **26**), and we were well aware of the prior studies by the Whitesell laboratory showing that Grignard reagents add to the keto group of (−)-8-phenylmenthyl pyruvate with high margins of diastereoselectivity (Scheme 6).[27]



Scheme 6.



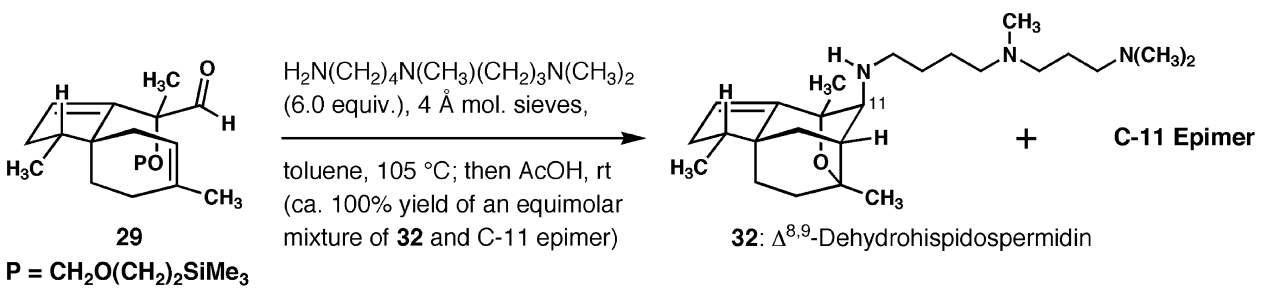
Scheme 7. *Reagents and conditions*: (a) *n*-BuLi (2.05 equiv.), Et_2O-THF, −78→-20°C; then $MgBr{\cdot}OEt_2$, −78°C; then **26**, −78°C→rt, 55%; (b) SEMCl, *n*-Bu_4NI, *i*-Pr_2NEt, CH_2Cl_2, 50°C, ca. 100%; (c) DIBAL-H, toluene, −78°C, 93%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; then *i*-Pr_2NEt, −78°C→rt, ca. 100%; (e) AcOH, rt, 2d, 83% or AcOH, 80°C, 3 h, 87% (2.5:1 mixture of diastereoisomers **30** and **31**). SEMCl=$ClCH_2OCH_2CH_2Si(CH_3)_3$.

It was encouraging that the putative vinyllithium reagent **20**, despite its sterically congested nature, could be trapped with certain carbon electrophiles to give new carbon–carbon bonds (Schemes 4 and 5). However, attempts to join **20** with (−)-8-phenylmenthyl pyruvate (**26**) through a carbonyl addition reaction were unsuccessful, presumably owing to the basicity of the organolithium reagent. Fortunately, a small procedural modification permitted a successful outcome. If the reaction of trisylhydrazone **17** with *n*-butyllithium is followed by the addition of $MgBr_2{\cdot}OEt_2$, a transmetalation of **20** to the corresponding Grignard reagent presumably occurs and this species is capable of attacking the reactive keto function of **26** (Scheme 7). While the yield for this key carbonyl addition step is moderate, we isolated a single tertiary alcohol diastereoisomer, which was tentatively assigned the stereochemistry shown in **27** by analogy to the stereochemical outcomes reported by Whitesell and co-workers.[27]

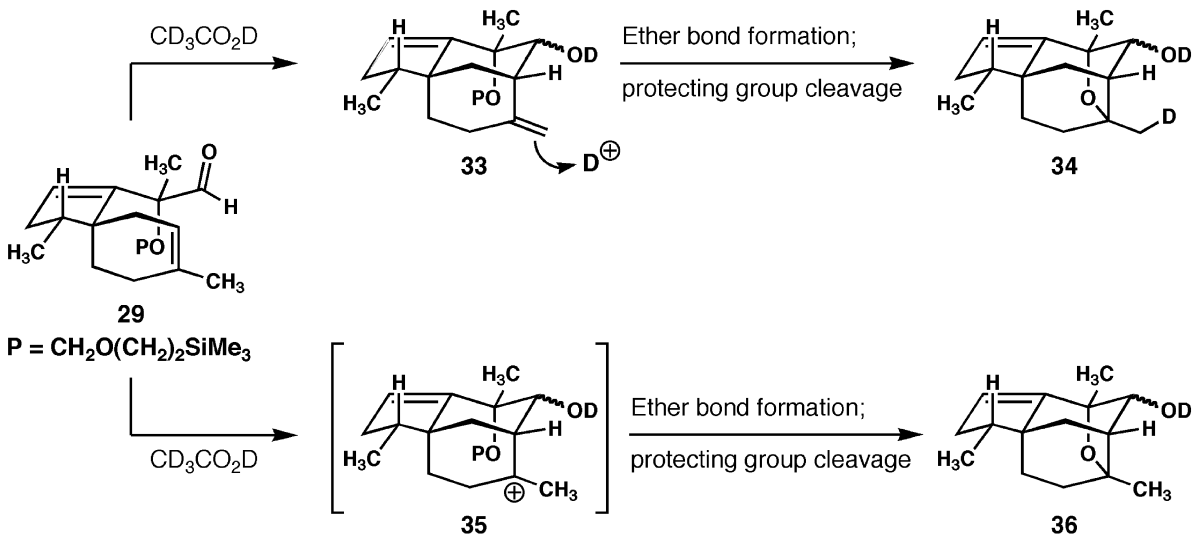
Having constructed the key hydroxyl-bearing stereocenter, we turned our attention to the challenge of forming the remaining two rings of (−)-hispidospermidin (**1**). Our initial hope was that a partial reduction of 8-phenylmenthyl ester **27** with diisobutylaluminum hydride (DIBAL-H) would result in the formation of the corresponding α-hydroxy aldehyde, an attractive substrate for a hydroxyl-assisted, intramolecular carbonyl ene reaction.[28,29] However, such an α-hydroxy aldehyde is likely unstable because several compounds were produced when **27** was treated with DIBAL-H. If the tertiary hydroxyl of **27** was first protected in the form of a 2-(trimethylsilyl)ethoxymethyl (SEM) ether[30] under the conditions shown, the subsequent reduction of the 8-phenylmenthyl ester with DIBAL-H was uneventful. This two-stage sequence afforded alcohol **28** in 93% yield and was followed by an efficient Swern oxidation[31] to bicyclic aldehyde **29**.

In light of some earlier observations by the Marshall laboratory,[32] we should have expected that even silica gel might induce the relatively electron-rich trisubstituted alkene of **29** to react with the proximate aldehyde function. In fact, both of the needed rings form to some extent when compound **29** is exposed to silica gel! This pleasing structural change afforded a 2.5:1 mixture of epimeric alcohols **30** and **31** and was much more efficient when **29** was dissolved in acetic acid and heated to 80°C for 3 h or simply allowed to stand for two days at room temperature. To us, the surprising aspect of this process was that the oxacycle of **1** formed via participation by the SEM ether oxygen. Although cleavage of the SEM ether in **29** could conceivably precede the formation of the six-membered ring, we observed that the SEM ether of alcohol **28** did not suffer any cleavage on standing in acetic acid at room temperature.

It was also possible to introduce the trimethylspermidine chain through a straightforward condensation reaction between aldehyde **29** and trimethylspermidine (Scheme 8).



Scheme 8.



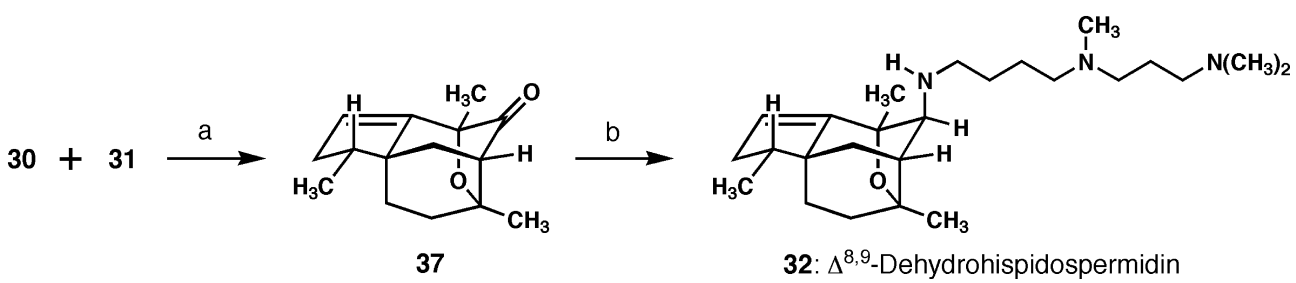
Scheme 9.

When the resulting crude imine was dissolved in acetic acid at room temperature, a high-yielding bicyclization to $\Delta^{8,9}$-dehydrohispidospermidin (**32**) and its equatorial side chain diastereoisomer occurred.[33] To gain some insight into the nature of these remarkable acid-induced transformations, we conducted the bicyclization of aldehyde **29** in d_4-acetic acid. Our hope was that this experiment might discriminate between the two distinct mechanistic scenarios shown in Scheme 9. If compound **33** is a genuine intermediate in this process, then one carbon-bound deuterium atom would be observed in the tetracyclic product **34**. On the other hand, if the observed bicyclization occurs via the fugitive tertiary carbocation **35**, then a carbon-deuterium bond would not be found in tetracycle **36**. In the key experiment, no deuterium was incorporated into the tetracyclic product, an outcome that is consistent with a Prins-like mechanism and a proximity-facilitated attack of a SEM ether oxygen on a transient tertiary carbocation. A carbonyl ene mechanism would have exclusively afforded the equatorial alcohol epimer **30** (Scheme 7)[32a] and would have given a deuterated product. The tertiary cation formed by the first ring closure bonds with the nearest oxygen of the SEM ether, thus causing cleavage of the protecting group and the formation of the desired tetracyclic structure.

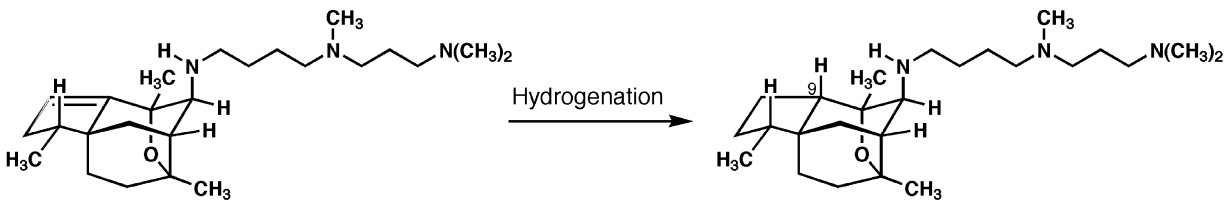
With the architecture of (−)-hispidospermidin (**1**) in place, we could address the problem of introducing the conspicuous trimethylspermidine side chain in a stereocontrolled fashion and the potentially challenging task of reducing the five-membered ring double bond in a stereoface-selective manner. To this end, the epimeric alcohols **30** and **31** were efficiently converted to tetracyclic ketone **37** via a Swern oxidation.[31] Under reaction conditions developed previously by the Danishefsky laboratory in the course of their pioneering synthesis of **1**,[5] ketone **37** was condensed with trimethylspermidine and the resulting imine was reduced cleanly and with complete diastereoselectivity with sodium cyanoborohydride to $\Delta^{8,9}$-dehydrohispidospermidin (**32**). The addition of hydride to the imine had occurred on the side away from the crowded cage-like framework; this outcome may also have been favored by an interaction between the reducing agent and the ether oxygen of the cage (Scheme 10).[5b]

To complete a synthesis of (−)-hispidospermidin (**1**), we needed only to hydrogenate **32** on the side of the Lewis basic amine chain (Scheme 11). Although the prospects for effecting a directed hydrogenation[34] of **32** were considered favorable due to the high haptophilicity of amines[35] and the close spatial relationship between the trimethylspermidine moiety and the ring alkene in **32**, this task proved difficult.

A number of hydrogenation catalysts, solid supports, solvents, and pressures were screened to optimize the hydrogenation reaction (Table 1). In many cases, the



Scheme 10. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; then *i*-Pr_2NEt, −78°C→rt, ca. 100%; (b) $H_2N(CH_2)_4N(CH_3)(CH_2)_3N(CH_3)_2$ (6 equiv.), PPTS (1.1 equiv.), 4 Å mol. sieves, toluene, 105°C, 3d; then $NaCNBH_3$ (2.2 equiv.), 10% AcOH in MeOH, rt, 12 h, 90%. PPTS=pyridinium *p*-toluenesulfonate.



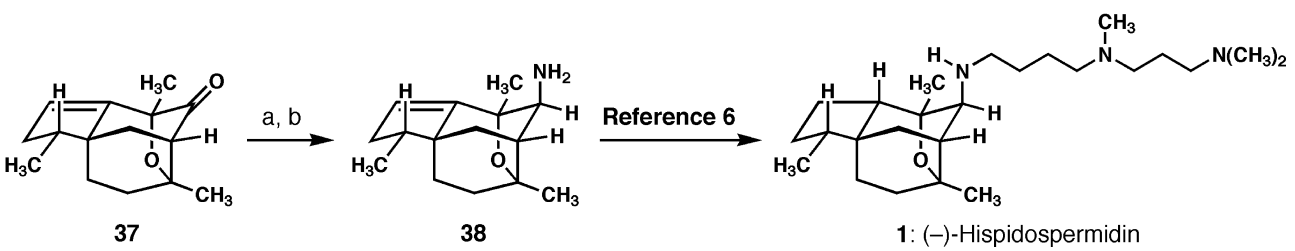
Scheme 11.

Table 1. Hydrogenation conditions

Catalyst	Support	Pressure (atm)	%Catalyst	Solvent	Yield	1:C-9 epimer
Rh	Alumina	1	5	EtOAc	NR	
	Alumina	82	10	EtOAc	NR	
	Alumina	82	20	EtOAc	~10%	2.5:1
	Alumina	82	200	EtOAc	60%	2.5:1
	Carbon	82	200	EtOAc	70%	3:1
Pt	Alumina	82	30	EtOAc	NR	
	Alumina	82	200	EtOAc	NR	
	Carbon	82	10	Diglyme	NR	
Pd	Alumina	82	30	EtOAc	NR	
	Alumina	82	200	EtOAc	30%	1:2.7
	Carbon	82	10	Diglyme	NR	
PtO_2	–	1	10	AcOH	Decomposition	
		82	25	EtOH	NR	
Raney Ni	–	82	200	MeOH	NR	
Crabtree:	–	1	10	CH_2Cl_2	NR	
$Ir(cod)py(PCy_3)PF_6$		82	10	CH_2Cl_2	NR	
Rh^+: $Rh(DIPHOS-4)^+$	–	82	25	CH_2Cl_2	NR	
Wilkinson: $Rh(PPh_3)_3Cl$	–	82	50	Benzene	NR	
Diimide (H–N=N–H)	–	1	300	MeOH	NR	

trimethylspermidine side chain poisoned the catalysts and the desired reduction did not proceed. We found that rhodium catalysts allowed the greatest coordination of the spermidine chain and gave the best selectivity for hydrogenation on the desired alkene stereoface. However, even rhodium was significantly poisoned by the polyamine side chain, and, with 20 mol% catalyst loading, only 10% of the product could be isolated. The best yield and stereoselectivity was obtained by hydrogenating **32** at 82 atm in ethyl acetate and in the presence of 2 equiv. of rhodium on carbon. These conditions afforded a 70% yield of a 3:1 mixture of diastereoisomeric reduction products in favor of (−)-hispidospermidin (**1**). Despite a strong effort, this 3:1 mixture of diastereomeric reduction products could not be resolved, even via HPLC.

In our search for a fully stereocontrolled solution to the problem of reducing the ring alkene, we reacted ketone **37** with hydroxylamine and obtained the expected oxime in 100% yield (Scheme 12). When a solution of this oxime in ether at room temperature was exposed to nickel aluminide, the black precipitate that arises when lithium aluminum hydride is reacted with nickel (II) chloride, a completely diastereoselective reduction took place and provided primary amine **38** in 97% yield. This two-step method is excellent for converting ketones into primary amines.[36] In their creative synthesis of (−)-hispidospermidin (**1**), Overman and Tomasi transformed **38** to **1** by a three-step reaction sequence featuring a completely diastereoselective, high-pressure hydrogenation of the alkene in **38**.[6] By this known pathway, we also converted **38** to **1**. The spectroscopic and physical properties of our sample of synthetic (−)-hispidospermidin matched those from an authentic sample of the natural product kindly provided to us by the Overman laboratory. Our concise, enantiospecific synthesis of (−)-hispidospermidin (**1**) from (*R*)-(+)-pulegone (**15**) based on a facile, acid-catalyzed bicyclization was thus complete.



Scheme 12. *Reagents and conditions*: (a) $HONH_2{\cdot}HCl$ (2.0 equiv.), $NaOAc{\cdot}3H_2O$ (4.0 equiv.), EtOH, rt, ca. 100%; (b) $LiAlH_4$ (6.3 equiv.), $NiCl_2$ (6.3 equiv.), Et_2O, rt, 97%.

3. Experimental

3.1. General

Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen. Tetrahydrofuran (THF), toluene, diethyl ether, and methylene chloride (CH_2Cl_2) were dried by passing through activated alumina columns. Commercial reagents of high purity were purchased and used without further purification unless otherwise noted. Organolithium reagents were titrated using *sec*-butanol in ether, with 1,10-phenanthroline as an indicator. Reactions were monitored by thin-layer chromatography (TLC) carried out on either 0.25 mm E. Merck silica gel plates (60 F_{254}) or aluminum oxide plates (60 F_{254}) using UV light and aqueous ceric sulfate-phophomolybdic acid or ethanolic *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel 60 (230–400 mesh) was used for flash column chromatography. Instrumentation: FT-IR spectra were obtained on a Perkin–Elmer Paragon 500 FT-IR. NMR spectra were obtained on Bruker DRX-600, DRX-500, or AMX-400 instruments and calibrated to the residual solvent peak. The multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, m=multiplet, app s=apparent singlet; app d=apparent doublet; app t=apparent triplet.

3.1.1. 2,4,6-Triisopropylbenzenesulfonyl hydrazone 17. Ketone **16** (see Ref. 15) (1.41 g, 7.9 mmol) and trisyl hydrazide (2.83 g, 9.5 mmol) were placed in a flask flushed with argon. Dry acetonitrile (3.95 mL) and concentrated hydrochloric acid (0.79 mL) were added. The reaction was protected from light and stirred at room temperature for 15 h. The reaction mixture was cooled to −20°C for 2 h and the solid was filtered off. The solid was mostly pure hydrazone, which was further purified by recrystallization in methanol to give hydrazone **17** (2.26 g, 4.91 mmol, 80%) as a colorless crystal. TLC: R_f=0.38 (SiO_2, 1:1 hexane/diethyl ether); IR (film) 3221, 2957, 1593, 1158, 1153 cm^{-1}; mp=145–147°C (dec.); ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 2H), 7.00 (s, 1H), 5.25 (s, 1H), 4.16 (heptet, J=6.8 Hz, 2H), 2.89 (heptet, J=7.0 Hz, 1H), 2.2 (m, 2H), 1.9 (m, 3H), 1.7–1.3 (band, 6H), 1.45 (s, 3H), 1.25 (d, J=7.0 Hz, 12H), 1.24 (d, J=7.0 Hz, 6H), 0.81 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 152.9, 151.0, 133.3, 131.2, 123.5, 118.9, 47.1, 39.8, 34.2, 33.9, 29.7, 28.1, 26.8, 25.1, 24.8, 24.7, 24.4, 23.6, 23.5, 23.4, 14.5; MS (ESI) $C_{27}H_{42}N_2O_2S$ *m/z* calcd for $[M+H]^+$ 460; found 460.

3.1.2. Enone 18. Trisyl hydrazone **17** (1.84 g, 4 mmol) was placed in a flame-dried flask with a glass magnetic stirring bar. It was dissolved in dimethoxyethane (150 mL) and cooled to −78°C. *n*-BuLi (1.6 M in hexane, 6.25 mL, 10 mmol) was added dropwise. The solution turns dark yellow then orange. The reaction was stirred at −78°C for 15 min. The cooling bath was removed and the solution was allowed to warm over 15 min during which nitrogen gas evolved. The solution was cooled to −78°C and *N*-methoxy-*N*-methyl acetamide (0.46 mL, 6 mmol) was added in one portion after which the reaction was stirred for 10 min. The reaction was warmed to room temperature and quenched with saturated aqueous ammonium chloride (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 9:1 hexane/diethyl ether) affording enone **18** (0.61 g, 3 mmol, 75%) as a colorless oil. TLC: R_f=0.38 (SiO_2, 4:1 hexane/diethyl ether); IR (film) 2923, 1668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (t, J=2.6 Hz, 1H), 5.29 (m, 1H), 2.63 (ddd, J=2.2, 7.0, 18.3 Hz, 1H), 2.44 (ddd, J=6.3, 11.8, 13.6 Hz, 1H), 2.28 (s, 3H), 2.27 (m, 1H), 2.14 (m, 1H), 2.04–1.82 (band, 3H), 1.74–1.52 (band, 2H), 1.65 (s, 3H), 0.92 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 149.9, 144.2, 133.8, 119.7, 49.5, 39.2, 38.9, 32.9, 28.2, 28.0, 24.4, 23.5, 16.7; MS (ESI) $C_{14}H_{20}O$ *m/z* calcd for $[M+H]^+$ 205; found 205.

3.1.3. Enal 22. Trisyl Hydrazone **17** (1.38 g, 3 mmol) was placed in a flame-dried flask with a glass magnetic stirring bar. It was dissolved in 1,2-dimethoxyethane (100 mL) and cooled to −78°C. *n*-BuLi (1.6 M in hexane, 4.7 mL, 7 mmol) was added dropwise. The solution turns dark yellow then orange. The reaction was stirred at −78°C for 15 min. The cooling bath was removed and the solution was allowed to warm over 15 min during which nitrogen gas evolved. The solution was cooled to −78°C and dimethylformamide (0.46 mL, 6 mmol) was added in one portion after which the reaction was stirred for 45 min. The reaction was warmed to room temperature and quenched with saturated aqueous ammonium chloride (100 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 9:1 hexane/diethyl ether) affording enal **22** (0.52 g, 2.7 mmol, 91%) as a colorless oil. TLC: R_f=0.40 (SiO_2, 4:1 hexane/diethyl ether); ^1H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 6.77 (t, J=2.7 Hz, 1H), 5.33 (m, 1H), 2.64 (ddd, J=2.6, 7.3, 18.7 Hz, 1H), 2.18 (m, 2H), 2.13 (m, 1H), 2.05 (dt, J=3.7, 19.1 Hz, 1H), 1.98 (m, 1H), 1.85 (m, 2H), 1.66 (s, 3H), 1.65 (m, 1H), 0.94 (d, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.2, 152.9, 152.1, 134.6, 120.2, 48.2, 42.2, 39.5, 33.9, 28.2, 25.4, 23.9, 16.3; MS (ESI) $C_{13}H_{18}O$ *m/z* calcd for $[M+H]^+$ 191; found 191.

3.1.4. Cyanophosphate 24. To a slurry of solid lithium cyanide (0.2 g, 6 mmol) in THF (20 mL) was added enal **22** (0.38 g, 2 mmol) and compound **23** (see Ref. 21) (1.46 g, 6 mmol) in THF (20 mL). The reaction was stirred at room temperature for 1 h at which time more lithium cyanide (200 mg, 6 mmol) was added. The reaction was quenched with water (50 mL) and the layers were separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 19:1 CH_2Cl_2/diethyl ether) to give **24** as a mixture of two diastereomers that were not separated (809 mg, 1.9 mmol, 95%). TLC: R_f=0.65 and 0.70 (SiO_2, 3:1 ethyl acetate/hexane); HRMS (MALDI-FTMS) $C_{24}H_{31}N_2O_3P$ *m/z* calcd for $[M+Na]^+$ 449.1970; found 449.1966.

3.1.5. Cyanophosphate 25. To a solution of the diastereoisomers shown as **24** (312 mg, 0.73 mmol) in THF (7 mL) at −108°C was added *n*-BuLi (1.7 M in hexane, 0.47 mL,

0.80 mmol) dropwise. The solution was stirred for 45 min at −108°C. *N*,*N*′-Dimethylpropyleneurea (0.13 mL) was added dropwise and the mixture was stirred for 45 min at −108°C. Methyl iodide (0.14 mL, 2.2 mmol) was added in one portion and the reaction was allowed to stir for 1 h. The reaction was quenched with aqueous saturated ammonium chloride (20 mL) and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (2×20 mL) and CH_2Cl_2 (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 25:1 CH_2Cl_2/diethyl ether) to give **25** (107 mg, 0.24 mmol, 33%) and starting material **24** (173 mg, 0.41 mmol, 56%). TLC: R_f=0.49 (SiO_2, 3:1 ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 5H), 6.06 (s, 1H), 5.35 (s, 1H), 4.91 (dd, *J*=1.5, 9.2 Hz, 1H), 3.30 (m, 1H), 2.62 (d, *J*=11.4 Hz, 3H), 2.60 (m, 1H), 2.42 (m, 1H), 2.24 (m, 1H), 2.15 (m, 1H), 2.14 (s, 3H), 2.06 (m, 2H), 1.91 (m, 2H), 1.80 (dd, *J*=3.3, 16.9 Hz, 1H), 1.72 (s, 3H), 1.16 (d, *J*=6.2 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9 (d, J_{CP}=6.7 Hz), 136.1 (d, J_{CP}=7.4 Hz), 133.5, 131.0, 129.1, 128.6, 127.1, 119.7, 119.0 (d, J_{CP}=3.1 Hz), 85.8, 72.9 (d, J_{CP}=9.8 Hz), 61.7 (d, J_{CP}=11.5 Hz), 50.6 (d, J_{CP}=2.6 Hz), 39.8, 37.4, 33.4, 28.2 (d, J_{CP}=3.1 Hz), 27.8, 27.7, 24.8, 23.5, 16.4, 15.2 (d, J_{CP}=10.5 Hz); HRMS (MALDI-FTMS) $C_{25}H_{33}N_2O_3P$ *m*/*z* calcd for $[M+Na]^+$ 463.2126; found 463.2127.

3.1.6. 8-Phenylmenthyl ester 27. To a solution of trisyl hydrazone **17** (2.30 g, 5 mmol) in diethyl ether/THF (5:1, 60 mL) at −78°C was added *n*-BuLi (1.5 M in hexane, 6.84 mL, 10.25 mmol) dropwise. The dark red solution was stirred for 10 min. The cooling bath was removed and the solution was allowed to warm to −20°C over 15 min during which nitrogen gas evolved. The solution was cooled to −78°C and magnesium bromide diethyletherate (0.83 M, 6.3 mL, 5.25 mmol) was added dropwise. The mixture was stirred for 10 min and then 8-phenylmenthyl pyruvate (**26**) (1.59 g, 5.25 mmol) in 5 mL of THF was added in one portion. After stirring at −78°C for 10 min, the reaction was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 15:1 hexane/diethyl ether) affording 8-phenylmenthyl ester **27** (1.27 g, 2.73 mmol, 55%) as a colorless oil. TLC: R_f=0.57 (SiO_2, 9:1 hexane/ethyl acetate); IR (film) 3512, 2957, 2922, 1710 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (m, 4H), 7.17 (m, 1H), 5.62 (app t, *J*=2.4 Hz, 1H), 5.28 (app s, 1H), 4.94 (dt, *J*=4.4, 11.0 Hz, 1H), 3.04 (s, 1H), 2.46 (ddd, *J*=1.7, 6.5, 16.2 Hz, 1H), 2.25–0.75 (band, 16H), 1.65 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 0.90 (d, *J*=6.5 Hz, 3H), 0.86 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 150.5, 149.4, 133.6, 128.0, 126.2, 125.4, 125.3, 120.0, 77.5, 75.7, 51.4, 50.0, 41.4, 40.1, 39.9, 37.4, 34.3, 33.7, 31.5, 29.3, 28.0, 27.2, 26.4, 25.7, 25.2, 24.8, 23.4, 22.6, 21.7, 16.5; $[\alpha]_D^{25}$=−34.7° (*c*=1.00, $CHCl_3$); HRMS (MALDI-FTMS) $C_{31}H_{44}O_2$ *m*/*z* calcd for $[M+Na]^+$ 487.3188; found 487.3195.

3.1.7. 2-(Trimethylsilyl)ethoxymethyl (SEM) ether of 27. To a solution of 8-phenylmenthyl ester **27** (0.95 g, 2 mmol) in CH_2Cl_2 (2 mL) was added trimethylsilylethoxymethyl chloride (0.53 mL, 3 mmol), tetrabutylammonium iodide (1.11 g, 3 mmol), and diisopropylethyl amine (0.52 mL, 3 mmol) and the mixture was heated to 50°C in a sealed flask for 14 h. The mixture was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate solution (10 mL) and the solvent was evaporated under reduced pressure. The aqueous layer was extracted with hexane (3×10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 24:1 hexane/diethyl ether) affording the SEM-protected ester (1.2 g, 2 mmol, 100%) as a colorless oil. TLC: R_f=0.38 (SiO_2, 9:1 hexane/diethyl ether); IR (film) 2947, 2918, 1720, 1016 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.16 (m, 1H), 5.55 (m, 1H), 5.28 (app s, 1H), 4.87 (dt, *J*=4.0, 10.5 Hz, 1H), 4.76 (d, *J*=7.4 Hz, 1H), 4.67 (d, *J*=7.0 Hz, 1H), 3.77 (m, 1H), 3.63 (m, 1H), 2.47 (m, 2H), 2.26 (dt, *J*=6.1, 12.7 Hz, 1H), 2.12–0.7 (band, 16H), 1.63 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H), 1.24 (s, 3H), 0.89 (d, *J*=7.0 Hz, 3H), 0.84 (d, *J*=6.1 Hz, 3H), 0.02 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 150.6, 147.9, 132.9, 128.0, 126.5, 125.7, 125.3, 120.5, 91.1, 82.4, 76.8, 65.9, 51.7, 50.6, 41.5, 40.5, 39.4, 37.4, 34.5, 33.0, 31.3, 31.2, 28.1, 27.6, 25.7, 24.2, 23.5, 22.8, 21.8, 18.2, 16.8, −1.5.

3.1.8. Alcohol 28. To a −78°C solution of the SEM ether of 8-phenylmenthyl ester **27** (0.50 g, 0.84 mmol) in toluene (28 mL) was added diisobutylaluminum hydride (1 M in toluene, 2.5 mL, 2.52 mmol). After 5 min, the mixture was warmed to 0°C and stirred for 10 min. The reaction was quenched by the slow addition of methanol (1 mL) then poured into 50 mL of saturated aqueous sodium potassium tartrate and 30 mL of ethyl acetate. After stirring for 10 min, the layers were separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, CH_2Cl_2) affording phenyl menthol (180 mg, 0.78 mmol, 93%) and alcohol **28** (285 mg, 0.78 mmol, 93%) as a colorless oil. TLC: R_f=0.18 (SiO_2, CH_2Cl_2); IR (film) 3466, 2954, 1019 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.60 (app s, 1H), 5.28 (app s, 1H), 4.77 (d, *J*=7.5 Hz, 1H), 4.65 (d, *J*=7.5 Hz, 1H), 3.72 (m, 2H), 3.58 (m, 2H), 2.99 (dd, *J*=4.4, 9.2 Hz, 1H), 2.53 (dd, *J*=4.9, 16.7 Hz, 1H), 2.13 (m, 2H), 2.02 (m, 2H), 1.87 (m, 1H), 1.78 (m, 2H), 1.68 (dd, *J*=3.3, 16.2 Hz, 1H), 1.65 (s, 3H), 1.41 (s, 3H), 0.94 (m, 2H), 0.88 (d, *J*=6.5 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 133.5, 127.1, 120.2, 89.6, 81.0, 67.7, 65.6, 51.1, 39.2, 37.3, 33.5, 28.1, 26.1, 23.4, 21.9, 18.2, 16.8, −1.5; $[\alpha]_D^{25}$=−11.5° (*c*=1.48, $CHCl_3$); MS (ESI) $C_{21}H_{38}O_3Si$ *m*/*z* calcd for $[M+Na]^+$ 389; found 389.

3.1.9. Aldehyde 29. To a solution of oxalyl chloride (139 μL, 1.6 mmol) in CH_2Cl_2 (10 mL) at −78°C was added dropwise DMSO (226 μL, 3.2 mmol) and the resulting solution was stirred at −78°C for 30 min. Alcohol **28** (194 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) was added and the resulting solution was stirred for 10 min at −78°C, then at −40°C for 20 min. Diisopropylethylamine (0.92 mL) was

added dropwise and the solution was stirred at −40°C for 10 min. then allowed to warm to room temperature. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 15:1 hexane/ethyl acetate with 1% Et_3N) to give aldehyde **29** (193 mg, 0.53 mmol, 100%) as a colorless oil. TLC: R_f=0.57 (SiO_2, CH_2Cl_2); IR (film) 2954, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 5.38 (m, 1H), 5.28 (app s, 1H), 4.84 (d, J=7.4 Hz, 1H), 4.66 (d, J=7.4 Hz, 1H), 3.78 (m, 1H), 3.53 (m, 1H), 2.56 (ddd, J=1.4, 6.2, 16.7 Hz, 1H), 2.25–1.65 (band, 8H), 1.65 (s, 3H), 1.49 (s, 3H), 0.97–0.83 (m, 2H), 0.87 (d, J=6.7 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 145.5, 133.5, 129.1, 120.0, 89.8, 83.6, 65.7, 51.3, 39.2, 37.9, 33.5, 28.0, 25.7, 23.5, 19.3, 18.0, 16.8, −1.5.

3.1.10. Tetracyclic alcohol epimers 30 and 31. Aldehyde **29** (185 mg, 0.51 mmol) in 3 mL of glacial acetic acid was heated to 80°C for 3 h. The acetic acid was evaporated under reduced pressure and the product was purified by column chromatography (SiO_2, 2:1 hexane/diethyl ether) to yield a 2.5:1 mixture of alcohol diastereoisomers **30** and **31** (104 mg, 0.44 mmol, 87%) as white solids. Equatorial alcohol **30** (major): TLC: R_f=0.21 (SiO_2, 1:1 hexane/diethyl ether); IR (film) 3418, 2929 1447 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.40 (app d, J=2.2 Hz, 1H), 3.61 (d, J=7.9 Hz, 1H), 2.33 (ddd, J=3.1, 7.4, 15.4 Hz, 1H), 2.25 (d, J=5.7 Hz, 1H), 2.01–1.57 (band, 8H), 1.43 (s, 3H), 1.38 (s, 3H), 1.10 (d, J=12.7 Hz, 1H), 0.95 (d, J=7.0 Hz, 3H); ^{13}C NMR (150 M Hz, $CDCl_3$) δ 155.6, 120.0, 84.0, 82.4, 82.0, 50.9, 47.8, 45.3, 39.2, 37.0, 32.1, 29.5, 26.0, 15.5, 14.6; $[\alpha]_D^{25}$=−84.9° (c=1.36, $CHCl_3$); MS (GC) $C_{15}H_{22}O_2$ m/z calcd for M^+ 234; found 234. Axial alcohol **31** (minor): TLC: R_f=0.29 (SiO_2, 1:1 hexane/diethyl ether); IR (film) 3379, 2928, 1456 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.53 (app d, J=2.2 Hz, 1H), 3.91 (dd, J=5.8, 8.3 Hz, 1H), 2.31 (m, 1H), 2.15 (t, J=5.2 Hz, 1H), 2.03–1.93 (m, 2H), 1.82 (dd, J=8.8, 14.0 Hz, 1H), 1.71 (dd, J=9.7, 12.3 Hz, 1H), 1.65 (m, 2H), 1.45–1.34 (band, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 0.98 (d, J=6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.7, 123.8, 80.0, 79.2, 76.5, 47.4, 46.1, 45.0, 38.8, 32.4, 30.7, 29.2, 25.9, 19.2, 14.8; $[\alpha]_D^{25}$=−75.0° (c=0.56, $CHCl_3$); MS (GC) $C_{15}H_{22}O_2$ m/z calcd for M^+ 234; found 234.

3.1.11. Tetracyclic ketone 37. To a solution of oxalyl chloride (114 μL, 1.3 mmol) in CH_2Cl_2 (15 mL) at −78°C was added dropwise DMSO (185 μL, 2.6 mmol) and the resulting solution was stirred at −78°C for 30 min. The epimeric mixture of alcohols **30** and **31** (108 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) was added and the resulting solution was stirred for 10 min at −78°C, then at −40°C for 20 min. Diisopropylethylamine (0.76 mL) was added dropwise and the solution was stirred at −40°C for 10 min then allowed to warm to room temperature. The mixture was diluted with saturated aqueous NH_4Cl (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 19:1 hexane/EtOAc) to give ketone **37** (106 mg, 0.46 mmol, 100%) as a colorless oil. TLC: R_f=0.44 (SiO_2, 2:1 hexane/diethyl ether); IR (film) 2927, 1762 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 5.48 (m, 1H), 2.39 (m, 1H), 2.37 (d, J=7.0 Hz, 1H), 2.15 (dd, J=5.9, 13.2 Hz, 1H), 2.05 (m, 1H), 2.01–1.94 (m, 2H), 1.83 (dd, J=9.6, 12.7 Hz, 1H), 1.70 (m, 1H), 1.58 (m, 1H), 1.46 (d, J=13.1 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H), 0.97, (d, J=7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.1, 155.4, 122.9, 79.5, 77.4, 51.3, 47.4, 44.7, 39.9, 39.7, 31.4, 28.7, 25.9, 14.6, 14.2; $[\alpha]_D^{25}$=−262.6° (c=1.37, $CHCl_3$); MS (GC) $C_{15}H_{20}O_2$ m/z calcd for M^+ 232; found 232.

3.1.12. $\Delta^{8,9}$-Dehydrohispidospermidin (32). To a solution of tetracyclic ketone **37** (17 mg, 0.073 mmol) and N,N', N'-trimethylspermidine (82 mg, 0.44 mmol) in toluene (2 mL) was added pyridinium p-toluenesulfonate (2 mg, 0.08 mmol), and 4 Å molecular sieves (17 mg). The mixture was heated to 105°C for 3 days. The solvent was removed under reduced pressure and the residue was dissolved in 10% acetic acid in methanol (2 mL) and sodium cyanoborohydride (10 mg, 0.16 mmol) was added in one portion. The mixture was stirred for 12 h. The reaction was quenched by the slow addition of concentrated HCl to adjust the pH to 1, dilution with 2 mL of water, and extraction with diethyl ether (1×2 mL). The pH of the aqueous layer was adjusted to 11 with KOH and then extracted with dichloromethane (5×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (Al_2O_3, 2% MeOH in CH_2Cl_2) to give $\Delta^{8,9}$-dehydrohispidospermidin (**32**) (26.5 mg, 0.066 mmol, 90%) as a pale yellow oil. TLC: R_f=0.30 (SiO_2, 8:2:0.2 CH_2Cl_2/MeOH/NH_4OH); IR (film) 2931, 2862, 2778, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, J=2 Hz, 1H), 2.89 (d, J=5.0 Hz, 1H), 2.53 (t, J=6.5 Hz, 2H), 2.4–2.25 (band, 7H), 2.20 (s, 6H), 2.19 (s, 3H), 2.12 (t J=5.0 Hz, 1H), 1.95–1.2 (band, 13H), 1.35 (s, 3H), 1.23 (s, 3H), 1.15 (d, J=12.6 Hz, 1H), 0.93 (d, J=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 121.4, 80.2, 79.7, 65.4, 57.8, 57.6, 55.7, 47.6, 47.4, 45.4, 45.2, 44.1, 42.1, 38.6, 32.3, 30.7, 29.0, 28.3, 26.0, 25.3, 24.9, 19.9, 14.6; $[\alpha]_D^{25}$=−34.8° (c=0.52, $CHCl_3$); HRMS (MALDI-FTMS) $C_{25}H_{45}N_3O$ m/z calcd for $[M+H]^+$ 404.3635; found 404.3641.

3.1.13. Oxime derived from tetracyclic ketone 37. To a solution of ketone **37** (26 mg, 0.11 mmol) in ethanol (0.5 mL) at room temperature was added hydroxylamine hydrochloride (15 mg, 0.22 mmol) and then sodium acetate trihydrate (61 mg, 0.45 mmol). A white precipitate formed immediately. The reaction was stirred for 1 h and then diluted with water (1 mL) and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 6:1 CH_2Cl_2/diethyl ether) to give the desired oxime (28 mg, 0.11 mmol, 100%). TLC: R_f=0.39 (SiO_2, 1:1 hexane/diethyl ether); ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (m, 1H), 3.35 (d, J=5.3 Hz, 1H), 2.35 (m, 1H), 1.98 (m, 4H), 1.79 (dd, J=9.5, 12.6 Hz, 1H), 1.70 (m, 1H), 1.52 (s, 3H), 1.53 (m, 1H), 1.35 (d, J=12.9 Hz, 1H), 1.23 (s, 3H), 0.98 (d,

J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 155.8, 120.0, 80.4, 78.4, 47.7, 44.8, 42.6, 39.3, 37.8, 31.2, 28.7, 26.0, 15.8, 14.6.

3.1.14. Primary amine 38. To a room temperature suspension of nickel (II) chloride (90 mg, 0.69 mmol) in diethyl ether (3 mL) was added lithium aluminum hydride (26 mg, 0.69m mmol) in one portion. A black precipitate formed immediately. The oxime prepared above (28 mg, 0.11 mmol) in diethyl ether (2 mL) was added to the suspension. After stirring for 5 min, the reaction was quenched with water (1 mL) and filtered over Celite® to remove the precipitate. The precipitate was washed with CH_2Cl_2 and methanol. The organic layer was evaporated and the pH of the aqueous layer was adjusted to 10 and extracted with CH_2Cl_2 (5×3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography (SiO_2, 19:1 CH_2Cl_2/MeOH) to give primary amine **38** (25 mg, 0.107 mmol, 97%). The 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR were identical to those reported by Overman. HRMS (MALDI-FTMS) $C_{15}H_{23}NO$ *m/z* calcd for $[M+H]^+$ 234.1852; found 234.1860.

3.1.15. (−)-Hispidospermidin (1). To a solution of $\Delta^{8,9}$-dehydrohispidospermidin (**32**) (5.4 mg, 0.013 mmol) in ethyl acetate (0.5 mL) was added 5% rhodium on carbon (51 mg). The reaction vessel was purged with H_2 (3×200 psi), then pressurized to 1100 psi with H_2. After 4 days, the mixture was filtered over Celite® and concentrated to give (−)-hispidospermidin (**1**) and its C-9 epimer as an inseparable mixture (3.8 mg, 70% overall yield). NMR analysis revealed a 3:1 mixture of diastereoisomers favoring **1**. Hispidospermidin was also synthesized from primary amine **38** following the procedure of Overman and Tomasi (see Ref. 6) and purified by column chromatography (Al_2O_3, 2% MeOH in CH_2Cl_2). Data for (−)-Hispidospermidin (**1**): The 600 MHz ^{1}H NMR, ^{13}C 150 MHz NMR, and TLC mobility were identical to an authentic sample. $[\alpha]_D^{25}=-51.0°$ (c=0.48, $CHCl_3$); HRMS (MALDI-FTMS) $C_{25}H_{47}N_3O$ *m/z* calcd for $[M+H]^+$ 406.3792; found 406.3793.

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