

Enantioselective Synthesis of Pachastrissamine (Jaspin B) Using Dirhodium(II)-Catalyzed C–H Amination and Asymmetric Dihydroxylation as Key Steps

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Enantioselective total synthesis of anhydrophytosphingosine pachastrissamine (jaspin B) was achieved using Sharpless asymmetric dihydroxylation and dirhodium(II)-catalyzed C–H amination as key steps.

Key words pachastrissamine; total synthesis; C–H amination; jaspin B; dirhodium(II); asymmetric dihydroxylation

Pachastrissamine (jaspin B, **1**) was isolated from the Okinawan marine sponge *Pachastrissa* sp. by Higa and co-workers in 2002¹⁾ and shortly after from a different sponge, *Jaspis* sp., by the Debitus group in 2003²⁾ as a naturally occurring novel anhydrophytosphingosine derivative. It exhibited cytotoxic activities against several human carcinoma cell lines. Because of the impressive biological activity and its novel structural features, **1** has attracted much attention from synthetic chemists. Recently, several total syntheses of **1** from chiral compounds such as serine, phytosphingosine, and xylose have been reported.^{3–10)} Dirhodium(II)-catalyzed C–H amination of carbamates to oxazolidinone derivatives has attracted much attention in recent synthetic organic chemistry as an important transformation^{11–18)} because of the introduction of nitrogen to unactivated C–H bond. Recently we reported applications of dirhodium(II)-catalyzed C–H amination reaction to a synthesis of an immunomodulator (+)-conagenin^{19,20)} and a facile preparation of optically active monoprotected 2-amino-2-methyl-1,3-propanediol.²¹⁾ We report here the enantioselective total synthesis of **1** using Sharpless asymmetric dihydroxylation and dirhodium(II)-catalyzed C–H amination as key steps.

We planned a simple and concise enantioselective synthesis of **1**. Our retrosynthetic analysis is depicted in Chart 1. Oxazolidinone (**2**) was selected as a temporary goal because this intermediate can be converted to pachastrissamine using alkali hydrolysis.⁴⁾ The oxazolidinone ring of **2** should be constructed using dirhodium(II)-catalyzed C–H amination reaction of carbamate (**3**). In C–H amination reaction of **3**, it has four possible reactive C–H groups. The C₂–H is the most reactive among them because it is tertiary and α to furan oxygen. However, as a result of the highly unfavorable ring strain associated with the *trans*-ring junction between the two

five-membered rings formed by the reaction with C₂–H and also with C₄–H $_{\beta}$, selective reaction with C₄–H $_{\alpha}$ forming the *cis*-fused bicyclic system (**2**) is predicted. Although ketone formation by the reaction of rhodium nitrenoid with C₃–H is also possible,¹²⁾ the large substituent at C-2 position might block its approach to the C₃–H. Compound (**3**) should be converted easily from alcohol (**4**). Compound (**4**) should be synthesized from diol (**5**) *via* iodination of primary alcohol and following tetrahydrofuran ring formation. The stereocenters of **5** should be constructed enantioselectively using Sharpless asymmetric dihydroxylation²²⁾ of the corresponding known (*E*)- α,β -unsaturated ester (**6**).^{23,24)}

Synthesis of the precursor of dirhodium-catalyzed C–H amination was started from known methyl (*2E*)-5-*p*-methoxybenzyl(PMB)oxy-2-pentanoate (**6**),^{23,24)} as illustrated in Chart 2. Asymmetric dihydroxylation of **6** was accomplished using AD-mix- α under usual conditions²²⁾ to give diol (**5**) in 89%. Optical purity of **5** was determined to be 98.1% ee by chiral HPLC analysis (hexane/*i*-PrOH, 90/10, 0.5 ml/min, Chiralpak AD-H; Daicel Chemical Industries, Ltd.). Protection of diol with acetonide afforded **7**, which was reduced with diisobutylaluminum hydride (DIBAL-H) at –80 °C to provide aldehyde (**8**). Compound (**8**) was homologated by Wittig reaction to give (*Z*)-alkene (**9**) in 88% yield as a single stereoisomer. The (*Z*)-stereochemistry of **9** was determined by coupling constant (*J* = 10.8 Hz) between vinyl protons in its ¹H-NMR spectrum. Both deprotection of PMB group and reduction of the C–C double bond of **9** proceeded simultaneously under hydrogenation conditions to produce alcohol (**10**) in 87% yield. Treatment of **10** with iodine and triphenylphosphine in the presence of imidazole yielded iodide (**11**) in quantitative yield. Acid deprotection of **11** and following cyclization using potassium carbonate converted it into tetrahydrofuran (**4**) in 79% yield. According to the usual procedure,^{19–21)} reaction of **4** with trichloroacetyl isocyanate in dichloromethane at room temperature gave the corresponding trichloroacetyl carbamate, which was treated with neutral alumina without purification to obtain the precursor (**3**) of C–H amination reaction in quantitative yield.

With the carbamate (**3**) in hand, we investigated C–H amination reaction of **3** (Table 1). Reaction of **3** with 10 mol% of dirhodium(II) tetraacetate, 4.2 equivalents of phenyliodine(III)

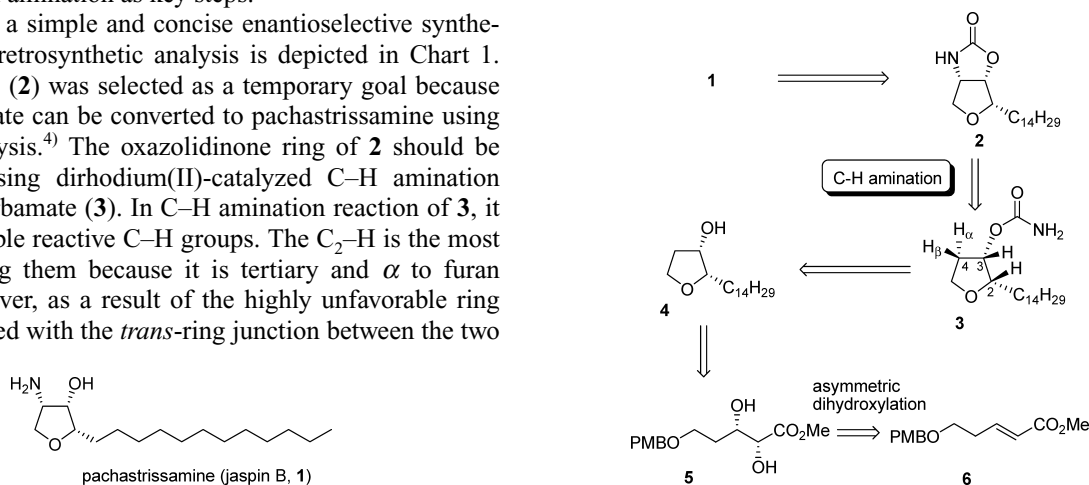
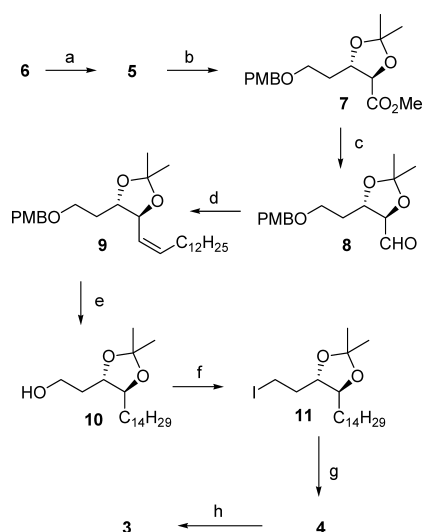


Fig. 1

Chart 1

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a) AD-mix- α , BuOH-H₂O, 0 °C, overnight (89%); b) Me₂C(OMe)₂, CSA, rt, 12 h (quant); c) DIBAL-H, CH₂Cl₂, -80 °C, 1 h (97%); d) Ph₃PCH₂C₁₂H₂₅Br, BuLi, THF, -20 °C, 1 h (88%); e) H₂ (3 atm), Pd-C, EtOAc, rt, 3 h (87%); f) I₂, Ph₃P, imidazole, CH₂Cl₂, rt, 1 h (quant); g) *c*-HCl, THF, rt, 2.5 h then K₂CO₃, MeOH, rt, 3 h (79%); h) CCl₃CON=C=O, CH₂Cl₂, rt, 1 h then neutral Al₂O₃ (quant).

Chart 2

Table 1. Rh(II)-Catalyzed C–H Amination of **3**^{a)}

Entry	Rh(II)	Solvent	Time (h)	Yield (%)	
				2	13
1	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	13	No reaction	
2	Rh ₂ (OAc) ₄	Benzene	13	0	58
3	Rh ₂ (OCOCPh ₃) ₄	Benzene	13	19	40
4	Rh(esp) ₂	Benzene	21	10	15

^{a)} Reactions were carried out using 10 mol% of Rh(II) catalyst, 4.2 eq of PhI(OAc)₂, and 6.9 eq of MgO under reflux.

diacetate, and 6.9 equivalents of magnesium oxide in dichloromethane under reflux,^{19–21)} however, gave no reaction with recovered starting **3** (Entry 1). A similar reaction in refluxing benzene for 13 h proceeded, unfortunately, to afford only undesired 2-tetradecatetrahydrofuran-3-one (**13**) in 58% yield with a complex mixture (Entry 2). The formation of **13** would be caused either by direct abstraction of C₃–H by rhodium nitrenoid intermediate (**A**) or through the generation of four-membered ring species (**14**) (Chart 3).¹²⁾ This speculation spurred our use of a dirhodium(II) catalyst having bulkier ligands. When **3** was treated with dirhodium(II) tetra(triphenylacetate), 4.2 equivalents of phenyliodine(III) diacetate, and 6.9 equivalents of magnesium oxide in benzene under reflux for 13 h, the desired **2** was obtained in 19% yield (Entry 3).²⁵⁾ However, ketone (**13**) was still produced as a major product in 40% yield. Use of dirhodium dirhodium(II) bis(α,α,α' , α' -tetramethyl-1,3-benzenedipropionate) [Rh₂(esp)₂]²⁶⁾ gave low yields of both **2** and **13** with a complex mixture (Entry 4).

Finally, **2** was hydrolyzed using potassium hydroxide in ethanol under reflux for 3 h to afford (+)-pachastrissamine

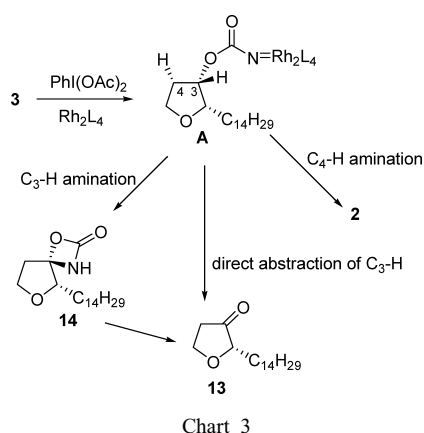
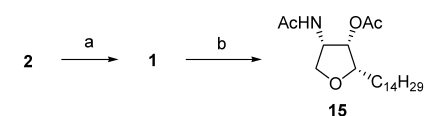


Chart 3



a) aq. KOH, EtOH, reflux, 3 h; b) Ac₂O, pyridine, rt, 12 h (85% in 2 steps)

Chart 4

(**1**), which was acetylated without purification to provide the *N,O*-diacetyl derivative (**15**), mp 108–111 °C, [α]_D²⁵ –26.2° (*c*=0.30, CHCl₃) {lit.⁵⁾ mp 95–98 °C, [α]_D²² –22.6° (*c*=1.0, CDCl₃), lit.⁷⁾ [α]_D –28.4° (*c*=1.0, CHCl₃)}, in 85% yield from **2** (Chart 4). Spectroscopic data of **15**²⁷⁾ were identical to those of the reported sample.

In summary, we demonstrated a simple and concise enantioselective total synthesis of (+)-**1** starting from α,β -unsaturated ester (**6**) using asymmetric dihydroxylation and C–H amination reaction as key steps. Further investigation for improvement of the C–H amination of **3** is now underway in our laboratory.

References and Notes

- Kuroda I., Musman M., Ohtani I. I., Ichiba T., Tanaka J., Gravalos D. G., Higa T., *J. Nat. Prod.*, **65**, 1505–1506 (2002).
- Ledroit V., Debitus C., Lavaud C., Massiot G., *Tetrahedron Lett.*, **44**, 225–228 (2003).
- Sudhakar N., Kumar A. R., Prabhakar A., Jagadeesh B., Rao B. V., *Tetrahedron Lett.*, **46**, 325–327 (2005).
- Bhaket P., Morris K., Stauffer C. S., Datta A., *Org. Lett.*, **7**, 875–876 (2005).
- van den Berg R. J. B. H. N., Boltje T. J., Verhagen C. P., Litjens R. E. J. N., van der Marel G. A., Overkleeft H. S., *J. Org. Chem.*, **71**, 836–839 (2006).
- Du Y., Liu J., Linhardt R. J., *J. Org. Chem.*, **71**, 1251–1253 (2006).
- Ribes C., Falomir E., Carda M., Marco J. A., *Tetrahedron*, **62**, 5421–5425 (2006).
- Ramana C. V., Giri A. G., Suryawanshi S. B., Gonnade R. G., *Tetrahedron Lett.*, **48**, 265–268 (2007).
- Lee T., Lee S., Kwak Y. S., Kim D., Kim S., *Org. Lett.*, **9**, 429–432 (2007).
- Reddy L. V. R., Reddy P. V., Shaw A. K., *Tetrahedron: Asymmetry*, **18**, 542–546 (2007).
- Espino C. G., Du Bois J., *Angew. Chem. Int. Ed.*, **40**, 598–600 (2001).
- Espino C. G., Du Bois J., “Modern Rhodium-Catalyzed Organic Reactions,” ed. by Evans P. A., Wiley-VCH, Weinheim, 2005, pp. 379–416.
- Davies H. M. L., Long M. S., *Angew. Chem. Int. Ed.*, **44**, 3518–3520 (2005).
- Trost B. M., Gunzner J. L., Dirat O., Rhee Y. H., *J. Am. Chem. Soc.*, **124**, 10396–10415 (2002).

- 15) Hinman A., Du Bois J., *J. Am. Chem. Soc.*, **125**, 11510—11511 (2003).
- 16) Huang H., Panek J. S., *Org. Lett.*, **5**, 1991—1993 (2003).
- 17) Parker K. A., Chang W., *Org. Lett.*, **5**, 3891—3893 (2003).
- 18) Parker K. A., Chang W., *Org. Lett.*, **7**, 1785—1788 (2005).
- 19) Yakura T., Yoshimoto Y., Ishida C., Mabuchi S., *Synlett*, **2006**, 930—932 (2006).
- 20) Yakura T., Yoshimoto Y., Ishida C., Mabuchi S., *Tetrahedron*, **63**, 4429—4438 (2007).
- 21) Yakura T., Yoshimoto Y., Ishida C., *Chem. Pharm. Bull.*, **55**, in press (2007).
- 22) Sharpless K. B., Amberg W., Bennani Y. L., Crispino G. A., Hartung J., Jeong K.-S., Kwong H.-L., Morikawa K., Wang Z.-M., Xu D., Zhang X.-L., *J. Org. Chem.*, **57**, 2768—2771 (1992).
- 23) Oka T., Murai A., *Tetrahedron*, **54**, 1—20 (1998).
- 24) Cordero F. M., Gensini M., Goti A., Brandi A., *Org. Lett.*, **2**, 2475—2477 (2000).
- 25) A suspension of **3** (38 mg, 0.116 mmol), $\text{PhI}(\text{OAc})_2$ (157 mg, 0.49 mmol), MgO (32 mg, 0.80 mmol), and $\text{Rh}_2(\text{OCOCPh}_3)_4$ (16 mg, 0.012 mmol) in benzene (2.5 ml) was refluxed for 13 h. After the mixture was cooled to room temperature, it was passed through a short Celite pad and the filtrate was concentrated. The residue was chromatographed on silica gel (Et_2O) to give **2** (7 mg, 19%) and **13** (13 mg, 40%). Spectroscopic data of **2** were identical to those of the reported sample.⁴⁾
- 26) Espino C. G., Fiori K. W., Kim M., Du Bois J., *J. Am. Chem. Soc.*, **126**, 15378—15379 (2004).
- 27) Compound **15**: mp 108—111 °C. $[\alpha]_D^{25}$ -26.2° ($c=0.30$, CHCl_3). IR (KBr) cm^{-1} : 3215, 1740, 1647. $^1\text{H-NMR}$ (270 MHz, CDCl_3) δ : 0.88 (3H, t, $J=6.6$ Hz), 1.16—1.36 (24H, br m), 1.40—1.56 (2H, m), 1.97 (3H, s), 2.17 (3H, s), 3.60 (1H, t, $J=8.1$ Hz), 3.86—3.95 (1H, m), 4.08 (1H, t, $J=8.5$ Hz), 4.82 (1H, qd, $J=8.1$, 5.4 Hz), 5.38 (1H, dd, $J=5.4$, 3.5 Hz), 5.58 (1H, br d, $J=7.8$ Hz). $^{13}\text{C-NMR}$ (67.5 MHz, CDCl_3) δ : 14.1, 20.7, 22.7, 23.2, 26.0, 29.29, 29.34, 29.46, 29.53, 29.57, 29.61, 29.64, 29.7, 31.9, 51.3, 70.0, 73.6, 81.2, 169.9 (2). HR-MS m/z : 383.30290 (Calcd for $\text{C}_{22}\text{H}_{41}\text{NO}_4$ (M^+): 383.30356).