Tetrahedron 68 (2012) 878–882

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of (−)-benzolactam-V8 by application of asymmetric aziridination

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ARTICLE INFO

Article history:
Received 8 October 2011
Received in revised form 11 November 2011
Accepted 12 November 2011
Available online 19 November 2011

Keywords:
(−)-Benzolactam-V8
Asymmetric synthesis
Guanidinium ylide
3-Arylaziridine-2-carboxylate
Ring-opening reaction

ABSTRACT

(−)-Benzolactam-V8, an artificially-designed cyclic dipeptide with strong tumor-promoter activity, was synthesized from benzyl (*S*)-*N*-(2-formylphenyl)-*N*-methylvalinate by application of guanidinium ylide-participated asymmetric aziridination followed by the reductive ring-opening reaction of 3-arylaziridine-2-carboxylate formed.

1. Introduction

Teleocidins [ex. teleocidin B-1 (**1**)], olivoretins [ex. olivoretin A (**2**)], and lyngbyatoxins [ex. lyngbyatoxin B (**3**)] (summarized as teleocidins in this paper) have been isolated from microorganisms (*Streptomyces* and *Streptoverticillium*) and blue-green alga (*Lyngbya* species) as strong tumor promoters.[1–10] They are structurally defined to be nine-membered cyclic dipeptides derived from (*S*)-tryptophan and (*S*)-valine units and their terpene-substituted structures are minimized to (−)-indolactam-V (**4**) as a common core skeleton,[11] which had also been isolated from *Actinomycetes*,[12] albeit with lower activity.[13] Chemical approaches to the biological activity of (−)-indolactam-V (**4**) have indicated that the 9*S*- and 12*S*-stereochemistries are essential for the tumor-promoting effects. In addition, although these nine-membered cyclic dipeptides are in equilibrium between twist and sofa conformations in solution,[7,9,14–17] the designation of an eight-membered (−)-benzolactam-V8 (**5**) and a nine-membered (−)-benzolactam-V9 (**6**) carrying phenyl ring, in place of indole unit in the natural tumor promoters, as model cyclic peptides[18] led to the results that the former eight-membered (−)-benzolactam-V8 (**5**) existed in only twist conformation and was more active than (−)-indolactam-V (**4**). Furthermore, it has been suggested that not only the 5*S*-configuration of (−)-benzolactam-V8[19] (**5**) as well as the 9*S*-configuration of (−)-indolactam-V[13] (**4**), but also hydrogen of the amide functionality in these lactams, play an important role for the biological activity[20] (Fig. 1).

We have recently developed guanidine chemistry,[21] and have found the unique formation of 3-aryl- (or unsaturated) aziridine-2-carboxylates, expandable to chiral version, by the reaction of guanidinium salt and aryl (or unsaturated) aldehyde in the presence of

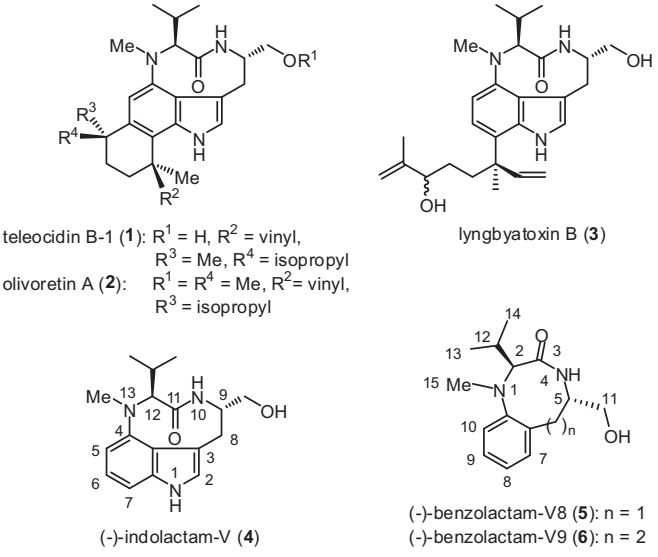

Fig. 1. Structures of teleocidins and the related compounds [Numbering of benzolactams is for benzolactam-V8 (**5**)].

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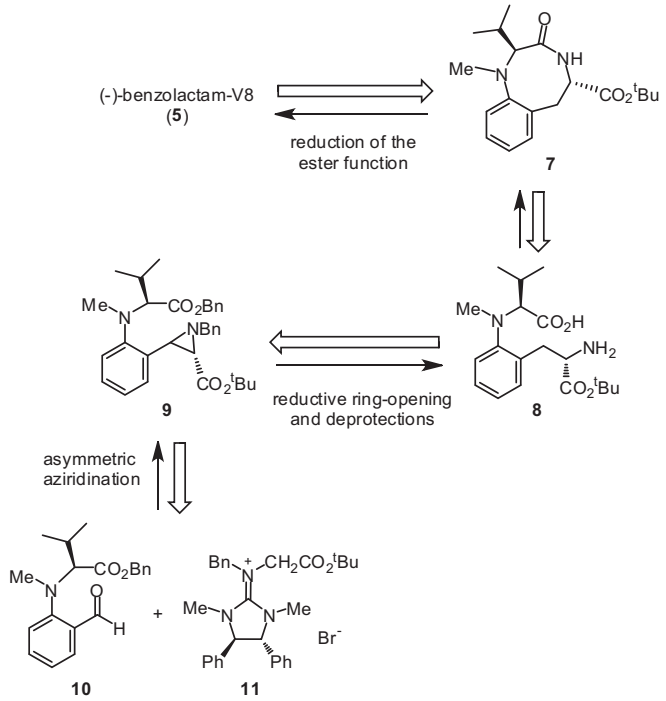
doi:10.1016/j.tet.2011.11.033

base.[22–25] In this paper we will present a new synthetic approach to (−)-benzolactam-V8 (**5**) by application of the asymmetric aziridination followed by the reductive ring-opening reaction of 3-arylaziridine-2-carboxylate formed.

2. Results and discussion

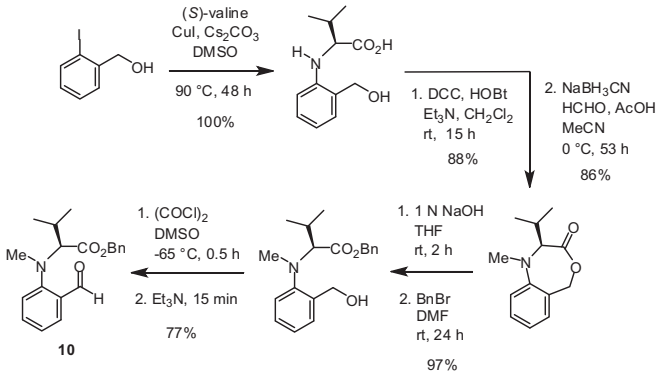
In the synthesis of benzolactam-V8 (**5**) and its analogs, construction of two amino acid components tethered by phenyl ring is crucial and, previously, the *N*-aryl-substituted (*S*)-valine unit had majorly been prepared by the displacement reaction of oxygen-substituted (*R*)-isovalerate with an aniline derivative,[26–37] instead Ma and co-workers had adopted the amination of either phenyl ring[38] or 1,3-cyclohexadienone[39] with (*S*)-valine. On the other hand, some variations were reported for the construction of (*S*)-phenylalanine unit except the use of phenylalanine itself[29–32] or its derivatives:[28,32,33] (1) diastereoselective alkylation of aminomalonate with benzyl bromide dependent on the stereochemistry of valine unit introduced,[26–28] (2) diastereoselective aldol-type condensation between valine-substituted benzaldehyde and nitroacetate,[38] (3) asymmetric alkylation of iminoacetate with benzyl alcohol in the presence of a chiral quinine-type phase transfer catalyst,[33] (4) use of the amine functionality of (*R*)-phenylglycinate acted as a chiral auxiliary after reductive cleavage,[34,36,37,39] and (5) oxyamination of allylbenzene.[35]

The direct amination of phenyl ring reported by Ma's group[38] attracted us as the ready preparation of *N*-aryl-substituted (*S*)-valine. On the other hand, for the preparation of (*S*)-phenylalanine unit our original asymmetric aziridination followed by regioselective ring-opening reaction of the formed aziridine was focused. The retrosynthesis is shown in Scheme 1, in which (2*S*)-3-phenylaziridine-2-carboxylate **9** carrying (*S*)-valine unit at the *ortho* position of the phenyl pendant is designed as a key intermediate. In the aziridination,[22–25] the following stereochemical evidences have generally been established: (1) *trans*-aziridines are diastereoselectively produced when electron-rich benzaldehydes are used, whereas *cis*-aziridines in the case of either benzaldehyde itself or benzaldehydes substituted with electron-withdrawing group and (2) asymmetric induction at the 2 position of 3-arylaziridine-2-carboxylates is controlled by the chiral center of guanidinium salt used; e.g., the predominant production of (2*S*,3*R*)-*trans*-3-[(3,4-methylenedioxy)phenyl]aziridine-2-carboxylate in the reaction of (3,4-methylenedioxy)benzaldehyde (piperonal) and (4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidinium salt. Thus, the key aziridine **9** should be obtained by asymmetric aziridination of the (*S*)-valine-substituted benzaldehyde **10** and the (*R*,*R*)-guanidinium bromide **11** and, then, be converted to the (*S*)-valine-substituted (*S*)-phenylalaninate **8** by regioselectively reductive ring-opening reaction of the aziridine **9** formed as a precursor for the benzolactam skeleton **7** with a cyclic dipeptide structure.



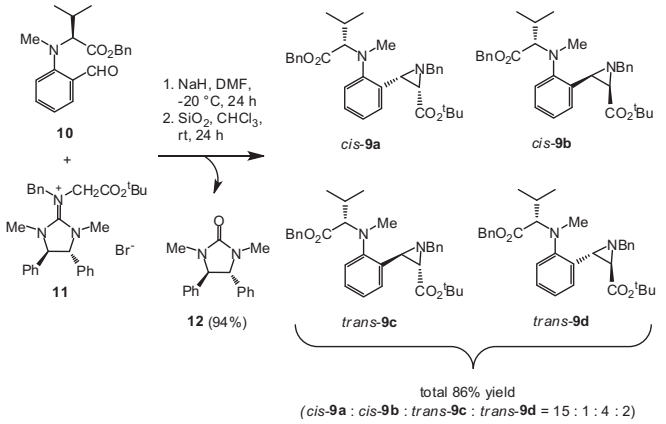
Scheme 1. Retrosynthesis of (−)-benzolactam-V8 (**5**).

The known benzyl (*S*)-*N*-(2-formylphenyl)-*N*-methylvalinate (**10**) was prepared from 2-iodobenzyl alcohol according to the reported procedure[38] with a slight modification of the amination step[40] (Scheme 2). The successive reactions of copper-catalyzed coupling reaction between 2-iodobenzyl alcohol and (*S*)-valine, lactonization, reductive N-methylation, alkaline hydrolysis followed by esterification with benzyl alcohol, and oxidation of the hydroxymethyl function in the *N*-phenyl substituent provided the benzaldehyde substrate **10** in overall 57% yield.



Scheme 2. Preparation of benzyl (*S*)-*N*-(2-formylphenyl)-*N*-methylvalinate (**10**) from 2-iodobenzyl alcohol.

At first, guanidinium ylide-participated aziridination under achiral conditions was preliminarily examined (see, Scheme 3). Treatment of the valine-substituted benzaldehyde **10** with the guanidinium bromide lacking phenyl pendants (see, **11**) in the presence of sodium hydride (NaH) in dimethylformamide (DMF) at −20 °C for 24 h, followed by stirring the resultant mixture with silica gel (SiO_2) in chloroform ($CHCl_3$) at room temperature (rt) for 24 h, afforded a crude product, showing two spots except that of the starting **10** on thin layer chromatography (TLC) (R_f=0.6 and 0.5



Scheme 3. Asymmetric aziridination of the valine-substituted benzaldehyde **10** and the (*R*,*R*)-guanidinium bromide **11** in the presence of NaH.

in diethyl ether/*n*-hexane=1:3). In general, a larger coupling constant between C2–H (δ ca. 2.5 ppm) and C3–H (δ ca. 3.5 ppm) is observed in *cis*-3-arylaziridine-2-carboxylates (J=ca. 7 Hz) than in the *trans*-derivative (J=ca. 2 Hz) in their ^{1}H NMR spectra.[22] Although each ^{1}H NMR spectrum of two products separated by preparative TLC showed relatively complicated signal patterns because of not homogeneous but a mixture composed of four possible aziridine isomers **9a**–**d** with a different composition ratio, we found that the ratio of each diastereoisomer could be reasonably determined by the careful analysis of characteristic signals due to the 3-arylaziridine-2-carboxylate skeleton in both the separates; e.g., for the less polar product, *cis*-**9a** (δ_{C2-H} 2.557: $J_{2,3}$=7.2 Hz): *cis*-**9b** (δ_{C2-H} 2.563: $J_{2,3}$=6.8 Hz): *trans*-**9c** (δ_{C2-H} 2.60: $J_{2,3}$=2.4 Hz): *trans*-**9d** (δ_{C2-H} 2.65: $J_{2,3}$=2.4 Hz)=ca. 6:2:9:3.

Next, we attempted asymmetric aziridination using the (*R*,*R*)-guanidinium bromide **11** under the same reaction conditions as achiral version (Scheme 3). Reaction was smoothly proceeded to provide a crude mixture of aziridine **9** (almost one spot on TLC: R_f=0.6 in diethyl ether/*n*-hexane=1:3) and the co-formed urea **12**. After removal of a chiral urea **12** (94% yield), which is re-useable as the precursor of guanidinium bromide **11**, by washing with *n*-hexane, purification of the combined washings by SiO_2 column chromatography after evaporation afforded an expected aziridine product **9** in 86% yield. The ratio of *cis*-**9a**/*cis*-**9b**/*trans*-**9c**/*trans*-**9d** was estimated to be 15:1:4:2 based on the assignment under the achiral version. Among them, the C2-stereochemistry of *cis*-**9a** and *trans*-**9c** obtained as each major isomer could be reasonably assigned to be *S*-configuration based on asymmetric induction as discussed above.[22–25] This means that these 2*S*-diastereoisomers are totally calculated to be 86% of the aziridine mixture **9** (72% excess).

Preferred formation of *cis*-isomers to *trans*-ones seems to be contrary to the expected preference of *trans*-isomers in the use of an electron-rich 2-aminobenzaldehyde derivative as an electrophile. However, the discrepancy may be explained by supposition that the steric bulkiness of the valine function located at the *ortho* position prohibits effective conjugation between amine group and aldehyde functionality through benzene ring, resulting in predominance by the electro-negative character of nitrogen atom due to inductive effect. In fact, this speculation could be supported by model study (Fig. 2). The geometry optimization of the valine-substituted benzaldehyde **10** using PM3 method allowed us to deduce two conformations **10A** and **10B** as the most stable conformations. The heat of formation of them was calculated to be −84.56 kcal/mol and −85.48 kcal/mol, respectively, and, in the more stable latter conformation **10B**, dihedral angles between the substituents and the phenyl ring were estimated to be 101.3° (C2–C1–C=O), −81.4° (C6–C1–C=O), 62.4° (C3–C2–N–Cα), and −119.3° (C1–C2–N–Cα), indicating difficult conjugation of the amine group with the aldehyde one through benzene ring.

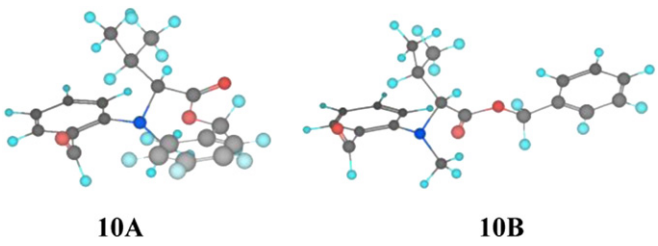
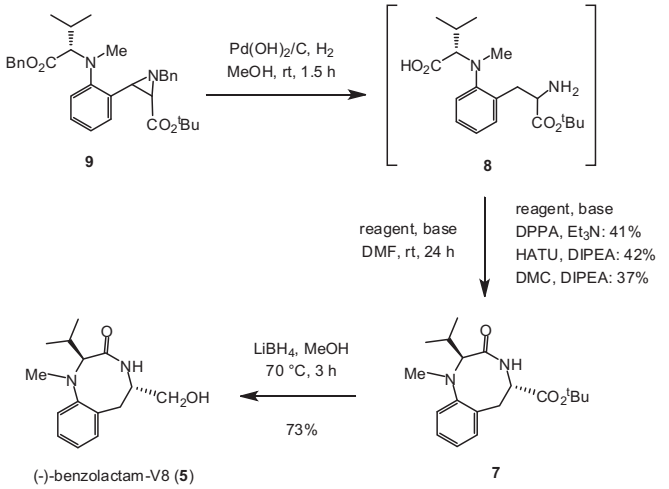


Fig. 2. Optimized structures of the valine-substituted benzaldehyde **10** using PM3 method.

It is not necessarily easy to separate the aziridine mixture **9** to each four pure component. Thus, we decided to detour the difficult separation because four components could at least convergent to two ones by destruction of the C3 chiral center in the aziridine system in next reductive ring-opening reaction. Stirring the aziridine mixture **9** in methanol in the presence of palladium hydroxide on carbon as a catalyst at rt for 90 min under hydrogen atmosphere[22,23,41] afforded a high polar product, which was expected to be phenylalaninate **8** incorporating (*S*)-valine as an additional α-amino acid unit. The crude **8**, without any purification, was further subjected to lactamization by the use of diphenyl phosphoryl azide (DPPA) as a condensation reagent according to the reported conditions[38] to give a benzolactam skeleton **7** as only an isolable product, after purification by SiO_2 column chromatography, in total 41% yield from the aziridine mixture **9**. We speculated above that the C2-stereochemistry of major *cis*-**9a** and *trans*-**9c** in the starting aziridine mixture could be deduced to be *S* and that the ratio of these 2*S*-diastereoisomers was estimated to be 86%. Therefore, the benzolactam skeleton **7** isolated could be assigned as a desired (2*S*,5*S*)-isomer. Additional trials for the construction of **7** using alternative condensation reagents, such as 1-[bis(dimethylamino) methylene]-1*H*-1,2,3-triazolo(4,5-*b*)pyridinium 3-oxide hexafluorophosphate (HATU) and 2-chloro-1,3-dimethylimidazolinium chloride (DMC),[42] in place of DPPA, resulted in not improving the conversion yields from **9** (42% with HATU; 37% with DMC).

Finally, reduction of the *tert*-butyl ester function of the benzolactam skeleton **7** with lithium borohydride in methanol at 70 °C for 3 h gave a desired alcohol in 73% yield, the data of which, including $[\alpha]_D$, was completely identical with those of (−)-benzolactam-V8 (**5**)[29] (Scheme 4).



Scheme 4. Preparation of (−)-benzolactam-V8 (**5**) from the aziridine mixture **9**.

In conclusion, we succeeded in the synthesis of (−)-benzolactam-V8, an artificially-designed cyclic dipeptide with strong tumor-promoter activity, from benzyl (*S*)-*N*-(2-formylphenyl)-*N*-methylvalinate through four steps by application of guanidinium ylide-participated asymmetric aziridination followed by reductive ring-opening reaction of the 3-arylaziridine-2-carboxylate formed as key steps.

3. Experimental

3.1. General

All melting points were measured on a micro-melting point hot stage (Yanaco) and are uncorrected. IR spectra were recorded with ATR (attenuated total reflectance system) on a JASCO FT/IR-300E spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JOEL JNM-ECP-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) in $CDCl_3$.

Chemical shifts (δ) were reported as parts per million from tetramethylsilane (0.00 ppm) as an internal standard for ^{1}H and from the middle resonance of $CDCl_3$ (77.00 ppm) as an internal standard for ^{13}C, respectively. MS spectra were measured on JEOL JMS-HX110A for FABMS and JEOL JMS-T100LP for ESIMS. Optical rotations were recorded on a JASCO P-1020 digital polarimeter. For SiO_2 column chromatography were used Kanto silica gel 60 (37564-85), spherical particle size 63–210 μm, or FL100D SiO_2 (Fuji Silysia Chemical Ltd). For TLC was used Merck DC-Fertigplatten Kieselgel 60 F_{254} (5715). Dehydrated DMF was purchased from Kanto Chemical Co. Inc.

3.2. Asymmetric aziridination of 10 and 11

A mixture of the benzaldehyde **10**[38] (0.1065 g, 0.37 mmol), the guanidinium bromide **11** (0.2125 g, 0.386 mmol) in DMF (0.7 mL) in the presence of NaH (60% oil suspension, 0.029 g, 0.721 mmol) was stirred at −20 °C for 24 h under argon atmosphere and, after addition of $CHCl_3$ (20 mL) and SiO_2 (0.47 g), the resultant mixture was stirred at rt for 24 h. The SiO_2 was filtered off and washed with $CHCl_3$ (20 mL). The filtrate was combined with the washing and concentrated under reduced pressure. The yellow residual oil was dissolved in Et_2O (80 mL), and the ethereal solution was washed with H_2O (2 mL×3) and brine (2 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (0.329 g). Trituration of the yellow oil with *n*-hexane afforded the urea **12** (0.0821 g, 94%) as colorless solids and a crude aziridine mixture **9** (0.172 g, 99%) as a yellow oil from the soluble part after evaporation. Purification of the crude **9** by SiO_2 column chromatography (Et_2O/*n*-hexane=1:10) afforded an oily aziridine mixture (0.149 g, 86%), composed of *cis*-**9a**, *cis*-**9b**, *trans*-**9c**, and *trans*-**9d** in ratio of 15:1:4:2 based on the ^{1}H NMR spectrum; TLC: R_f 0.7 (very small spot), 0.6 (main spot) (EtOAc/*n*-hexane=1:5); IR ν_{max} cm^{-1}: 1723 (CO); ^{1}H NMR δ: 0.80 (4/22×3H, d, *J*=6.6 Hz, CH*Me*$_2$ in *trans*-**9c**), 0.87 (3/22×3H, d, *J*=6.6 Hz, CH*Me*$_2$ in *cis*-**9b** and *trans*-**9d**), 0.90 (1/22×3H, d, *J*=6.6 Hz, CH*Me*$_2$ in *cis*-**9b**), 0.94 (15/22×3H, d, *J*=6.4 Hz, CH*Me*$_2$ in *cis*-**9a**), 1.10 (15/22×9H, s, CMe$_3$ in *cis*-**9a**), 1.10 (4/22×3H, d, *J*=5.1 Hz, CH*Me*$_2$ in *trans*-**9c**), 1.19 (15/22×3H, d, *J*=6.8 Hz, CH×*Me*$_2$ in *cis*-**9a**), 1.19 (1/22×9H, s, CMe$_3$ in *cis*-**9b**), 1.22 (2/22×3H, d, *J*=6.6 Hz, CH*Me*$_2$ in *trans*-**9d**), 1.35 (2/22×9H, s, CMe$_3$ in *trans*-**9d**), 1.40 (4/22×9H, s, CMe$_3$ in *trans*-**9c**), 2.2–2.4 (1H, m, CHC*H*Me$_2$), 2.56 (16/22×1H, d, *J*=7.0 Hz, C2–H in *cis*-**9a** and *cis*-**9b**), 2.60 (2/22×1H, d, *J*=2.7 Hz, C2–H in *trans*-**9d**), 2.65 (4/22×1H, d, *J*=2.2 Hz, C2–H in *trans*-**9c**), 2.77 (15/22×3H, s, NMe in *cis*-**9a**), 2.82 (4/22×3H, s, NMe in *trans*-**9c**), 2.85 (2/22×3H, s, NMe in *trans*-**9d**), 2.90 (1/22×3H, s, NMe in *cis*-**9b**), 3.15 (1/22×1H, d, *J*=7.0 Hz, C3–H in *cis*-**9b**), 3.30 (15/22×1H, d, *J*=10.6 Hz, NC*H*CH(C) in *cis*-**9a**), 3.40 (2/22×1H, d, *J*=10.6 Hz, NC*H*CH(C) in *trans*-**9d**), 3.43 (4/22×1H, d, *J*=7.0 Hz, NC*H*CH(C) in *trans*-**9c**), 3.44 (15/22×1H, d, *J*=7.0 Hz, C3–H in *cis*-**9a**), 3.49, 3.64 (each 1/22×1H, d, *J*=14.2 Hz, NCH$_2$Ph in *cis*-**9b**), 3.57 (1/22×1H, d, *J*=10.1 Hz, NC*H*CH(C) in *cis*-**9b**), 3.65 (4/22×1H, d, *J*=1.6 Hz, C3–H in *trans*-**9c**), 3.69, 3.82 (each 15/22×1H, d, *J*=14.3 Hz, NCH$_2$Ph in *cis*-**9a**), 3.69 (2/22×1H, d, *J*=2.6 Hz, C3–H in *trans*-**9d**), 4.07, 4.23 (each 2/22×1H, d, *J*=14.2 Hz, NCH$_2$Ph in *trans*-**9d**), 4.16, 4.25 (each 4/22×1H, d, *J*=14.2 Hz, NCH$_2$Ph in *trans*-**9c**), 4.91, 4.97 (each 15/22×1H, d, *J*=12.2 Hz, OCH$_2$Ph in *cis*-**9a**), 4.94 (each 2/22×2H, s, OCH$_2$Ph in *trans*-**9d**), 5.05, 5.10 (each 4/22×1H, d, *J*=12.1 Hz, OCH$_2$Ph in *trans*-**9c**), 5.11, 5.22 (each 1/22×1H, d, *J*=12.2 Hz, OCH$_2$Ph in *cis*-**9b**), 7.1–7.6 (14H, m, Ar*H*); ^{13}C NMR δ: 18.9, 19.2 (*cis*-**9a**), 19.3, 19.5, 19.6, 19.75 (*cis*-**9a**), 19.80, 20.0, 27. 7 (*cis*-**9a**), 27.9, 27.98, 27.99, 28.09 (*cis*-**9a**), 28.14, 28.5, 28.9, 34.6 (*cis*-**9a**), 35.3, 35.7, 36.3, 44.1, 44.7, 45.3 (*cis*-**9a**), 45.80, 45.83, 46.2, 47.65, 47.70 (*cis*-**9a**), 54.6, 54. 7, 63.1, 63.3 (*cis*-**9a**), 65.4, 65.5 (*cis*-**9a**), 65.7, 66.0, 71.4, 72.0 (*cis*-**9a**), 72.29, 72.31, 81.0, 81.2 (*cis*-**9a**), 81. 5, 81.6, 120.4, 121.6, 121.9 (*cis*-**9a**), 122.0, 122.05, 122.06, 123.5 (*cis*-**9a**), 123.85, 123.93, 125.8, 126.1, 126.6, 126.7, 126.88, 126.91 (*cis*-**9a**), 127.6 (*cis*-**9a**), 127.66 (*cis*-**9a**), 127.67, 127.69, 127.74, 127.86, 127.92, 127.95, 127.97 (*cis*-**9a**), 128.1, 128.18, 128.20, 128.23 (*cis*-**9a**), 128.26 (*cis*-**9a**), 128.29, 128.34, 128.35, 128.42, 128.43, 128.57, 128.58, 128.64 (*cis*-**9a**), 129.4 (*cis*-**9a**), 129.78, 129.84 (*cis*-**9a**), 132.7, 135. 6 (*cis*-**9a**), 135. 7, 135. 8, 138.1 (*cis*-**9a**), 138.3, 139.5, 139.6, 150.8, 151.5 (*cis*-**9a**), 151.79, 151.80, 166.8 (*cis*-**9a**), 167.5, 167.7, 168.0, 171.3 (*cis*-**9a**), 171.5, 171.7, 172.5; HRFABMS *m*/*z*: 529.3079 (calcd for $C_{33}H_{41}N_2O_4$: 529.3066); $[\alpha]_D^{26}$ −6.1 (*c* 0.55, $CHCl_3$).

3.3. Reductive ring-opening reaction of an aziridine mixture 9 followed by lactamization

3.3.1. With DPPA. A mixture of the aziridine mixture **9** (0.0761 g, 0.144 mmol), and 20% Pd(OH)$_2$/C (0.0153 g) in MeOH (0.3 mL) was stirred at rt for 1.5 h at atmospheric pressure under hydrogen and the catalyst was filtered off through Celite pad. Evaporation of the filtrate gave a crude ring-opened **8** (0.0663 g) as solids, which was dissolved in DMF (15 mL). After addition of Et_3N (0.04 mL, 0.287 mmol) and DPPA (0.04 mL, 0.176 mmol) at 0 °C under argon atmosphere the resultant solution was stirred at the same temperature for 5 min and then at rt for 24 h, and evaporated under reduced pressure. The residue was partitioned with EtOAc (80 mL) and H_2O (4 mL). The aqueous solution was extracted with EtOAc (20 mL×2). The combined EtOAc solution was washed with H_2O (2 mL×2) and brine (2 mL×2) and dried (Na_2SO_4), and evaporated. After removal of an insoluble solid by trituration with Et_2O, the oily residue was evaporated and purified by SiO_2 column chromatography (EtOAc/*n*-hexane=1:5) afforded lactam **7** (0.0196 g, 41%) as a yellow oil; TLC: R_f 0.4 (EtOAc/*n*-hexane=1:2); IR ν_{max} cm^{-1}: 3380 (NH), 1730, 1665 (CO); ^{1}H NMR δ: 0.95, 1.08 (each 3H, d, *J*=6.8 Hz, CH*Me*$_2$), 1.50 (9H, s, CMe$_3$), 2.42 (1H, octet, *J*=7.0 Hz, CHC*H*Me$_2$), 2.78 (3H, s, NMe), 3.00 (1H, dd, *J*=16.3, 8.8 Hz, ArC*H*$_2$CH), 3.37 (1H, d, *J*=7.7 Hz, NC*H*CH), 3.54 (1H, dd, *J*=16.1, 3.8 Hz, ArC*H*$_2$CH), 4.92 (1H, br s, NHC*H*(CH)CH$_2$), 6.23 (1H, d, *J*=4.0 Hz, NH, exchangeable), 6.97 (1H, t, *J*=7.4 Hz, Ar*H*), 7.07 (1H, d, *J*=7.7 Hz, Ar*H*), 7.12 (1H, d, *J*=7.9 Hz, Ar*H*), 7.22 (1H, t, *J*=7.3 Hz, Ar*H*); ^{13}C NMR δ: 19.5, 20.2, 28.0, 28.6, 36.8, 39.3, 54.8, 73.3, 82.8, 121.6, 123.3, 128.1, 131.6, 131.9, 151.9, 170.9, 171.8; HRFABMS *m*/*z*: 333.2174 (calcd for $C_{19}H_{29}N_2O_3$: 333.2178); $[\alpha]_D^{27}$ −150 (*c* 0.348, $CHCl_3$).

3.3.2. With HATU. After ring-opening reaction using **9** (0.0762 g, 0.144 mmol) and 20% Pd(OH)$_2$/C (0.0153 g) and MeOH (0.3 mL) as described above, the crude **8** (0.0637 g) was dissolved in DMF (26 mL). After the resultant solution was stirred with DIPEA (0.06 mL, 0.344 mmol) at 0 °C for 10 min under argon atmosphere HATU (0.0786 g, 0.207 mmol) was added at 0 °C and the whole was stirred at the same temperature for 20 min and then at rt for 24 h, and evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the resultant solution was washed with 10% citric acid (2 ml×2), satd $NaHCO_3$ aq (2 ml×2), and brine (2 ml×2), and dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (EtOAc/*n*-hexane=1:5) afforded lactam **7** (0.0200 g, 42%).

3.3.3. With DMC. After ring-opening reaction using **9** (0.0358 g, 0.068 mmol) and 20% Pd(OH)$_2$/C (0.0072 g) and MeOH (0.3 mL) as described above, the crude **8** (0.0382 g) was dissolved in DMF (12 mL). After the resultant solution was stirred with DIPEA (0.03 mL, 0.173 mmol) at 0 °C for 10 min under argon atmosphere a 1 M solution of DMC in DMF (0.09 mL, 0.09 mmol) was added at 0 °C and the whole was stirred at the same temperature for 10 min and then at rt for 24 h, and evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL) and the resultant solution was washed with 10% citric acid (2 ml×2), satd $NaHCO_3$ aq (2 ml×2), and brine (2 ml×2), dried (Na_2SO_4), and evaporated. Purification of the residue by SiO_2 column chromatography (EtOAc/*n*-hexane=1:5) afforded lactam **7** (0.0084 g, 37%).

3.4. (−)-Benzolactam-V8 (5)

A mixture of lactam **7** (0.0107 g, 0.0322 mmol) and $LiBH_4$ (0.0021 g, 0.0964 mmol) in dry MeOH (0.6 mL) was heated at 70 °C for 3 h and, after quenched with H_2O (1 mL) at rt, was extracted with EtOAc (15 mL×2). The organic solution was washed with H_2O (1 mL×2) and brine (1 mL×2), dried ($MgSO_4$), and evaporated. Purification of the residual yellow solids by SiO_2 column chromatography (EtOAc/*n*-hexane=2:1) afforded (−)-benzolactam-V8 (**5**) (0.0062 g, 73%) as colorless prisms, mp 113–114 °C (lit. no data); TLC: R_f 0.2 (EtOAc/*n*-hexane=1:1); IR ν_{max} cm^{-1}: 3349 (NH), 3300 (br, OH), 1629 (CO); ^1H NMR δ: 0.89, 1.07 (each 3H, d, J=6.6 Hz, $CHMe_2$), 2.40–2.49 (1H, m, $CHCHMe_2$), 2.81 (3H, s, NMe), 2.82 (1H, dd, J=16.9, 2.3 Hz, $ArCH_2CH$), 3.10 (1H, dd, J=16.9, 8.1 Hz, $ArCH_2CH$), 3.47 (1H, d, J=8.6 Hz, NCH(C)CH), 3.54 (1H, dd, J=10.7, 8.7 Hz, $CHCH_2OH$), 3.73 (1H, dd, J=10.7, 4.0 Hz, $CHCH_2OH$), 4.06 (1H, br s, $CH_2CH(N)CH_2$), 6.48 (1 h, br s, NH), 6.88 (1H, dt, J=7.2, 1.2 Hz, ArH), 7.02 (1H, dd, J=8.0, 1.0 Hz, ArH), 7.04 (1H, dd, J=8.0, 1.0 Hz, ArH), 7.19 (1H, dt, J=7.7, 1.4 Hz, ArH); ^{13}C NMR δ: 19.9, 20.3, 28.4, 35.6, 37.3, 54.1, 65.8, 70.9, 120.2, 121.8, 127.7, 131.4, 131.7, 151.8, 174.2; HRESIMS m/z: 285.16023 (calcd for $C_{15}H_{22}N_2NaO_2$: 285.15790); $[\alpha]_D^{22}$ −276 (c 0.36, $CHCl_3$) {lit.[29] $[\alpha]_D^{20}$ −271 (c 0.08, $CHCl_3$)}.

Acknowledgements

One of authors (I.K.) greatly thanks Rajamangala University of Technology Thanyaburi, Thailand, for scholarship.

Supplementary data

NMR charts of an aziridine mixture **9**, a benzolactam skeleton **7**, and (−)-benzolactam-V8 (**5**). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.033.

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