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Asymmetric synthesis of (+)-tetrahydropseudodistomin☆

S. Chandrasekhar,* S. Shameem Sultana, N. Kiranmai and Ch. Narsihmulu†

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—An efficient asymmetric synthesis of (+)-tetrahydropseudodistomin is described. The important synthetic features include a Maruoka asymmetric allylation and a Sharpless asymmetric dihydroxylation as key steps for the generation of chirality at C-2, -4, and -5 of the trisubstituted piperidine ring.

The Okinawan tunicate *Pseudodistoma* sp. is a rich source of bioactive piperidine alkaloids, the most remarkable of these being pseudodistomins A–F. These isomeric alkaloids contain a 2-substituted 5-amino-4-piperidinol as a common core and only differ in the stereochemistry of the stereogenic carbons and in the nature of the side chain (Fig. 1). Pseudodistomins A–C were isolated from *Pseudodistoma kanoko* by Kobayashi et al. and exhibited potent in vitro inhibitory effects on calmodulin activated brain phosphodiesterase. In addition, they also displayed cytotoxicity against both murine leukemia and human epidermoid carcinoma KB cells.[1] In addition, the extract of *Pseudodistoma megalarva* provided pseudodistomins D–F which were found to be active in a cell-based assay for DNA damage induction.[2]

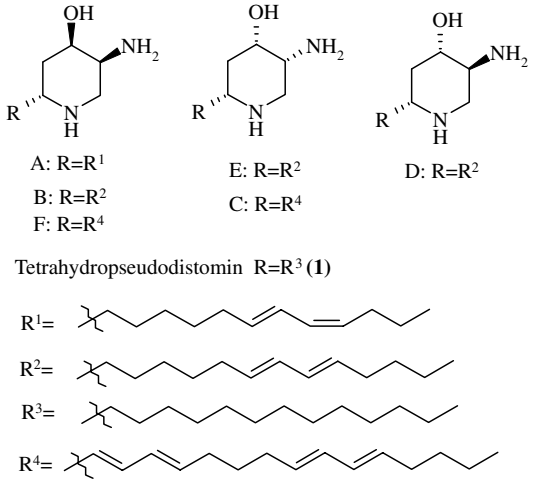

Figure 1.

In view of their promising biological activity, pseudodistomins have attracted extensive synthetic studies.[3] In this article, we report a practical synthesis of (2*R*,4*R*,5*S*)-tetrahydropseudodistomin **1**. Our primary objective was to delineate a strategy that would allow installation of the three asymmetric centers at C-2, C-4, and C-5 with flexibility so as to enable syntheses of other stereo analogs as well. The vicinal 1,2-amino alcohol functionality and piperidine skeleton are privileged functionalities and novel methods for their construction are welcome.

Accordingly, the retrosynthetic analysis envisioned the installment of the three stereogenic centers of **1** through application of a Maruoka asymmetric allylation and a Sharpless asymmetric dihydroxylation as key reactions, starting from tetradecanol **4** (Scheme 1).

As illustrated in Scheme 2, Swern oxidation of tetradecanol **4** gave aldehyde **5**, which was subjected to an enantioselective Maruoka allylation by treatment with titanium complex (***R***,***R***)-**I** and allyltri-*n*-butyltin using known reaction conditions[4] to afford homoallylic alcohol **3** in 86% yield with excellent enantioselectivity, 98% ee (determined by chiral HPLC).[5]

Keywords: Marouka asymmetric allylation; Sharpless asymmetric dihydroxylation.
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* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: srivaric@iict.res.in
† Present address: Centre for Drug Design, University of Minnesota, Minneapolis, USA.

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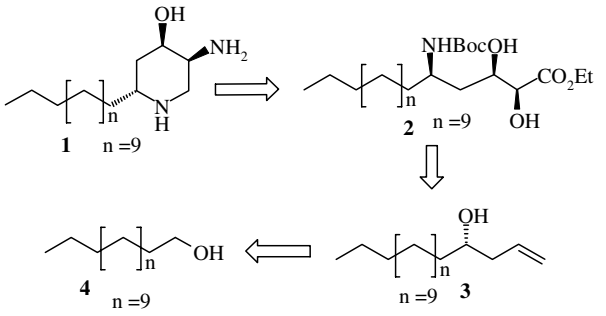
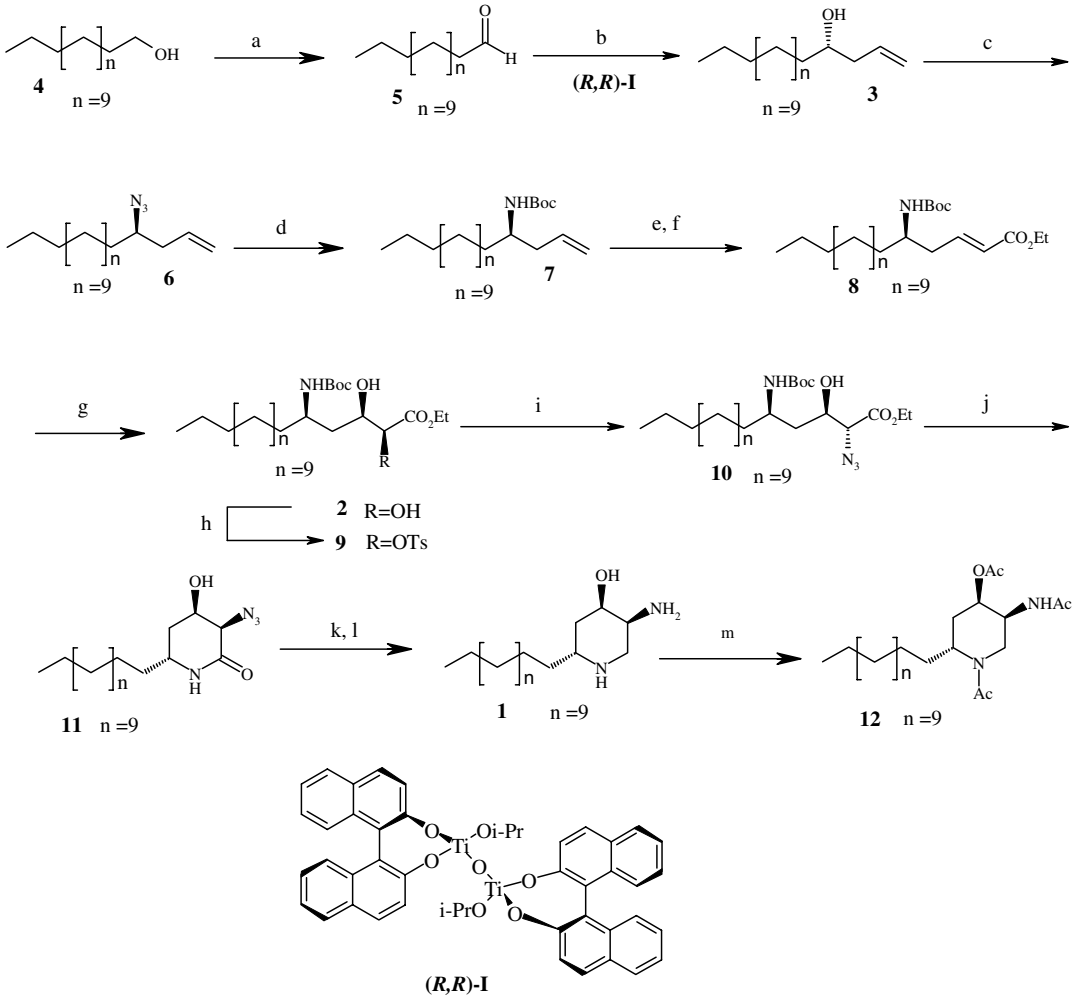


Scheme 1.

Homoallylic alcohol **3** was then converted to the corresponding homoallylic azide **6** via Mitsunobu inversion[6] using diphenylphosphoryl azide (DPPA) in 71% yield. Azido compound **6** was reduced using Staudinger reaction conditions (TPP, THF:H_2O) in the presence of $(Boc)_2O$ to provide the *N*-Boc protected amine **7** in 68% yield.

Ozonolysis of the double bond in **7** provided the corresponding aldehyde, which was elaborated by Wittig olefination to α,β-unsaturated ester **8**, obtained as a single isomer (*E*) in 76% yield, ready for the installation of vicinal chirality. Sharpless asymmetric dihydroxylation using AD-mix β was explored to generate the C-4, C-5 stereogenic centers and the expected diol **2** was obtained in good yield and diastereoselectivity (9:1). The diastereomers were easily separated by column chromatography. The azido group at C-5 was introduced by a two-step reaction sequence. First, regioselective α-tosylation[7] of diol **2** using TsCl and DIPEA in CH_2Cl_2 afforded the mono-tosylated product **9**, which was treated with NaN_3/DMF to provide azido alcohol **10** in 67% yield.

Completion of the synthesis of **1** and its *N*,*N*′,*O*-triacetate **12** involved cyclization of **10** using TFA:DCM (1:1) to give azidolactam **11** in 87% yield and concomitant reduction of both the azide and amide functionalities in **11** using $LiAlH_4$ albeit, in a poor yield. Thus, a sequential reduction strategy was adopted. Stepwise



Scheme 2. Reagents, conditions, and yields: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 2 h, 87%; (b) (***R*,*R***)-**I** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 86%; (c) DPPA, TPP, DEAD, THF, 0 °C, 12 h, 71%; (d) TPP, THF:H_2O, $(Boc)_2O$, rt, 24 h, 68%; (e) O_2, DMS, −78 °C; (f) $PPh_3{=}CHCO_2Et$, benzene, rt, 3 h, 76%; (g) AD-mix β, $MeSO_2NH_2$, ^{t}BuOH–H_2O (1:1), 0 °C, 24 h, 78%; (h) TsCl, DIPEA, CH_2Cl_2, 0 °C, 12 h, 70%; (i) NaN_3, DMF, 60 °C, 6 h, 67%; (j) TFA:DCM (1:1), 0 °C, 3 h, 87%; (k) $Pd(OH)_2$/C, H_2, MeOH, rt; (l) BH_3·THF, THF, reflux, 12 h; (m) Ac_2O, pyridine, CH_2Cl_2, 1 h, 55% (for 3 steps).

reduction of **11** with Pd/C, H_2 resulted in selective reduction of the azide to an amine. Amide reduction to diamino alcohol **1** was achieved using excess (5 equiv) BH_3·THF. Triacetyl derivative **12** was synthesized to enable comparison with the known data. Treatment of **1** with Ac_2O/pyridine gave triacetate **12**,[8] which showed spectral and physical data consistent with the literature {$[\alpha]_D^{25}$ 31.6 (*c* 0.5, MeOH), lit. $[\alpha]_D^{23}$ 33 (*c* 1.0, MeOH)}.[1a]

In conclusion, we have achieved the asymmetric synthesis of (+)-tetrahydropseudodistomin **1** using Maruoka asymmetric allylation and Sharpless asymmetric dihydroxylation reactions as key steps. Application of the present strategy to the asymmetric synthesis of other pseudodistomins is in progress and will be reported in due course along with their biological profiles.

Acknowledgements

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References and notes

1. (a) Ishibashi, M.; Ohizumi, Y.; Sasaki, T.; Nakamura, H.; Hirata, Y.; Kobayashi, J. *J. Org. Chem.* **1987**, *52*, 450–453; (b) Kobayashi, J.; Naitoh, K.; Doi, Y.; Deki, K.; Ishibashi, M. *J. Org. Chem.* **1995**, *60*, 6941–6945.
2. Freyer, A. J.; Patil, A. D.; Killmer, L.; Troupe, N.; Mentzer, M.; Carte, B.; Faucette, L.; Johnson, R. K. *J. Nat. Prod.* **1997**, *60*, 986–990.
3. (a) Haddad, M.; Larcheveque, M.; Tong, H. M. *Tetrahedron Lett.* **2005**, *46*, 6015–6017; (b) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823–826; (c) Langlois, N. *Org. Lett.* **2002**, *4*, 185–187; (d) Kiguchi, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Naito, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 893–899; (e) Naito, T.; Yuumoto, Y.; Kiguchi, T.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 281–288; (f) Doi, Y.; Ishbashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573–4580; (g) Naito, T.; Ikai, M.; Shirakawa, M.; Fujimoto, K.; Ninomiya, I.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 773–775; (h) Knapp, S.; Hale, J. L. *J. Org. Chem.* **1993**, *58*, 2650–2651; (i) Naito, T.; Yuumoto, Y.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1992**, *33*, 4033–4036; (j) Utsunomiya, I.; Ogawa, M.; Natsume, M. *Heterocycles* **1992**, *33*, 349–356.
4. (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708–1709; (b) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S. *Tetrahedron Lett.* **2004**, *45*, 9299–9301.
5. (a) Homoallyl alcohol **7** was converted to its 4-nitrobenzoate for determination of the ee by chiral HPLC {Chiralcel OB-H, ^{i}PrOH/hexane (1:99), flow rate 0.4 ml/min, $t_R = 8.36$ (minor), $t_R = 9.26$ (major)}; (b) Chen, J.; Li, Y.; Cao, X. P. *Tetrahedron: Asymmetry* **2006**, *17*, 933–941.
6. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *23*, 1977–1980.
7. Denis, J.-N.; Correa, A.; Green, A. E. *J. Org. Chem.* **1990**, *55*, 1957–1980.
8. Representative analytical data: Compound **3**: Waxy white solid; $[\alpha]_D^{25}$ −5.43 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.86–5.72 (m, 1H), 5.12 (m, 2H), 3.64–3.54 (m, 1H), 2.31–2.32 (m, 1H), 2.15–2.05 (m, 1H), 1.43–1.38 (m, 2H), 1.35–1.25 (m, 22H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.9, 118.0, 70.6, 41.9, 36.8, 31.9, 29.6–29.3, (overlapping signals) 25.6, 22.6, 14.1. (ESI-MS): *m*/*z* 277 [M+Na]. HRMS calcd for $C_{17}H_{34}ONa$: 277.2507 (M^++Na), found: 277.2517.
Compound **11**: White solid mp 92–94 °C; $[\alpha]_D^{25}$ 90.38 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.44 (br s, 1H), 4.18–4.13 (m, 1H), 3.96 (d, 1H, $J = 3.4$ Hz), 3.77–3.71 (m, 1H), 2.54 (m, 1H), 2.18–2.11 (m, 2H), 1.51–1.25 (m, 24H), 0.88 (t, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 66.0, 62.1, 48.3, 36.3, 33.5, 31.8, 29.6–29.2 (overlapping signals), 25.0, 22.6, 14.0. (ESI-MS): *m*/*z* 361 [M+Na]. HRMS calcd for $C_{18}H_{35}N_4O_2$: 339.2760 (M^++1), found: 339.2774.
Compound **12**: Colorless liquid; $[\alpha]_D^{25}$ 31.6 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (d, 1H, $J = 6.6$ Hz), 5.14 (m, 1H), 4.91 (br s, 1H), 4.34 (br s, 1H), 3.93 (d, 1H, $J = 14.2$ Hz), 3.27 (d, 1H, $J = 14.2$ Hz), 2.05 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.71–1.61 (m, 2H), 1.29 (br s, 24H), 0.88 (t, 3H, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 170.0, 169.7, 66.9, 47.6, 47.0, 43.9, 32.0, 30.2, 29.7–29.2 (overlapping signals), 28.3, 26.3, 23.2, 22.8, 21.8, 21.0, 14.2. (ESI-MS): *m*/*z* 447 [M+Na]. HRMS calcd for $C_{24}H_{44}N_2O_4Na$: 447.3198 (M^++Na), found: 447.3213.