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DYKAT of Vinyl Aziridines: Total Synthesis of (+)-Pseudodistomin D

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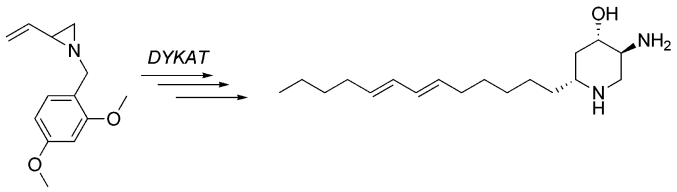
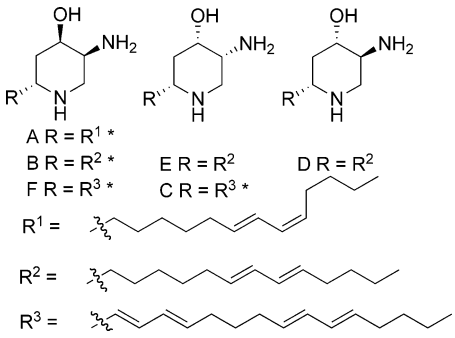
ABSTRACT



A concise total synthesis of (+)-pseudodistomin D was developed. The absolute stereochemistry was established through a dynamic kinetic asymmetric cycloaddition of an isocyanate to a vinyl aziridine. The piperidine core was constructed through a silver(I)-catalyzed hydroamination of an alkyne and subsequent diastereo- and regioselective reduction.

The synthesis of natural products constitutes an important arena in organic chemistry by not only providing sufficient quantities of biologically active materials but also by developing useful methodologies. Such efforts have focused on the pseudodistomin alkaloids (Scheme 1). Pseudodistomins A−C were isolated from the Okinawan tunicate *Pseudodistomina kanoko* by Kobayashi et al.[1] The structure of pseudodistomins A and B were subsequently revised by degradation and synthetic studies.[2] Later, the extract of the ascidian *Pseudodistomina megalarva* provided pseudodistomins B−F.[3] These alkaloids exhibit calmodulin-antagonistic activity and potent cytotoxicity against both murine leukemia and human epidermoid carcinoma KB cells.[1]

Scheme 1. Pseudodistomins



Progress toward the synthesis of the pseudodistomins has been limited. Only pseudodistomins A−C and F have been synthesized,[2,4,5] although several racemic and asymmetric syntheses of the substituted piperidine core have been

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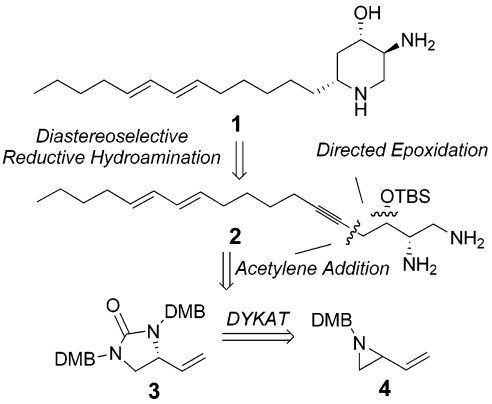
reported.[4] Pseudodistomin D, which contains a unique piperidine core from the synthesized pseudodistomins, has not been synthesized, although its piperidine core has been constructed in several nonselective approaches[4f,g] and one route from D-glucosamine.[4a] Herein we report the first total synthesis of (+)-pseudodistomin D **1**.

Recently, we reported the dynamic kinetic asymmetric cycloaddition of isocyanates to vinyl aziridines as an efficient process for the construction of chiral diamines.[6] We therefore began our studies toward the synthesis of pseudodistomin D where all other stereocenters would be directed by the stereocenter created through our DYKAT methodology (Scheme 2). We envisioned the piperidine core to be

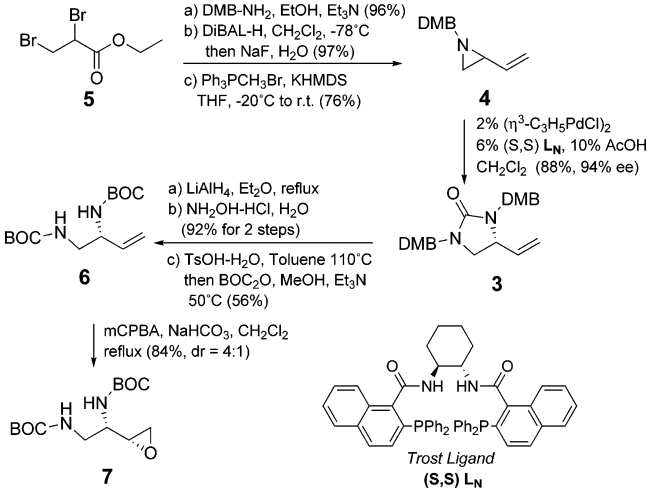
Scheme 2. Retrosynthesis



constructed through a novel catalytic diastereo- and regioselective reductive intramolecular hydroamination of diamino alkyne **2**. The requisite diamine **2** could be furnished through an aluminum-mediated acetylene addition to a terminal epoxide, which in turn could be constructed through a directed expoxidation. Finally, the absolute stereochemistry could be established through a dynamic kinetic asymmetric transformation (DYKAT) of vinyl aziridine **4**.

The synthesis of the head portion **7** was performed as illustrated in Scheme 3. Standard bis-substitution of commercially available ethyl 2,3-dibromopropionate **5** with 2,4-dimethoxybenzylamine followed by DIBAL-H reduction to the corresponding aldehyde and Wittig olefination furnished the protected vinyl aziridine **4** in high yield. The subsequent dynamic kinetic asymmetric cycloaddition of 2,4-dimethoxybenzyl isocyanate to the vinyl aziridine **4** provided DMB-protected vinyl imidazolidinone **3** in 94% ee and 88% yield. Following our previously reported procedure for the synthesis of diamines from imidazolidinones,[6] LAH reduction of the imidazolidinone **3** provided the sensitive imidazolidine in nearly quantative yield. Subsequent hydrolysis with hydroxylamine under weakly acidic conditions furnished (*R*)-1,2-bis-

Scheme 3. Synthesis of the Head Portion **7**[a]

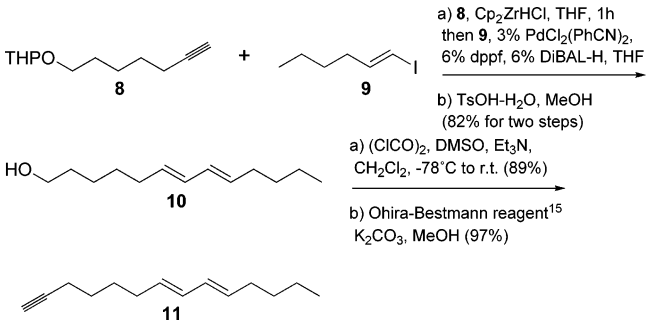


[a] DMB = 2,4-dimethoxybenzyl.

(2,4-dimethoxybenzylamino)-3-butene in 92% yield for two steps. Initial efforts to synthesize the BOC-protected diamines **6** from the bis-DMB-protected amines focused on first installing the BOC group prior to DMB deprotection. Unfortunately, standard conditions for DMB deprotection with DDQ afforded irreproducible results with only moderate yields. Removal of the DMB groups under acidic conditions using TsOH[8] and subsequent BOC protection of the primary amines in situ with excess Et_3N[9] afforded the requisite BOC-protected amines **6** in a reasonable 56% yield after recrystallization. Directed epoxidation with buffered *m*CPBA of olefin **6** afforded the desired diamino epoxide **7** in 84% yield and 4:1 dr.[10] The diastereomers can be tentatively assigned by correlation of the proton chemical shifts of the *threo* and *erythro* products to analogous BOC-protected amino epoxides[10a] and confirmed by the completion of the total synthesis.

The synthesis of the tail portion **11** commences with the coupling of alkyne **8**, readily prepared in two operations from 3-heptyn-1-ol according to published procedures[11] and known vinyl iodide **9** (Scheme 4).[12] The hydro-zirconated adduct of alkyne **8** was directly cross-coupled with vinyl iodide **9** under a modified Negishi protocol[13] to furnish the THP-

Scheme 4. Synthesis of the Tail Portion **11**



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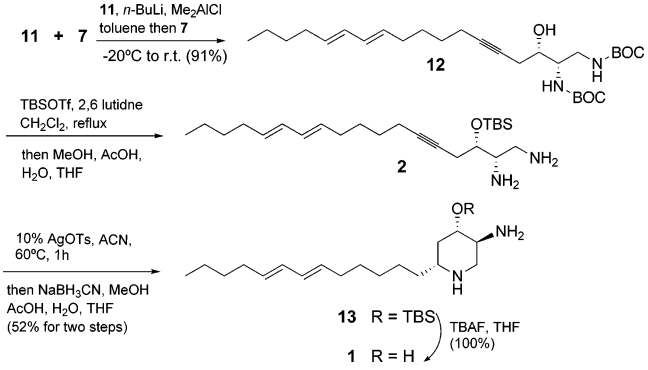
protected adduct of diene **10**. Standard THP deprotection of the cross-coupling product afford dienyl alcohol **10** in 82% yield for both steps. Moffatt−Swern oxidation of alcohol **10** and subsequent Ohira−Bestmann modification of the Seyferth−Gilbert reaction[14,15] furnished alkyne **11** in excellent yield.

The addition of the dimethylaluminum alkyne adduct of alkyne **11** to epoxide **7** efficiently furnished the complete carbon skeleton of pseudodistomin D (Scheme 5). Treatment

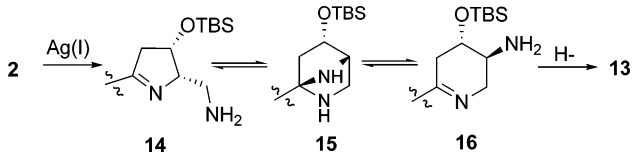
Scheme 5. Synthesis of Pseudodistomin D



of compound **12** with TBSOTf and 2,6-lutidine[16] and subsequent hydrolysis of the resulting TBS carbamates in one pot cleanly deprotected the BOC groups while simultaneously protecting the alcohol in near quantitative yield to provide silyl ether **2**. Of the plethora of transition metal catalysts for hydroamination of alkynes,[17] we focused on silver and gold catalysis due to their increased tolerance of Lewis basic functionalities over other systems.[18] Initial hydroamination experiments with 10% AgOTs at 60 °C in acetonitrile for 1 h proved to be problematic due to competitive decomposition of the imine intermediate by the catalyst. Furthermore, hydroamination with the more reactive $AuCl_3$−HCl catalyst resulted in complete decomposition within 10 min at 60 °C.[19] To minimize the competing decomposition, optimization studies were focused on utilizing less reactive hydroamination conditions. Hydroamination with 10% silver tosylate in acetonitrile at 40 °C for 2 h proved to be optimal. The hydroamination reaction was immediately quenched, by reduction of the Ag(I) catalyst, and the intermediate imine reduced in situ by sodium cyanoborohydride to provide piperidine **13** in a reasonable 52% yield for the overall two-step BOC deprotection and reductive hydroamination sequence. The reductive hydroamination proceeded with no detectable diastereomer or pyrrolidine byproducts.[20] Standard and quantitative silyl deprotection provided pseudodistomin D $[\alpha]^{25}_D = +6°$ (*c* 0.2, MeOH) (lit.[3] $[\alpha]^{25}_D = +5°$ (*c* 0.26, MeOH)). The ^{1}H and ^{13}C NMR spectra correlate with the listed chemical shifts and coupling constants reported for the isolated material.[3]

The piperidine core of pseudodistomin D, where all of the substituents can occupy equatorial positions in a chair conformation, presented a unique opportunity to exploit a reductive hydroamination strategy. By utilizing the free diamines in compound **2**, the hydroamination proceeded in a significantly increased rate over related 6-exo-dig cyclizations[18,19] and circumvented the need for another protecting group. There are several explanations that can be put forward to rationalize the selective formation of the piperidine product. One rationalization is that the hydroamination of alkyne **2** proceeds through a kinetic 5-exo-dig cyclization to furnish imine **14**, which is in a rapid equilibrium with imine **16** (Scheme 6). Due to the significant difference in

Scheme 6. Reductive Hydroamination of Alkyne **2**



reduction rates of an sp^2 to a sp^3 carbon between a 5 and six-membered rings,[21] the reduction of imine **16** is favored.[22] Therefore, a Curtin−Hammett situation is created wherein the reduction specifically yields the desired piperidine **13**.

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(19) ^{1}H NMR experiment with 10% $AuCl_3$−HCl and **2** in CD_3CN afforded complete decomposition in 10 min at 60 °C. No competitive decomposition was observed under analogous hydroamination conditions with undec-5-ynylamine.
(20) Using a more standard strategy in which the appropriate keto-diamine undergoes an intramolecular reductive amination, the pyrrolidine and/or piperidine products were obtained in modest yields. Given the additional steps necessary to furnish the keto-diamine and the modest yield of the subsequent reductive amination, this strategy was disfavored over the reductive hydroamination reported herein. By both chromatographic and spectroscopic methods, the pyrrolidine and piperidine are easily distinguishable.
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An alternate rationalization relates to the equilibrium strongly favoring imine **16**,[23] and the observed selectivity is simply the result of the reduction of the dominant species.

In conclusion, we have completed the first total synthesis of pseudodistomin D in a concise fashion. In addition to establishing the absolute stereochemistry of pseudodistomin D, we utilized the DYKAT technology to establish the absolute stereochemistry and developed a unique hydroamination approach to efficiently synthesize diamino heterocycles.

(23) Semiempirical PM3 calculations indicate that the equilibrium favors imine **16** over imine **14** by 3−7 kcal/mol. Spartan '02; Wave Function, Inc.: Irivine, CA, 2002.

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Supporting Information Available: Complete experimental procedures, characterization data, and copies of NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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