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A stereoselective approach to the synthesis of pseudodistomin D

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Abstract—A stereoselective total synthesis of the core unit of pseudodistomin D, starting from L-serine, is described. The key step is a stereoselective intramolecular Michael reaction in which the piperidine ring is formed with the obtention of **1**.

Pseudodistomins A–F are piperidine alkaloids isolated from marine organisms. They have a common core skeleton which is a 2-substituted 5-amino-4-piperidinol. They only differ in the stereochemistry of stereogenic carbons, and in the nature of the side chain as shown in Figure 1.

Pseudodistomins A and B were isolated from the Okinawan tunicate *Pseudodistoma kanoko* and have demonstrated an in vitro antitumor activity against L1210 and L5178 leukemia cells,[1] while pseudodistomin C, isolated from the same tunicate, exhibited a cytotoxic activity against L1210 and human epidermoid carcinoma KB cells in vitro.[2] The initial structures were revised,[3] and their configurations was later determined.[4] Pseudodistomins D–F were isolated from the Micronesian ascidian *Pseudodistoma megalarva*, and were found to be active toward DNA repair-competent as well as DNA repair-deficient strains of the yeast *Saccharomyces cerevisiae*.[5]

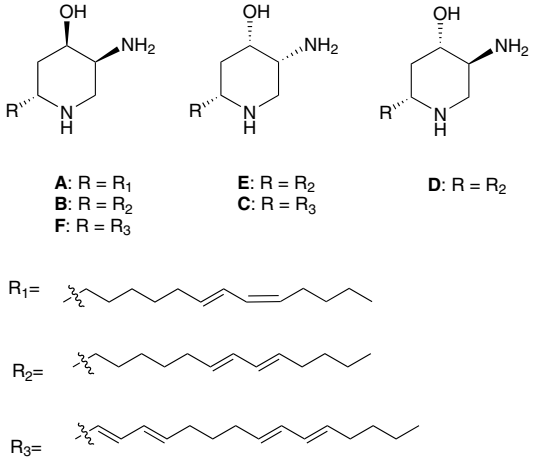
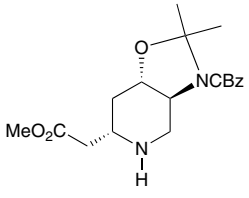


Figure 1.

Although, several synthesis of pseudodistomins have been reported, only one total synthesis of (+)-pseudodistomin D has been recently described,[6] and one stereoselective route to its piperidine core has been reported, starting from D-glucosamine.[7]

In this letter, we report a new asymmetric synthesis of 2,4,5-trisubstituted piperidine **1**, a key intermediate in the total synthesis of pseudodistomin D. Indeed, the presence of an ester function in **1** would allow the introduction of the side chain by condensation of an appropriate organometallic compound.



1

Our synthesis started from the *N*,*O*-protected L-serine methyl ester **2**, easily accessible from the corresponding free aminoacid.[8] The developed strategy is shown below: diastereoselective addition of allyltrimethylsilane to *N*,*O*-protected L-serinal as described by Jurczak and

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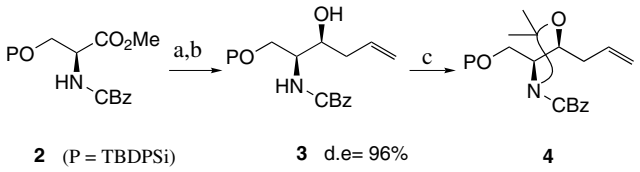


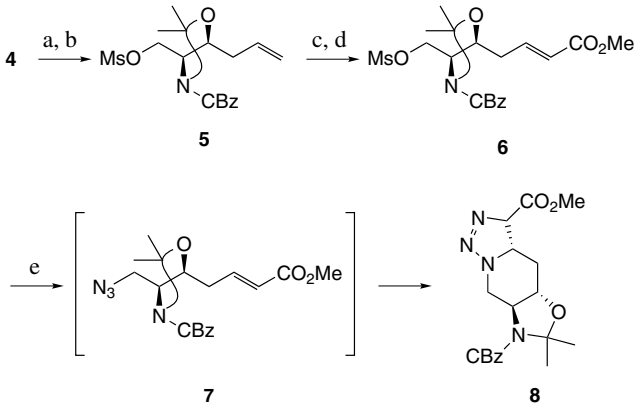
Scheme 1. Reagents and conditions: (a) Dibal-H, toluene, −78 °C, 6 h, 80%; (b) allyltrimethylsilane, $SnCl_4$, −78 °C, 4 h, 70%; (c) $(CH_3)_2C(OCH_3)_2$, APTS, benzene, reflux, 80%.

co-workers[9] afforded the allylalcohol **3** which was protected under its acetonide form **4** (Scheme 1).

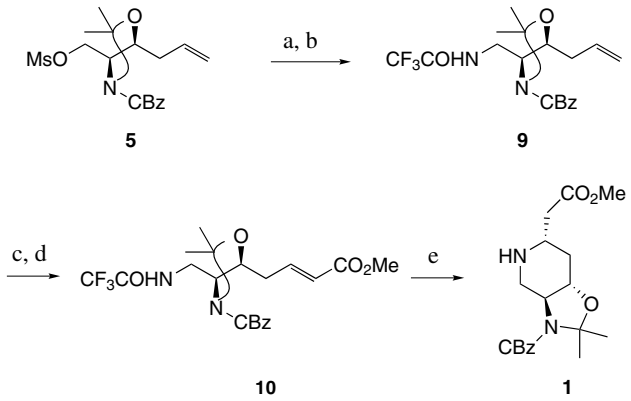
In a first approach, the silyl group was removed and the free alcohol was activated with methanesulfonyl chloride to give **5**. Next, the carbon chain was extended by oxidative cleavage of the double bond followed by Wittig reaction[10] leading to the unsaturated ester **6**. Substitution of the mesylate group using sodium azide afforded **7**. Unfortunately, the azide **7** revealed to be unstable and was converted on standing into the triazoline **8** as demonstrated by mass and IR spectra (Scheme 2). This result indicated that cyclization is possible even under the acetonide form.

In view of these results, we decided to slightly modify our strategy. For this purpose, compound **5** was reacted in the following manner (Scheme 3): the mesyl group was substituted with sodium azide, and the resulting azide was reduced with triphenylphosphine in the presence of water to give the free amine.[11] The latter was used without purification and protected under its trifluoroacetate form **9**. Compound **9** was treated in the same conditions as described above to yield the unsaturated ester **10**.[12] Deprotection of the trifluoroacetate group was achieved by treatment of **10** with an excess of sodium borohydride in methanol[4] which was followed by an intramolecular Michael reaction to form selectively the cyclized product **1** as a single product.[13]

The stereochemistry of **1** was established by NMR experiments: the COSY data allowed the proton assign-



Scheme 2. Reagents and conditions: (a) nBu$_4$ NF, THF, rt, 3 h, 90%; (b) MsCl, NEt_3, CH_2Cl_2, 85%; (c) $NaIO_4$, OsO_4 cat, dioxane, H_2O, 70%; (d) tetramethylguanidin, $(CH_3O)_2P(O)CH_2CO_2CH_3$, THF, −78 °C to rt, 81%; (e) NaN_3, DMSO, 40–45 °C, 12 h, 65%.



Scheme 3. Reagents and conditions: (a) NaN_3, DMSO, 40–45 °C, 65%; (b) PPh_3, H_2O, THF, rt then $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, 76%; (c) $NaIO_4$, OsO_4 cat, dioxane, H_2O, 72%; (d) tetramethylguanidin, $(CH_3O)_2P(O)CH_2CO_2CH_3$, THF, −78 °C to rt, 80%; (e) $NaBH_4$ (10 equiv), MeOH, 0 °C to rt, 50%.

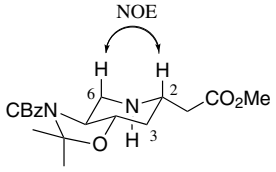


Figure 2.

ment; however, owing to the complexity of the signals, it was not possible to calculate the coupling constant for each proton. The NOE data revealed a clear interaction between H-2 and H-6, indicating that all the substituents of the piperidinic ring occupied an equatorial position in a chair conformation as shown in Figure 2.

In conclusion, we have developed an efficient and highly stereoselective method to access the conveniently substituted piperidine **1**, a key intermediate toward the synthesis of pseudodistomin D.

Acknowledgment

We are grateful to Marie-Noëlle Rager for NMR experiments and help for the determination of the stereochemistry of the final compound **1**.

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12. Characteristic data for compound **10**: IR (neat) ν_{max} 3313, 3088, 2986, 2950, 1728, 1716, 1557 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 3H), 1.56 (s, 3H), 2.53 (m, 1H), 2.58–2.68 (m, 1H), 3.18–3.24 (m, 1H), 3.60–3.68 (m, 1H), 3.72 (s, 3H), 3.75–3.95 (m, 2H), 5.17 (s, 2H), 5.94 (d, $J = 15.6$ Hz, 1H), 6.93 (dt, $J = 7.2$ Hz and $J = 15.6$ Hz, 1H), 7.36 (s, 5H), 8.28–8.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.5, 27.9, 35.1, 42.4, 51.5, 53.4, 62.2, 67.9, 76.1, 77.2, 95.3, 115.8 (q, $J = 287$ Hz, CF_3), 124.2, 128.2, 128.5, 128.7, 135.5, 142.9, 154.4, 157.4 (q, $J = 37.7$ Hz, *CO*CF_3), 166.4; $[\alpha]_D^{25}$ −10.2 (*c* 1.1, CH_2Cl_2); MS (CI, NH_3) *m*/*z* 476 $[MNH_4]^+$.
13. Characteristic data for compound **1**: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30–1.65 (m, 6H, and H_3), 2.06 (dt, $J = 3.2$ Hz and $J = 11.2$ Hz, $H_{3'}$), 2.10–2.30 (m, NH, and H_6), 2.35–2.70 (m, $H_{6'}$, and CH_2), 2.87–3.13 (m, H_2, and H_5), 3.50 (m, with $J = 3.6$ Hz, H_4), 3.53 (s, 3H), 4.95–5.18 (m, OCH_2), 7.31 (s, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.0, 25.5, 36.3, 40.3, 49.1, 51.4, 51.7, 60.4, 66.8, 77.3, 78.5, 95.2, 128.1, 128.5, 136.2, 152.8, 172.2; $[\alpha]_D^{25}$ +30.4 (*c* 2.4, CH_2Cl_2); MS (CI, NH_3) *m*/*z* 363 $[MH]^+$.