Total Synthesis of a Pyrrolidin-2-one with the Structure Proposed for the Alkaloid Rigidiusculamide A

by **Palakodety Radha Krishna*** and **Bonepally Karunakar Reddy**

D-211, Discovery Laboratory, Organic & Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India
(phone: +91-40-27193158; fax: +91-40-27160387; e-mail: prkgenius@iict.res.in)

The total synthesis of the pyrrolidinone alkaloid rigidiusculamide A is reported starting from L-tyrosine, using amidation, ring-closing metathesis, and dihydroxylation as the key reactions.

Introduction. – Several γ-lactams (pyrrolidin-2-ones) and their oxy and hydroxylated derivatives from a family of alkaloids were isolated from marine sponges and *Streptomyces* species [1]. Some of the pyrrolidinone derivatives, such as aza sugars and tetramic acids, are natural products from plants and fungi [2], and many γ-lactams have potential uses in the agriculture and medicine [3]. Oxygenated pyrrolidin-2-ones are rarely found as natural products but have remarkable biological activities [3]. Recently, *Che* and co-workers [4] isolated hydroxylated pyrrolidin-2-ones, rigidiusculamides A – D, as secondary metabolites from the crude extract of the ascomycete fungus *Albonectria rigidiuscula*. Amongst them, rigidiusculamide A (**1**) and B showed modest cytotoxicities against the human tumor cell lines HeLa and MCF-7. Due to the interesting bioactivities and rare availability of these hydroxylated γ-lactams [3], we felt a need for a general synthetic strategy amenable to access different amino acid-derived pyrrolin-2-ones, which can be transformed into oxygenated pyrrolidin-2-ones that may or may not be naturally occurring.

As part of our program on syntheses of bioactive natural and nonnatural products, we extensively used the ring-closing metathesis (RCM) and cross-metathesis (CM) as the key reactions, and the olefin thus generated was transformed to different functional groups, *e.g.*, to the pyrrolidine aza sugars [5], piperidine natural products [6], cyclic GABA receptors [7], macrolactams [8], *etc.* In continuation, we embarked on the total synthesis of rigidiusculamide A with the proposed structure **1** (*Fig.*), as described by *Che* and co-workers [4]. *Huang* and co-workers reported the first total synthesis of **1** and revised the structure of rigidiusculamide A to **2** based on extensive NMR studies [9]. The data of our synthetic sample were in agreement with those of the recently synthesized compound **1** [9]. Here, we describe our results.

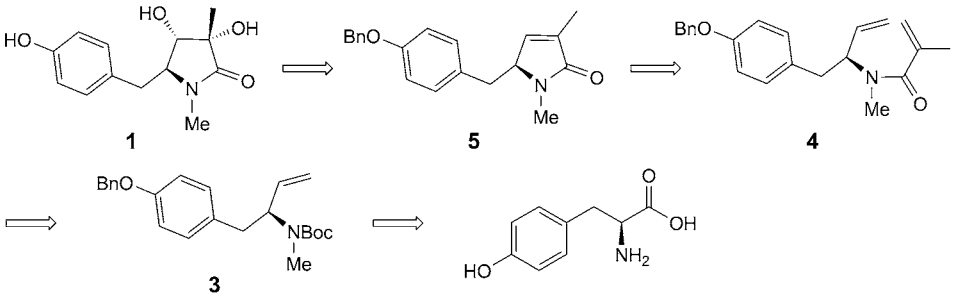
Results and Discussion. – Our envisaged synthetic strategy for rigidiusculamide A was based on its proposed structure **1** and should be amenable to access related molecules (*Scheme 1*). Accordingly, we chose L-tyrosine as the starting material, and the key transformations involved herein were amidation of **3** with methacrylic acid to

1 Proposed structure of rigidiusculamide A [4] **2** Revised structure of rigidiusculamide A [9]

Figure. *Proposed and revised structures of rigidiusculamide A*

furnish the bis(alkenyl) amide **4**, subsequent ring-closing metathesis [10] reaction for a facile construction of the pyrrolidinone ring, followed by the diastereoselective *cis*-dihydroxylation, and deprotection to complete the synthesis. The main idea of using a ring-closing metathesis (RCM) reaction was to generate a γ-lactam (pyrrolin-2-one) **5** so that the alkene thus generated, prompted by its cyclic structure, could be subjected to a highly diastereoselective *cis*-dihydroxylation to access the pyrrolidin-2-one moiety [9].

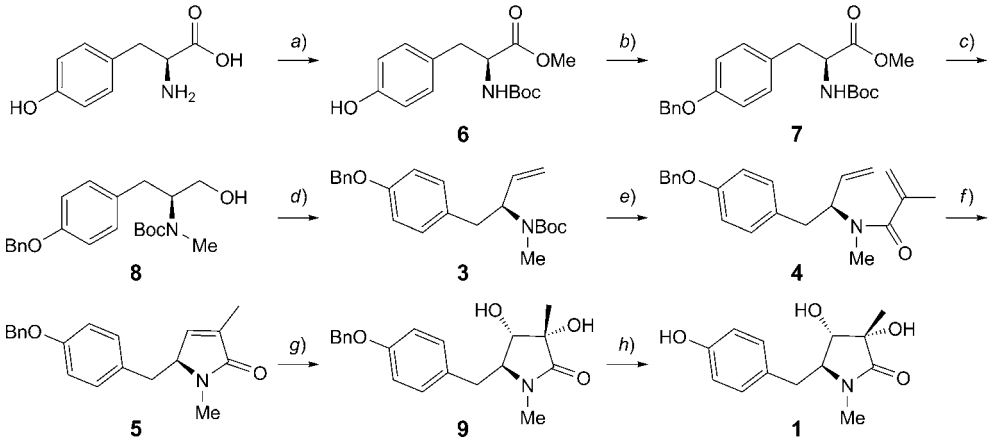
Scheme 1. *Retrosynthetic Analysis*



In *Scheme 2*, the synthesis of **1** starting from the natural amino acid L-tyrosine is depicted. Methylation of L-tyrosine ($SOCl_2$, MeOH), followed by Boc protection, afforded *N*-(*tert*-butyloxy)carbonyl (Boc) L-tyrosine methyl ester (**6**) [11][12], which was protected as its benzyl ether **7** [11] (BnBr, K_2CO_3, acetone). Compound **7** was transformed into its *N*-Me derivative (MeI, Ag_2O, DMF), followed by reduction of the ester group to give the primary alcohol **8** [13]. The latter, upon *Swern* oxidation ($(COCl)_2$/DMSO/Et_3N), followed by C_1-*Wittig* olefination ($Ph_3P^+CH_2I^-$/^{t}BuOK/THF), afforded the Boc-protected allyl amide **3** (73% over two-steps). Boc Deprotection (TFA/CH_2Cl_2), followed by amidation with commercially available methacrylic acid, using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI)/1-hydroxybenzotriazole (HOBT) in CH_2Cl_2 as the coupling reagent afforded the bis(alkenyl) *N*-methyl amide **4** (78% over two-steps), which, on RCM reaction using *Grubbs II* catalyst (5 mol-%) in toluene, gave the crucial intermediate 2,5-dihydro-1*H*-pyrrol-2-one **5** [9] in 81% yield. The latter was thoroughly characterized and was identified as an advanced intermediate in the synthesis of **1**. By adopting the *Upjohn* dihydroxylation [14] method (OsO_4 (cat.)/*N*-methylmorpholine *N*-oxide (NMO)/acetone/H_2O), we obtained **9** (69%) as a single diastereoisomer as determined by ^{1}H-NMR spectra [14b]. Finally, compound **1** (72%) was achieved by the deprotection

of the BnO group using catalytic hydrogenation (Pd/C 10%/H_2/MeOH). However, both the ^{1}H- and ^{13}C-NMR data were not in agreement with those of the natural rigidiusculamide A reported by *Che* and co-workers [4], but evidenced with the structure of **1** reported by *Huang* and co-workers [9].

Scheme 2. *Synthesis of Compound* **1**



a) 1. $SOCl_2$, MeOH, r.t., 8 h; 2. $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t., 6.5 h; 65% (over two steps). *b*) BnBr, K_2CO_3, acetone (reflux), 12 h; 82%. *c*) 1. MeI, Ag_2O, DMF, r.t., 12 h; 2, $LiAlH_4$, THF, 0°, 1.5 h; 79% (over two steps). *d*) 1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°, 1.5 h; 2. $Ph_3P^+CH_2I^-$, ^{t}BuOK, THF, overnight; 73% (over two steps). *e*) 1. CF_3COOH/CH_2Cl_2 1:1, 1 h; 2. methacrylic acid, EDCI (=1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide), HOBt (=1-hydroxybenzotriazole), EtN^iPr_2, CH_2Cl_2, 6 h; 78% (over two steps). *f*) *Grubbs II* catalyst (5 mol-%), toluene (reflux), 4 h; 81%. *g*) OsO_4, NMO, acetone/H_2O 1:1, 48 h; 69%. *h*) Pd/C, H_2, MeOH, 6 h; 72%.

Conclusions. – The total synthesis of compound **1**, with the structure proposed for rigidiusculamide A, was achieved by employing RCM, amidation, and dihydroxylation using L-tyrosine as starting material. This synthesis once more established that compound **1** was not the natural product rigidiusculamide A and the structural revision was indeed vindicated. The strategy described is general and scalable, and may be adopted for the synthesis of similar dihydropyrrol-2-ones and hydroxylated pyrrolidin-2-ones.

One of the authors (*B. K. R.*) thanks the *CSIR*, New Delhi, for financial support in the form of a fellowship. The authors thank the funding for this work from the *ORIGIN PROJECT* from the *CSIR*, New Delhi, India.

Experimental Part

General. Reactions were carried under N_2 in anh. solvents such as CH_2Cl_2 and THF. All reactions were monitored by TLC (silica-coated plates and visualizing with α-naphthol and ninhydrin charring). Org. soln. were dried (Na_2SO_4) and concentrated below 40° under reduced pressure on a *Büchi* rotary evaporator. Column chromatography (CC): silica gel (*Acme*; 60–120), with AcOEt and hexane as eluents. TLC: *Merck 60 F_{254}* silica-gel plates. Yields refer to chromatographically and spectroscopically

(^{1}H- and ^{13}C-NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe and double-ended needle. Optical rotations: *JASCO P-1020* instrument. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H-NMR Spectra: *Varian Gemini 200* MHz, *Bruker Avance-300* MHz, *Unity 400* MHz, and *Inova 500* MHz; ^{13}C-NMR spectra (50 MHz and 75 MHz) with *Varian Gemini FT-200* MHz and *Bruker Avance 300* MHz spectrometers, with 7 – 10 mM soln. in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Finnigan Mat 1210* double-focusing mass spectrometers operating at a direct inlet system; ESI-MS: an ion-trap mass spectrometer; in m/z. Nomenclature: software ACD/Name Version 1.0, developed by *Advanced Chemistry Development Inc.*, Toronto, Canada.

*Methyl (2*S*)-2-{[(*tert*-Butyloxy)carbonyl]amino}-3-(4-hydroxyphenyl)propanoate* (**6**) [11][12]. To the stirred soln. of L-tyrosine (3.0 g, 16.57 mmol) in MeOH (30.0 ml) in an oven-dried round-bottom flask at 0° was added $SOCl_2$ (2.32 ml, 21.5 mmol) under N_2, and the mixture was stirred for 8 h at r.t. After completion of the reaction, the solvent was evaporated under reduced pressure, and the crude L-tyrosine methyl ester hydrochloride was used for the next reaction without further purification.

To the above obtained hydrochloride in CH_2Cl_2 (40.0 ml) was added Et_3N (5.06 ml, 36.46 mmol), followed by di-(*tert*-butyloxy)carbonyl anhydride (Boc_2O; 3.97 g, 18.2 mmol) at 0°, and the mixture was stirred for 6.5 h. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (2 × 20 ml), washed with H_2O (30.0 ml) and brine (30.0 ml), dried ($NaSO_4$), and concentrated under reduced pressure. The crude residue was purified by CC (AcOEt/hexane 1:4) to afford **6** (3.17 g, 65%). White solid. M.p. 101 – 102°. $[\alpha]_D^{25} = +10.64$ ($c = 0.48$, EtOH) ([12]: $[\alpha]_D^{25} = +12.0$ ($c = 2.2$, EtOH)). IR (KBr): 1694, 1706, 1763, 3383. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.94 (d, $J = 8.5$, 2 arom. H); 6.72 (d, $J = 8.4$, 2 arom. H); 6.56 (br. *s*, OH); 5.02 (br. *d*, $J = 8.2$, NH); 4.45 – 4.61 (*m*, CHN); 3.71 (*s*, MeO); 2.90 – 3.07 (*m*, CH_2CH); 1.42 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.1; 155.2; 130.4; 127.3; 115.5; 80.3; 54.7; 52.4; 37.7; 28.2. HR-ESI-MS: 318.1100 ($[M + Na]^+$, $C_{18}H_{17}NNaO_3^+$; calc. 318.1106).

*Methyl (2*S*)-2-{[(*tert*-Butyloxy)carbonyl]amino}-3-{4-[(phenylmethyl)oxy]phenyl}propanoate* (**7**) [11]. To a soln. of **6** (3.1 g, 10.50 mmol) in acetone (30.0 ml) were added BnBr (1.79 g, 10.50 mmol) and K_2CO_3 (3.68 g, 26.27 mmol), and the mixture was stirred for 12 h at reflux. The solvent was removed *in vacuo*, and the residue was extracted with AcOEt. The extract was washed with H_2O (2 × 25 ml) and brine (15 ml), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by CC (AcOEt/hexane 1:9) to afford **7** (3.31 g, 82%). White solid. M.p. 61 – 63° ([11h]: m.p. 61 – 64°). IR (KBr): 3045, 1662, 1535, 1120, 1095. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30 – 7.37 (*m*, 5 arom. H); 6.99 (d, $J = 7.9$, 2 arom. H); 6.85 (d, $J = 8.4$, 2 arom. H); 5.01 (*s*, PhCH_2); 4.86 (d, $J = 6.9$, NH); 4.49 (d, $J =$ 5.4, CHN); 3.70 (*s*, MeO); 2.95 – 3.04 (*m*, CHCH_2); 1.42 (*s*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.3; 157.9; 155.0; 137.1; 130.3; 128.5; 128.2; 127.9; 127.4; 114.9; 79.9; 69.9; 54.5; 52.2; 37.5; 28.3. HR-ESI-MS: 408.1804 ($[M + Na]^+$, $C_{22}H_{27}NNaO_5^+$; calc. 408.1786).

1,1-Dimethylethyl N-*[(1*S*)-2-Hydroxy-1-{[4-(phenylmethoxy)phenyl]methyl}ethyl]*-N-*methylcarbamate* (**8**) [13]. To a stirred soln. of **7** (2.0 g, 5.06 mmol) in dry DMF (15.0 ml) were added Ag_2O (1.52 g, 6.58 mmol) and, after 5 min, MeI (0.79 ml, 5.56 mmol), and the mixture was stirred at r.t. for 12 h. The reaction was quenched with sat. aq. NH_4Cl soln. (10.0 ml), and the mixture was extracted with AcOEt (2 × 50.0 ml). The combined org. layers were washed with H_2O (30.0 ml) and brine (30.0 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was used for the next reaction without further purification.

To a soln. of $LiAlH_4$ (0.19 g, 5.06 mmol) in dry THF (20.0 ml) was added the above obtained compound in dry THF (5.0 ml) at 0°, and the mixture was stirred for 1.5 h at 0°. The reaction was quenched with sat. $NaSO_4$ soln., and the mixture was extracted with AcOEt (2 × 20.0 ml) and filtered through *Celite* pad, then the solvent was evaporated under reduced pressure, and the residue was purified by CC (AcOEt/hexane 1:3) to afford **8** (1.48 g, 79%). Syrup. $[\alpha]_D^{25} = -42.3$ ($c = 0.18$, $CHCl_3$). IR (neat): 3435, 1670, 1628, 1505, 1190, 1082. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.27 – 7.38 (*m*, 5 arom. H); 6.97 – 7.11 (*m*, 2 arom. H); 6.85 (d, $J = 8.3$, 2 arom. H); 5.02 (*s*, PhCH_2); 3.95 – 4.26 (br. *s*, OH); 3.59 – 3.77 (*m*, CH_2O); 2.53 – 2.89 (*m*, CH, CH_2, MeN); 1.44 (*s*, Me_3C). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.4; 137.0; 130.6; 129.8; 128.5; 127.8; 127.4; 114.8; 79.7; 69.9; 62.9; 59.7; 34.0; 31.2; 28.2. HR-ESI-MS: 394.1989 ($[M + Na]^+$, $C_{22}H_{29}NNaO_4^+$; calc. 394.1994).

1,1-Dimethylethyl N-*Methyl*-N-*[(1*S*)-1-{[4-(phenylmethoxy)phenyl]methyl}prop-2-en-1-yl]carbamate* (**3**). To a soln. of $(COCl)_2$ (0.12 ml, 1.33 mmol) in dry CH_2Cl_2 (3.0 ml) at $-78°$, dry DMSO (0.14 ml, 1.75 mmol) was added dropwise, and the mixture was stirred for 10 min. Compound **8** (0.5 g, 1.35 mmol) in dry CH_2Cl_2 (3.00 ml) was added, and the mixture was stirred for 1 h at $-78°$. After treatment with Et_3N (1.12 ml, 8.09 mmol) and dilution with CH_2Cl_2 (15.0 ml), the mixture was washed with H_2O (2 × 10.0 ml) and brine (8.0 ml), dried ($NaSO_4$), and evaporated to furnish the corresponding aldehyde, which was used for the next reaction.

To a soln. of (methylene)(triphenyl)phosphonium iodide (1.39 g, 3.37 mmol), in dry THF (5.0 ml), ^{t}BuOK (0.3 g, 2.69 mmol) was added at $-10°$, and the mixture was stirred for 4 h. The above obtained aldehyde in dry THF (3.0 ml) was added at $-10°$, and the mixture was stirred for 3 h. The reaction was quenched with sat. aq. NH_4Cl soln., and the mixture was extracted with AcOEt (2 × 10.0 ml). The combined org. layers were washed with brine (10.0 ml), dried ($NaSO_4$), and concentrated. The crude residue was purified by CC (AcOEt/hexane 1:9) to afford **3** (0.36 g, 73%). Colorless oil. $[\alpha]_D^{25} = -46.64$ ($c = 0.18$, $CHCl_3$). IR (neat): 3056, 1664, 1525, 1210, 1073. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29–7.39 (*m*, 5 arom. H); 6.99–7.12 (*m*, 2 arom. H); 6.83 (*d*, *J* = 8.3, 2 arom. H); 5.82 (*ddd*, *J* = 4.9, 10.9, 16.2, olefinic H); 5.06–5.18 (*m*, olefinic H); 5.01 (*s*, PhCH_2); 4.68–4.95 (*m*, 1 H, CH_2CH); 2.59–2.84 (*m*, MeN, 1 H of CH_2CH); 1.26–1.38 (*m*, ^{t}Bu). ^{13}C-NMR (75 MHz, $CDCl_3$): 157.3; 155.8; 137.2; 130.6; 130.1; 128.6; 127.8; 127.4; 116.2; 114.7; 79.3; 70.0; 58.9; 57.3; 36.5; 28.2. HR-ESI-MS: 390.2050 ($[M + Na]^+$, $C_{23}H_{29}NNaO_3^+$; calc. 390.2045).

N,*2-Dimethyl*-N-*[(1*S*)-1-({4-[(phenylmethyl)oxy]phenyl}methyl)prop-2-en-1-yl]prop-2-enamide* (**4**). To stirred soln. of **3** (0.35 g, 0.95 mmol) in dry CH_2Cl_2 (2.0 ml) was added CF_3COOH (TFA; 0.3 ml) at 0°, and the mixture was stirred at r.t. for 2 h. After the reaction was completed, TFA was removed under vacuum. Then, EtN^iPr_2 (0.12 ml, 1.2 mmol) was added. After 5 min, the soln. of methacrylic acid (0.095 g, 1.1 mmol) in dry CH_2Cl_2 (1.0 ml) was added, followed by addition of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDCI; 0.186 g, 1.2 mmol) and 1-hydroxybenzotriazole (HOBT; 0.135 g, 1.10 mmol) at 0°, and the mixture was stirred at r.t. for 6 h. The reaction was quenched with sat. aq. NH_4Cl (10.0 ml) soln., the mixture was extracted with $CHCl_3$ (2 × 12.0 ml). The combined org. layers were washed with 1N HCl (10.0 ml), H_2O (10.0 ml), sat. aq. $NaHCO_3$ (15.0 ml) soln., and brine (10.0 ml), dried (Na_2SO_4), and evaporated. The crude residue purified by CC (AcOEt/hexane 1:9) to give **4** (0.266 g, 78%, over two steps). Colorless oil. $[\alpha]_D^{25} = -43.6$ ($c = 0.15$, $CHCl_3$). IR (neat): 3018, 2930, 1671, 1655, 1507, 1414, 1255, 1046. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.27–7.38 (*m*, 5 arom. H); 6.94–7.12 (*m*, 2 arom. H); 6.84 (*d*, *J* = 8.3, 2 arom. H); 5.83 (*ddd*, *J* = 4.1, 10.5, 15.4, olefinic H); 5.44 (br. *s*, CHN); 5.15–5.26 (*m*, olefinic H); 5.02 (*s*, PhCH_2); 4.90–4.96 (*m*, 1 H, CH_2CH); 4.68 (br. *s*, CHN); 4.60 (*s*, olefinic H); 2.73–2.94 (*m*, 1 H of CH_2CH, MeN); 1.41 (*s*, allylic Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.2; 157.7; 141.1; 137.0, 136.7; 130.0; 128.6; 127.8; 127.2; 116.8; 115.1; 114.5; 114.1; 69.8; 62.1; 36.9; 27.7; 20.1. HR-ESI-MS: 358.1790 ($[M + Na]^+$, $C_{22}H_{25}NNaO_2^+$; calc. 358.1782).

*(5*S*)-1,5-Dihydro-1,3-dimethyl-5-({4-[phenylmethyl)oxy]phenyl}methyl)-2*H*-pyrrol-2-one* (**5**). Compound **4** (0.21 g, 0.65 mmol) was taken in an oven-dried round-bottom flask, and toluene (5.0 ml) was added under N_2, followed by addition of *Grubbs* II-generation catalyst (0.027 g, 5 mol-%) and stirring for 4 h. After completion of the reaction, toluene was evaporated, and the crude residue was purified by CC (AcOEt/hexane 1:9) to afford **5** (0.16 g, 81%). Colorless oil. $[\alpha]_D^{25} = +142.3$ ($c = 0.13$, $CHCl_3$). IR (neat): 2956, 2840, 1660, 1645, 1499, 1390, 1245, 1030. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.31–7.45 (*m*, 5 arom. H); 7.07 (*d*, *J* = 8.5, 2 arom. H); 6.91 (*d*, *J* = 8.5, 2 arom. H); 6.49–6.53 (*m*, olefinic H); 5.05 (*s*, PhCH_2); 3.94–4.02 (*m*, CH_2CH); 3.10 (*dd*, *J* = 5.2, 13.3, CH_2CH); 3.00 (*s*, MeN); 2.51 (*dd*, *J* = 9.0, 13.3, CH_2CH); 1.84 (*s*, MeC). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.9; 157.6; 139.6; 137.2; 135.4; 130.3; 128.7; 128.6; 128.0; 127.4; 114.9; 69.8; 63.7; 37.0; 27.7; 11.2. HR-ESI-MS: 330.1480 ($[M + Na]^+$, $C_{20}H_{21}NNaO_2^+$; calc. 330.1469).

*(3*S*,4*S*,5*S*)-3,4-Dihydroxy-1,3-dimethyl-5-({4-[(phenylmethyl)oxy]phenyl}methyl)pyrrolidin-2-one* (**9**). To a cooled mixture of **5** (0.10 g, o.325 mmol) in acetone/H_2O 4:1 (1.0 ml) were added OsO_4 (0.3 ml, 0.005M in toluene) and *N*-methylmorpholine *N*-oxide (NMO; 0.07 ml, 50% in H_2O), and the mixture was stirred for 2 d. The reaction was quenched with Na_2SO_3 (0.2 g), the solvent was evaporated, the residue was extracted with AcOEt (2 × 3.0 ml), washed with H_2O (2 × 5.0 ml) and brine soln. (1 × 4.0 ml), dried (Na_2SO_4), evaporated, and purified by CC (AcOEt/hexane 6:4) to afford **9** (0.074 g, 69%). White solid. M.p. 131.8°. $[\alpha]_D^{25} = +14.6$ ($c = 0.08$, MeOH). IR (KBr): 3420, 2992, 1670, 1615, 1530, 1225. ^{1}H-NMR

(300 MHz, $CDCl_3$): 7.28–7.37 (*m*, 5 arom. H); 7.08 (*d*, *J* = 8.3, 2 arom. H); 6.88 (*d*, *J* = 8.3, 2 arom. H); 5.02 (*s*, PhCH_2); 4.83 (br. *s*, C–OH); 3.55–3.77 (*m*, C–CH, CHN); 3.51 (br. *s*, CH–OH); 2.90 (*dt*, *J* = 6.0, 14.3, 1 H, CH_2); 2.75–2.81 (*m*, MeN, 1 H of CH_2); 1.32 (*s*, MeC). ^{13}C-NMR (75 MHz, $CDCl_3$): 175.1; 157.8; 136.8; 130.0; 128.7; 128.5; 127.9; 127.4; 115.3; 74.6; 73.3; 70.1; 67.4; 36.7; 28.9; 23.94. HR-ESI-MS: 364.1522 ($[M + Na]^+$, $C_{20}H_{21}NNaO_4^+$; calc. 364.1523).

*(3*S*,4*S*,5*S*)-3,4-Dihydroxy-5-[(4-hydroxyphenyl)methyl]-1,3-dimethylpyrrolidin-2-one* (**1**). To a soln. of **9** (0.052 g, 0.152 mmol) in MeOH (1.0 ml) was added Pd/C (0.005 g, 10 mol-%), and the mixture was stirred under H_2 for 6 h. After completion of the reaction, the mixture was filtered through a *Celite* pad and concentrated under reduced pressure. The residue was purified by CC (AcOEt/hexane 8 : 2) to give **1** (0.027 g, 72%). White solid. M.p. 177–178°. $[\alpha]_D^{25} = +17.8$ (*c* = 0.15, MeOH). IR (KBr): 3380, 2898, 1678, 1615, 1524, 1430, 1380, 1240, 1076. ^{1}H-NMR (500 MHz, (D_6)acetone): 7.12 (*d*, *J* = 8.2, 2 arom. H); 6.80 (*d*, *J* = 8.2, 2 arom. H); 3.68–3.63 (*m*, CHO); 3.54 (*ddd*, *J* = 3.2, 5.4, 7.3, CHN); 2.99 (*dd*, *J* = 14.6, 5.4, 1 H, CH_2); 2.79 (*dd*, *J* = 7.3, 15.5, 1 H, CH_2); 2.78 (*s*, MeN); 1.24 (*s*, MeC). ^{13}C-NMR (75 MHz, (D_6)acetone): 175.2; 157.3; 131.8 (2 C); 129.7; 116.8 (2 C); 76.1; 74.2; 67.6; 37.4; 29.2; 24.3. HR-ESI-MS: 274.1068 ($[M + Na]^+$, $C_{13}H_{17}NNaO_4^+$; calc. 274.1055).

REFERENCES

[1] S. Isaacs, R. Berman, Y. Kashman, T. Gebreyesus, T. Yosief, *J. Nat. Prod.* **1991**, *54*, 83; S. Aoki, K. Higuchi, Y. Ye, R. Satari, M. Kobayashi, *Tetrahedron* **2000**, *56*, 1833; M. Daferner, T. Anke, O. Sterner, *Tetrahedron* **2002**, *58*, 7781; N. U. Sata, S. Wada, S. Matsunaga, S. Watabe, R. W. M. Soest, N. Fusetani, *J. Org. Chem.* **1999**, *64*, 2331; K. JoMon, Y. Kuroda, M. Ajisaka, H. Sakai, *J. Antibiot.* **1972**, *25*, 271; S. Sakuda, M. Ono, K. Furihata, J. Nakayama, A. Suzuki, A. Isogai, *J. Am. Chem. Soc.* **1996**, *118*, 7855.

[2] Y. Wang, C. Long, F. Yang, X. Wang, Q. Sun, H. Wang, Y. Shi, G. Tang, *J. Nat. Prod.* **2009**, *72*, 1151; A. P. Michael, E. J. Grace, M. Kotiw, R. A. Barrow, *J. Nat. Prod.* **2002**, *65*, 1360; J. Y. Li, G. Strobel, J. Harper, E. Lobkovsky, J. Clardy, *Org. Lett.* **2000**, *2*, 767; G. Lang, A. L. J. Cole, J. W. Blunt, M. H. G. Munro, *J. Nat. Prod.* **2006**, *69*, 151; J. Ondeyka, G. Harris, D. L. Zink, A. Basilio, F. Vicente, G. Bills, G. Platas, J. Collado, A. Gonzalez, M. Cruz, J. Martin, J. N. Kahn, S. Galuska, N. Giacobbe, G. Abruzzo, E. Hickey, P. Liberator, B. Jiang, D. Xu, T. Roemer, S. B. Singh, *J. Nat. Prod.* **2009**, *72*, 134.

[3] A. I. Laskin, H. A. Lechevalier, 'CRC Handbook of Microbiology', 2nd edn., 5, CRC Press, Inc.; Boca Raton, FL, 1984, and refs. cit. therein.

[4] J. Li, S.-C. Liu, S.-B. Niu, W.-Y. Zhuang, Y.-S. Che, *J. Nat. Prod.* **2009**, *72*, 2184.

[5] P. Radha Krishna, M. Alivelu, T. P. Rao, *Eur. J. Org. Chem.* **2012**, *3*, 616.

[6] P. Radha Krishna, K. Lopinti, *Synlett* **2007**, 1742; P. Radha Krishna, A. Srishailam, *Tetrahedron Lett.* **2007**, *48*, 6924; P. Radha Krishna, G. Dayaker, *Tetrahedron Lett.* **2007**, *48*, 7279; P. Radha Krishna, B. K. Reddy, *Tetrahedron Lett.* **2010**, *51*, 6262; P. Radha Krishna, B. K. Reddy, P. Srinivas, *Tetrahedron* **2012**, *68*, 841.

[7] P. Radha Krishna, P. S. Reddy, *J. Comb. Chem.* **2008**, *10*, 426.

[8] P. Radha Krishna, K. Anitha, *Tetrahedron Lett.* **2011**, *52*, 4546.

[9] G.-Y. Chen, H. Huang, J.-L. Ye, A.-E. Wang, H.-Y. Huang, H.-K. Zhang, P.-Q. Huang, *Chem. – Asian J.* **2012**, *7*, 504.

[10] A. K. Chatterjee, R. H. Grubbs, *Angew. Chem., Int. Ed.* **2002**, *41*, 3171; R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117.

[11] a) S. Papst, A. F. M. Noisier, M. A. Brimble, Y. Yang, G. W. Krissansen, *Bioorg. Med. Chem.* **2012**, *20*, 5139; b) X.-C. Cheng, R.-L. Wang, Z.-K. Dong, J. Li, Y.-Y. Li, R.-R. Li, *Bioorg. Med. Chem.* **2012**, *20*, 5738; c) S. Hanazawa, M. A. Arai, X. Li, M. Ishibashi, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 95; d) W. L. Scott, J. G. Martynow, J. C. Huffman, M. J. O'Donnel, *J. Am. Chem. Soc.* **2007**, *129*, 7077; e) C. Sorg, E. Rüde, O. Westphal, *Justus Liebigs Ann. Chem.* **1970**, *734*, 180; f) M. J. Oila, J. E. Tois, A. M. P. Koskinen, *Tetrahedron* **2005**, *61*, 10748; g) C. Wolf, C. J. Francis, P. A. Hawes, M. Shah, *Tetrahedron: Asymmetry* **2002**, *13*, 1733; h) H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981; i) L. S. Richter, T. R. Gadek, *Tetrahedron Lett.* **1994**, *35*, 4705.

[12] Y. Saito, H. Ouchi, H. Takahata, *Tetrahedron* **2006**, *62*, 11599; A. M. Kolodziejczyk, M. Manning, *J. Org. Chem.* **1981**, *46*, 1944.
[13] H. Mizutani, J. Takayama, Y. Soeda, T. Honda, *Tetrahedron Lett.* **2002**, *43*, 2411; H. Mizutani, J. Takayama, Y. Soeda, T. Honda, *Heterocycles* **2004**, *62*, 343.
[14] a) V. Vanrheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976**, *17*, 1973; b) T. Muramatsu, S. Yamashita, Y. Nakamura, M. Suzuki, N. Mase, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2007**, *48*, 8956.

Received November 2, 2012