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.

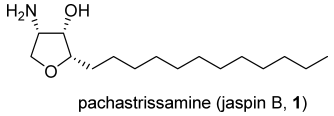
Key words pachastrissamine; total synthesis; C–H amination; jaspin B; dirhodium(II); asymmetric dihydroxylation

Pachastrissamine (jaspin B, **1**) was isolated from the Okinawan marine sponge *Pachastrissa* sp. by Higa and co-workers in 2002[1] and shortly after from a different sponge, *Jaspis* sp., by the Debitus group in 2003[2] 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 hydorolysis.[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 C_2–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 C_2–H and also with C_4–H_β, selective reaction with C_4–H_α forming the *cis*-fused bicyclic system (**2**) is predicted. Although ketone formation by the reaction of rhodium nitrenoid with C_3–H is also possible,[12] the large substituent at C-2 position might block its approach to the C_3–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 dihydroxylation[22] 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 (2*E*)-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 conditions[22] 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 ^{1}H-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 quantative 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)



pachastrissamine (jaspin B, **1**)

Fig. 1

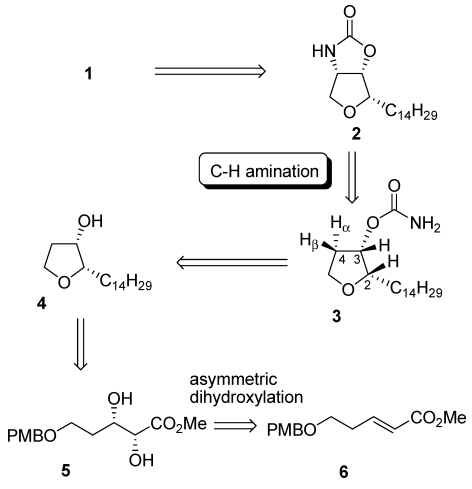


Chart 1

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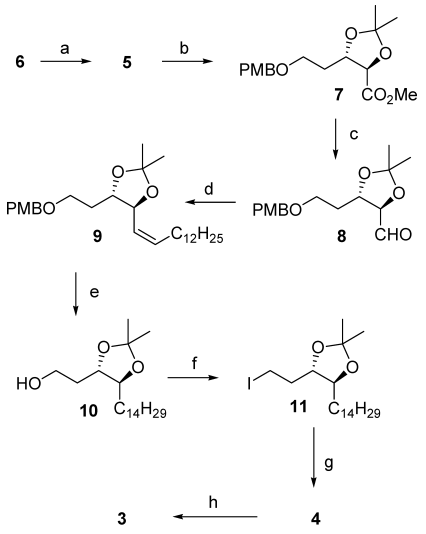


a) AD-mix-α, BuOH-H_2O, 0 °C, overnight (89%); b) $Me_2C(OMe)_2$, CSA, rt, 12 h (quant); c) DIBAL-H, CH_2Cl_2, -80 °C, 1 h (97%); d) $Ph_3PCH_2C_{12}H_{25}Br$, BuLi, THF, -20 °C, 1 h (88%); e) H_2 (3 atm), Pd-C, EtOAc, rt, 3 h (87%); f) I_2, Ph_3P, imidazole, CH_2Cl_2, rt, 1 h (quant); g) *c*-HCl, THF, rt, 2.5 h then K_2CO_3, MeOH, rt, 3 h (79%); h) $CCl_3CON{=}C{=}O$, CH_2Cl_2, rt, 1 h then neutral Al_2O_3 (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_2Cl_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 C_3–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($\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropanoate) $[Rh_2(esp)_2]$[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

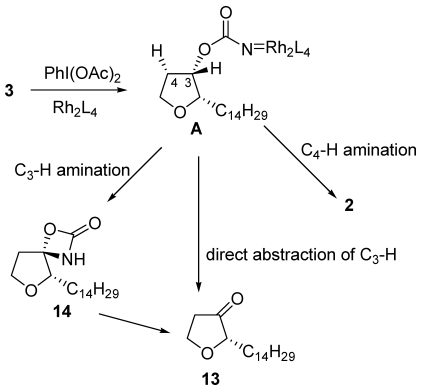
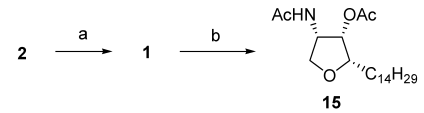


Chart 3



a) aq. KOH, EtOH, reflux, 3 h; b)Ac_2O, 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, $[\alpha]_D^{25}$ −26.2° (*c*=0.30, $CHCl_3$) {lit.[5] mp 95—98 °C, $[\alpha]_D^{22}$ −22.6° (*c*=1.0, $CDCl_3$), lit.[7] $[\alpha]_D$ −28.4° (*c*=1.0, $CHCl_3$)}, 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

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25) A suspension of **3** (38 mg, 0.116 mmol), $PhI(OAc)_2$ (157 mg, 0.49 mmol), MgO (32 mg, 0.80 mmol), and $Rh_2(OCOCPh_3)_4$ (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}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}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 $C_{22}H_{41}NO_4$ (M^+): 383.30356).