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Total synthesis of (−)-2-*epi*-lentiginosine by use of chiral 5-hydroxy-1,5-dihydropyrrol-2-one as a building block

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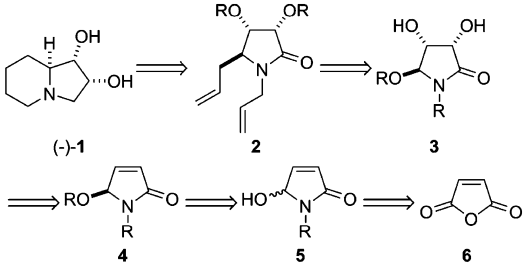
Abstract—We have developed a practical synthesis of the chiral lactam as a new chiral building block for alkaloid synthesis. Lipase-catalyzed kinetic resolution of hydroxylactam **8**, followed by isolation–racemization of the chiral acetoxylactam **9** provided the optically pure hydroxylactam **8** in 96.0% yield with >99% ee after five cycles of kinetic resolution–racemization process. Chemical transformation of (*S*)-hydroxylactam **8** furnished chiral (−)-2-*epi*-lentiginosine (**1**) in 20% yield in 10 steps with no loss of enantiomeric excess.

Polyhydroxylated indolizidines including (−)-2-*epi*-lentiginosine (**1**) are potent inhibitors of glycosidases and are of potential use in cancer chemotherapy.[1] (−)-2-*epi*-Lentiginosine is a metabolite of the fungus *Rhizoctonia leguminicol* and has been postulated to arise biosynthetically from L-lysine via L-pipecolic acid.[2,3] Although a large number of synthetic methods of polyhydroxylated indolizidines have been developed, these asymmetric syntheses are mainly based on chiral pool approaches.[1] More efficient methods for the preparation of such bioactive compounds are highly desired. Recently, biocatalysts have become an important tool for the production of pharmaceuticals and fine chemicals due to their high enantio-, regio-, and chemo-selectivity.[4] In addition, they often provide more environmentally friendly processes than chemical catalysts. Suitable biocatalysts for industrial and laboratory uses are commercially available now; however, they are still very limited. Therefore, the search for a superior biocatalyst to synthesize new chiral building blocks is an important field of study. Recently, we reported that extremely high enantioselectivity (E value $=>1000$) was achieved in the lipase-catalyzed kinetic resolution of racemic 5-hydroxy-1,5-dihydropyrrol-2-one (*rac*)-**5**.[5] Both enantiomers of **5** were easily attained in 49% yield with >99% ee. Herein, we report how the new chiral building block **5** can be utilized to prepare (−)-2-*epi*-lentiginosine (**1**) in high enantiomeric excess. The retrosynthesis is depicted in Scheme 1. Ring-closure metathesis of diallyl lactam **2** is a key reaction to form a bicyclic compound containing the three contiguous chiral centers. The chiral diol **3** is generated from the α,β-unsaturated lactam **4** employing a stereoselective dihydroxylation. The chiral lactam **4** is obtained by lipase-catalyzed kinetic resolution of the racemic hydroxylactam **5** prepared from maleic anhydride (**6**).

The *p*-methoxybenzyl (PMB) protecting group was chosen as it can be removed selectively in later transformations. PMB-protected maleimide **7** was obtained in 90% yield according to Toru's procedure,[6] following regioselective 1,2-reduction[7] using $NaBH_4/CeCl_3$ to afford the



Scheme 1. Retrosynthesis of (−)-2-*epi*-lentiginosine (**1**) from maleic anhydride (**6**).

Keywords: (−)-2-*epi*-Lentiginosine; Lipase-catalyzed kinetic resolution; Chiral building block.
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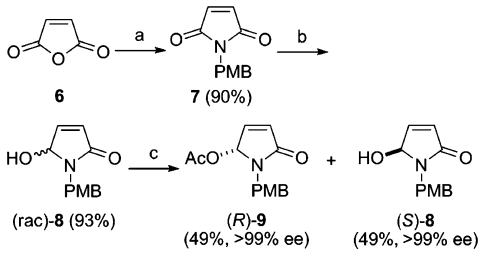


Scheme 2. Reagents and conditions: (a) $PMBNH_2$, $ZnCl_2$, HMDS, toluene, reflux, 2 h; (b) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 °C, 2 h; (c) $AcOCH{=}CH_2$, lipase PS-D (*Burkholderia cepacia*, Amano Enzyme Co, Ltd), 1,4-dioxane, rt, 24 h.

racemic hydroxylactam (*rac*)-**8** in 84% yield in two steps. Lipase PS-D catalyzed kinetic resolution of (*rac*)-**8** furnished acetate **9** with (*R*) stereochemistry in 49% yield with >99% ee, along with the recovered alcohol **8** with (*S*) stereochemistry in 49% yield with >99% ee (Scheme 2).[8]

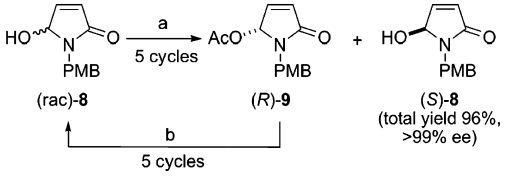
We further investigated a racemization of the chiral alcohol (*S*)-**8** and the chiral acetate (*R*)-**9** to improve the total chemical yield (Scheme 3). Chiral acetate (*R*)-**9** was subjected to racemization in the presence of scandium trifluoromethanesulfonate to give the racemic alcohol **8** in quantitative yield at 50 °C; similarly, the chiral alcohol **8** was completely racemized at 25 °C. This racemization probably proceeded through the same iminium cation intermediate **10**.[9] Alternatively, a more practical racemization was attained under basic conditions using sodium hydroxide. It is probable that the achiral anion intermediate **11** is formed during the racemization process.

Theoretically, chiral (*S*)-**8** and/or (*R*)-**9** should be obtained in 97% yield after five cycles of resolution–racemization processes. In fact, lipase-catalyzed kinetic resolution of hydroxylactam (*rac*)-**8**, followed by isolation–racemization of the chiral acetoxylactam (*R*)-**9** provided the optically pure hydroxylactam (*S*)-**8** in 96.0% yield with >99% ee after five cycles of kinetic resolution–racemization process (Table 1). The similar synthetic sequence including racemization of (*S*)-**8** to (*rac*)-**8** may be used to prepare (*R*)-**9** in high chemical total yield.

Stereoselective dihydroxylation of lactam (*S*)-**9** was performed by osmium oxidation. Exposure of (*S*)-**9** to osmium tetraoxide/NMO catalyst in a mixed aqueous solvent for 3 h afforded diol **12** in 91% yield with (2*S*,3*R*,4*S*) configuration as a single diastereomer. Protection of the dihydroxy group with dimethoxypropane furnished acetonide **13** in 82% yield accompanied by the replacement of the acetoxy group to a methoxy group (Scheme 4).

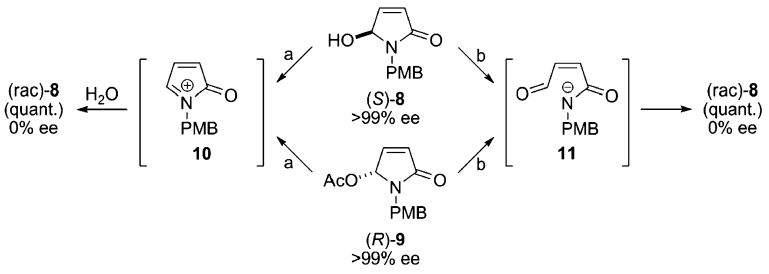
Acetonide **13** is a good substrate for the stereoselective nucleophilic addition of trimethylsilyl compounds promoted by boron trifluoride etherate via a well-known *N*-acylpyrrolidinium ion intermediate (Scheme 5).[9] Stereoselective allylation of **13** with allyltrimethylsilane led to the lactam **14** in 96% yield as a single diastereomer, which is a good precursor of gastroprotective AI-77-B agent as reported by Kotsuki et al.[10] Treatment of **13** with the trimethylsilyl enol ether of pinacolone furnished lactam **15** in 70% yield as a single diastereomer, which has been transformed to the naturally occurring (+)-calyculin A and (−)-calyculin B as reported by Smith et al.[9] Cyanation of **13** with trimethylsilyl cyanide also gave lactam **16** as a mixture of diastereomers ((2*S*,3*S*,4*S*): (2*R*,3*S*,4*S*) = 4:1), but they were easily separated by silica gel chromatography to give the chiral lactam **16** in 72% yield. The obtained cyanide **16** was converted to chiral 3,4-dihydroxyglutamic acid **17** as performed by Oba/Nishiyama et al.[11]

Table 1. Cycles of kinetic resolution and racemization

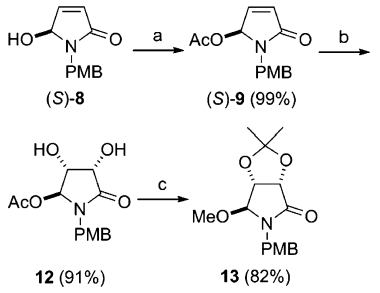


Cycles	Kinetic resolution (*rac*)-**8**→(*R*)-**9** + (*S*)-**8**		Racemization (*R*)-**9**→(*rac*)-**8**
	(*R*)-**9** Yield (ee), %	(*S*)-**8** Yield (ee), %	*rac*-**8** Yield (%)
1st	50 (>99)	48 (>99)	99
2nd	49 (>99)	50 (>99)	99
3rd	49 (>99)	48 (>99)	98
4th	50 (>99)	50 (>99)	95
5th	50 (>99)	50 (>99)	99

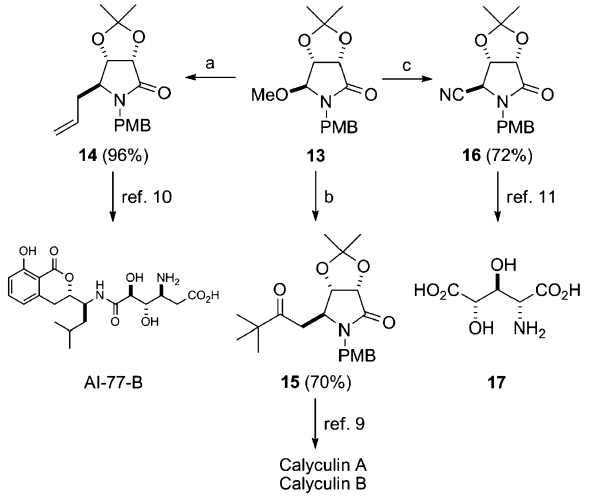
Reagents and conditions: (a) $AcOCH{=}CH_2$, lipase PS-D (*Burkholderia cepacia*, Amano Enzyme Co., Ltd), 1,4-dioxane, rt, 24 h; (b) NaOH (1 equiv), H_2O (2 equiv), THF, 25 °C, 24 h.



Scheme 3. Reagents and conditions: (a) from (*S*)-**8**: $Sc(OTf)_3$ (1 equiv), H_2O (2 equiv), THF, 25 °C, 7 h; from (*R*)-**9**: $Sc(OTf)_3$ (1 equiv), H_2O (2 equiv), THF, 50 °C, 22 h; (b) NaOH (1 equiv), H_2O (2 equiv), THF, 25 °C, 24 h.



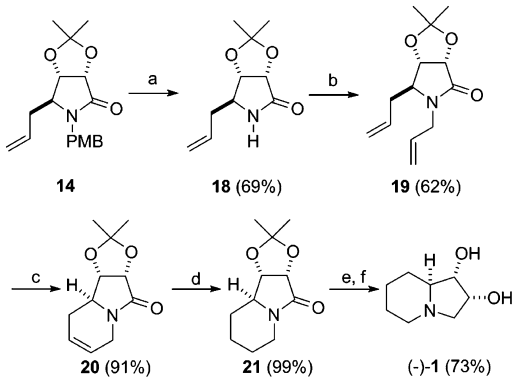
Scheme 4. Reagents and conditions: (a) Ac_2O, Et_3N, CH_2Cl_2, rt, 10 h; (b) OsO_4, NMO, H_2O/acetone/MeCN = 1:1:1, rt, 3 h; (c) $Me_2C(OMe)_2$, *p*-TsOH, acetone, rt, 24 h.



Scheme 5. Reagents and conditions: (a) $Me_3SiCH_2CH{=}CH_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C–rt, 20 h; (b) $Me_3SiOC(t\text{-}Bu){=}CH_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C–rt, 20 h; (c) Me_3SiCN, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C–rt, 20 h.

Lactam **14** was subjected to deprotection of the PMB group with cerium ammonium nitrate (CAN), and then allylation of **18** with allyl bromide gave lactam **19** in 62% yield. Ring-closing olefin metathesis of diallyl lactam **19** in the presence of Grubbs' first-generation catalyst effectively proceeded to give the bicyclic lactam **20** in 91% yield. Platinum oxide catalyzed hydrogenation of **20** followed by borane reduction and desalting on Dowex 1 × 8–50 afforded (−)-2-*epi*-lentiginosine (**1**). The physical properties of synthetic (−)-2-*epi*-lentiginosine (−)-**1** were in complete agreement with those reported in the literature[2,3,12] ($[\alpha]_D^{24}$ −31.3 (*c* 0.54, $CHCl_3$), lit.[2e] $[\alpha]_D^{25}$ −32.5 (*c* 0.44, $CHCl_3$). The same synthetic sequence may be used to prepare *ent*-**1** starting from readily available (*R*)-**9** (Scheme 6).

In summary, we have developed a practical synthesis of the chiral lactams (*S*)-**8** and/or (*R*)-**9** as new chiral building blocks for a multitude of important optically pure products. Lipase-catalyzed kinetic resolution of lactam **8** demonstrates excellent enantioselectivity. Furthermore, these lactams are easily racemized under acidic and/or basic conditions. Therefore, the kinetic resolution–racemization processes provided chiral lactam



Scheme 6. Reagents and conditions: (a) CAN, H_2O-MeCN, 0 °C, 3 h; (b) NaH, $BrCH_2CH{=}CH_2$, DMF, 0 °C–rt, 4 h; (c) Grubbs cat., CH_2Cl_2, rt, 3 h; (d) PtO_2, H_2 (0.4 MPa), AcOEt, rt, 4 h; (e) $BH_3{\cdot}THF$, THF, 55 °C, 12 h, then 1 N HCl, reflux, 30 min; (f) Dowex 1X8-50 (OH^- form).

(*S*)-**8** and/or (*R*)-**9** in high total chemical yield. Chemical transformation of (*S*)-alcohol **8** provided chiral (−)-2-*epi*-lentiginosine (−)-**1** in 20% yield in 10 steps with no loss of enantiomeric excess. Further studies focusing on the use of the chiral lactam (*S*)-**8** and/or (*R*)-**9** as a new chiral building block in total synthesis of natural compounds are currently under investigation and will be reported in due course.

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12. *Compound* **12**: $[\alpha]_D^{26}$ +80.1 (*c* 0.51, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.98$ (s, 3H, –OAc), 3.00–5.00 (br s, 2H, 2 × –OH), 3.79 (s, 3H, $-OCH_3$), 4.22 (d, $J = 4.8$ Hz, 1H, $-CH_\alpha$), 4.26 (d, $J = 14.8$ Hz, 1H, $-CH_2$), 4.56 (d, $J = 4.8$ Hz, 1H, $-CH_\beta$), 4.65 (d, $J = 14.8$ Hz, 1H, $-CH_2$), 5.94 (s, 1H, –C*H*OAc), 6.84 (d, $J = 8.7$ Hz, 2H, H-2, H-6), 7.18 (d, $J = 8.7$ Hz, 2H, H-3, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 174.62$ (C═O), 169.76 (C═O), 158.81 (C), 129.16 (CH), 127.15 (C), 113.57 (CH), 85.16 (CH), 69.86 (CH), 69.15 (CH), 54.65 (OCH_3), 44.38 (CH_2), 20.04 (CH_3); MS (EI) *m*/*z* 295 (M^+, 1), 235 (15),178 (28), 136 (34), 121 (100); Anal. Calcd: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.75; H, 5.72; N, 4.61. *Compound* **13**: $[\alpha]_D^{25}$ +58.9 (*c* 0.79, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.33$ (s, 3H, $-CH_3$), 1.34 (s, 3H, $-CH_3$), 3.30 (s, 3H, $-OCH_3$), 3.78 (s, 3H, $ArOCH_3$), 3.94 (d, $J = 14.5$ Hz, 1H, $-CH_2$), 4.43 (d, $J = 6.0$ Hz, 1H, $-CH_\alpha$), 4.47 (d, $J = 0.7$ Hz, 1H, –C*H*OCH_3), 4.78 (dd, $J = 0.7$, 6.0 Hz, 1H, $-CH_\beta$), 4.92 (d, $J = 14.5$ Hz, 1H, $-CH_2$), 6.85 (d, $J = 8.7$ Hz, 2H, H-2, H-6), 7.18 (d, $J = 8.7$ Hz, 2H, H-3, H-5); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 171.05$ (C═O), 159.39 (C), 129.90 (CH), 127.15 (C), 114.15 (CH), 113.22 (C), 91.04 (CH), 76.97 (CH), 76.33 (CH), 55.20 (OCH_3), 54.75 (OCH_3), 43.43 (CH_2), 26.92 (CH_3), 25.70 (CH_3); MS (EI) *m*/*z* 307 (M^+, 17), 87 (100); Anal. Calcd: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.38; H, 6.81; N, 4.38. *Compound* **14**: registry number (3a*S*, 6*S*, 6a*S*)-154850-78-9; $[\alpha]_D^{28}$ +39.2 (*c* 0.75, $CHCl_3$), (lit.[9] $[\alpha]_D^{22}$ +37.0 (*c* 2.0, $CHCl_3$)); ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 1.34$ (s, 3H, $-CH_3$), 1.39 (s, 3H, $-CH_3$), 2.1–2.5 (m, 2H), 3.53 (dd, $J = 7.0$, 3.6 Hz, 1H), 3.79 (s, 3H, $-OCH_3$), 3.89 (d, $J = 14.8$ Hz, 1H), 4.39 (d, $J = 5.7$ Hz, 1H), 4.67 (dd, $J = 5.7$, 0.6 Hz, 1H), 4.99 (d, $J = 14.8$ Hz, 1H), 5.06–5.22 (m, 2H), 5.48–5.72 (m, 1H), 6.85 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 8.6$ Hz, 2H). *Compound* **18**: registry number (3a*S*, 6*S*, 6a*S*)-154850-79-0; ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 1.37$ (s, 3H, $-CH_3$), 1.47 (s, 3H, $-CH_3$), 2.1–2.5 (m, 2H), 3.73 (t, $J = 6.3$ Hz, 1H), 4.45 (d, $J = 5.9$ Hz, 1H), 4.45 (d, $J = 5.9$ Hz, 1H), 5.02–5.30 (m, 2H), 5.6–5.9 (m, 1H), 6.98 (bs, 1H, N–H). *Compound* **19**: ^{1}H NMR (90 MHz, $CDCl_3$) $\delta = 2.05$–2.65 (m, 2H), 1.37 (s, 3H, $-CH_3$), 1.43 (s, 3H, $-CH_3$), 3.30–3.90 (m, 2H), 4.20–4.35 (m, 1H), 4.43 (d, $J = 5.6$ Hz, 1H), 4.64 (d, $J = 5.6$ Hz, 1H), 5.05–6.10 (m, 6H); MS (EI) *m*/*z* 237 (M^+, 0.5), 196 (19), 85 (53), 41 (100). *Compound* **20**: ^{1}H NMR (90 MHz, $CDCl_3$) $\delta = 1.55$–2.65 (m, 2H), 1.39 (s, 3H, $-CH_3$), 1.46 (s, 3H, $-CH_3$), 3.40–3.85 (m, 2H), 4.20–4.35 (m, 1H), 4.42 (d, $J = 6.5$ Hz, 1H), 4.67 (d, $J = 6.5$ Hz, 1H), 5.50–5.95 (m, 2H); MS (EI) *m*/*z* 209 (M^+, 4), 194 (21), 134 (22), 100 (16), 85 (32), 81 (26), 54 (74), 43 (100). *Compound* **21**: registry number (3a*S*, 9a*S*, 9b*S*)-359866-28-7; $[\alpha]_D^{24}$ +31.3 (*c* 0.89, $CHCl_3$) (lit.[3c] $[\alpha]_D^{25}$ +31.3 (*c* 1.00, $CHCl_3$)); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta = 1.00$–1.70 (m, 4H), 1.35 (s, 3H, $-CH_3$), 1.42 (s, 3H, $-CH_3$), 1.71–2.15 (m, 2H), 2.50–2.95 (m, 1H), 3.47 (dd, $J = 2.6$, 12.3 Hz, 1H), 4.05–4.40 (m, 1 H), 4.32 (d, $J = 6.0$ Hz, 1H), 4.62 (d, $J = 6.0$ Hz, 1H); MS (EI) *m*/*z* 211 (M^+, 2), 196 (30), 136 (31), 100 (30), 83 (80), 55 (55), 43 (100). *Compound* (−)-**1**: registry number (1*S*,2*R*,8a*S*)-108866-42-8((−)-2-*epi*-lentiginosine); $[\alpha]_D^{24}$ −31.3 (*c* 0.54, $CHCl_3$) (lit.[2e] $[\alpha]_D^{25} = -32.5°$ (*c* 0.44, $CHCl_3$)); ^{1}H NMR (90 MHz, $CDCl_3$) $\delta = 1.05$–1.40 (m, 2H), 1.41–1.75 (m, 2H), 1.76–2.40 (m, 7H), 2.80–3.22 (m, 1H), 3.23–3.85 (m, 2H), 4.05–4.50 (m, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$) $\delta = 74.8$ (CH), 67.9 (CH), 67.1 (CH), 61.8 (CH_2), 52.8 (CH_2), 28.5 (CH_2), 24.9 (CH_2), 23.7 (CH_2); MS (EI) *m*/*z* 157 (M^+, 14), 140 (8), 97 (100), 84 (24), 69 (39).