HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 1309 - 1316. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2014, Accepted, 23rd July, 2014, Published online, 5th August, 2014
DOI: 10.3987/COM-14-S(K)67

SYNTHESIS OF RHODOTORULIC ACID AND ITS 1,4-DIMETHYLATED DERIVATIVE

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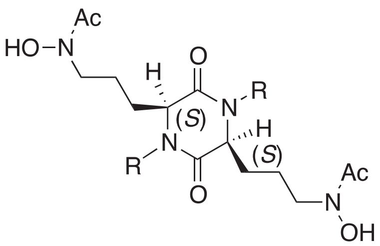
Abstract – Facile syntheses of rhodotorulic acid, isolated from *Rhodotorula pilimanae* as a siderophore, and its 1,4-dimethylated derivative have been achieved by microwave-assisted cyclization of the corresponding dipeptide precursors.

Siderophores are iron-chelating compounds utilized by bacteria and fungi under iron-limiting conditions.[1] Rhodotorulic acid [(*S*,*S*)-**1**] is a dihydroxamate siderophore isolated from *Rhodotorula pilimanae*,[2] and its biological activities[3] as well as its iron-chelating ability[4] have been investigated. It can be assumed that the diketopiperazine (DKP) ring of (*S*,*S*)-**1** is biosynthesized starting with L-ornithine, and that two *N*-hydroxyacetamide moieties serve as a tetradentate ligand for Fe(III) coordination. Therefore, (*S*,*S*)-**1** has been considered to form a 3 : 2 complex with Fe(III) based on CD spectra and potentiometric titrations, in contrast to hexadentate siderophores such as desferrioxamine B, which forms a 1 : 1 complex with Fe(III).[5] The coordination pattern of (*S*,*S*)-**1** with Fe(III) has also been suggested by electrospray ionization mass spectrometry.[6] Despite its interesting structural features, there are only a few examples of (*S*,*S*)-**1** synthesis.[7-10] Herein, we describe a convenient synthesis of (*S*,*S*)-**1** and its 1,4-dimethylated derivative [(*S*,*S*)-**2**] through microwave-assisted cyclization of the corresponding dipeptide precursors.

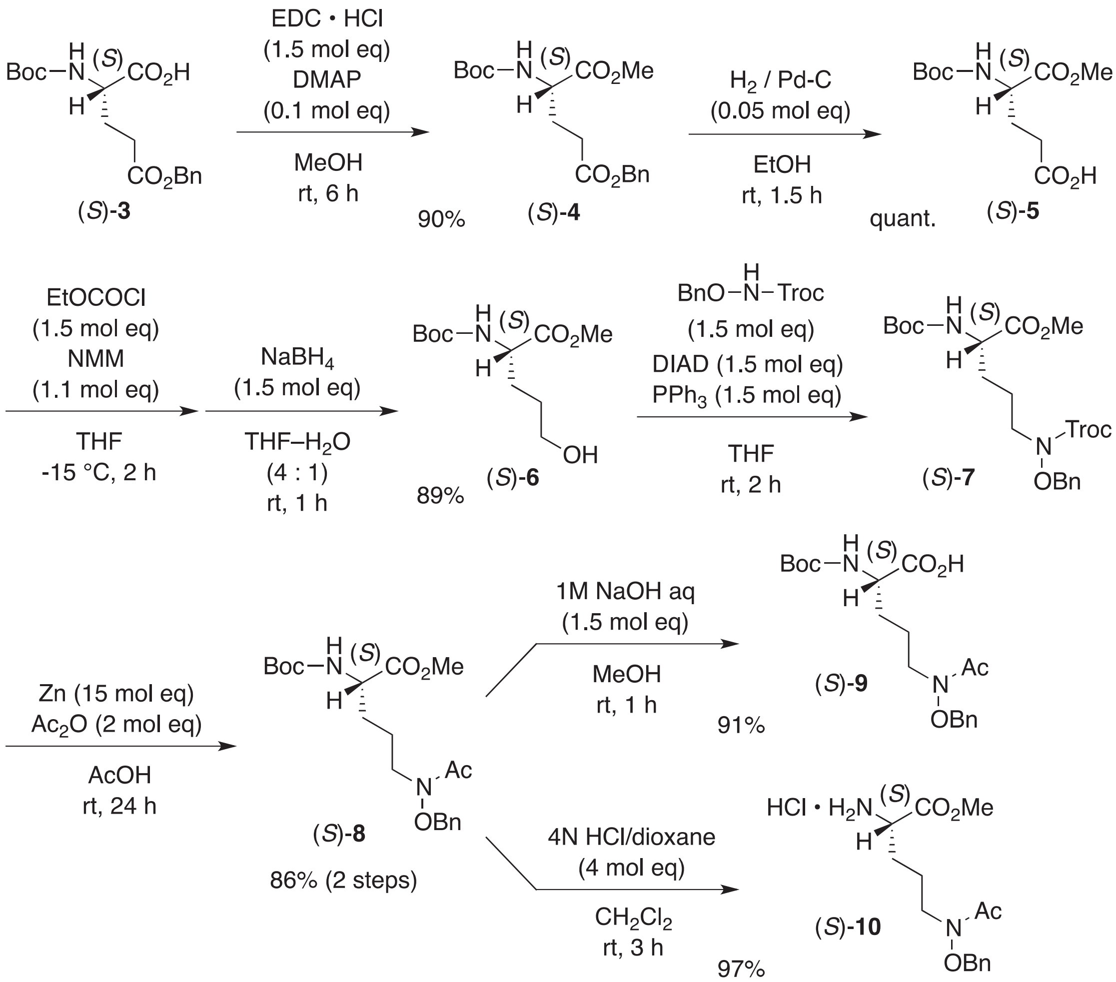


R = H: rhodotorulic acid [(*S*,*S*)-**1**]
R = Me: 1,4-dimethylated rhodotorulic acid [(*S*,*S*)-**2**]

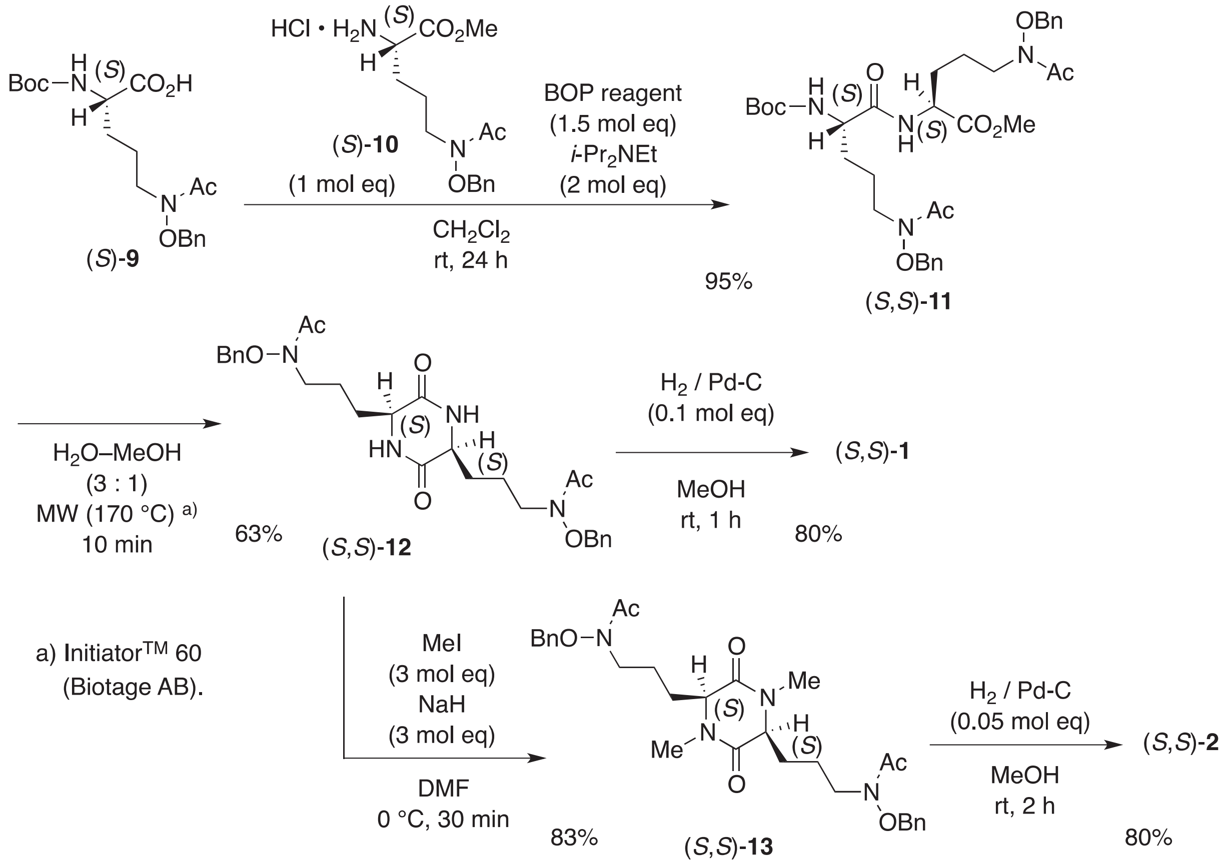
Figure 1. Rhodotorulic acid [(*S*,*S*)-**1**] and its 1,4-dimethylated derivative [(*S*,*S*)-**2**]

Amino acid building blocks, (*S*)-5-[*N*-(benzyloxy)acetamido]-2-[(*tert*-butoxycarbonyl)amino]pentanoic acid [(*S*)-**9**] and methyl (*S*)-2-amino-5-[*N*-(benzyloxy)acetamido]pentanoate hydrochloride [(*S*)-**10**], for dipeptide precursors were synthesized as shown in Scheme 1. Esterification of Boc-L-Glu(OBn)-OH

[(*S*)-**3**] with methanol using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) as a coupling reagent in the presence of a catalytic amount of *N*,*N*-dimethyl-4-aminopyridine (DMAP) followed by deprotection of the benzyl ester *via* catalytic hydrogenolysis under hydrogen with palladium on carbon (10 wt. % loading) afforded the carboxylic acid (*S*)-**5** in 90% yield (2 steps). Formation of a mixed anhydride of (*S*)-**5** with ethyl chloroformate in the presence of *N*-methylmorpholine (NMM) followed by reduction with sodium borohydride gave the primary alcohol (*S*)-**6** in 89% yield. One-step transformation of the hydroxy group of (*S*)-**6** into the protected hydroxylamino group was performed under Mitsunobu conditions. The reaction of (*S*)-**6** with *N*-[(2,2,2-trichloroethoxy)carbonyl]-*O*-benzylhydroxylamine in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF provided the Mitsunobu product (*S*)-**7**. Without further purification, reductive cleavage of the 2,2,2-trichloroethoxycarbonyl (Troc) group of (*S*)-**7** with zinc powder followed by acetylation of the resulting hydroxylamine with acetic anhydride furnished (*S*)-**8**[7,9] in 86% yield (2 steps). Finally, hydrolysis of (*S*)-**8** under aqueous alkaline conditions gave the corresponding *N*-protected amino acid (*S*)-**9**.[7,9] In contrast, amino acid ester hydrochloride (*S*)-**10**[9] was obtained by deprotection of the Boc group of (*S*)-**8** under acidic conditions.



Scheme 1. Synthesis of amino acid building blocks (*S*)-**9** and (*S*)-**10**



Scheme 2. Synthesis of rhodotorulic acid [(*S*,*S*)-**1**] and its 1,4-dimethylated derivative [(*S*,*S*)-**2**]

Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) was used in the condensation of both building blocks (*S*)-**9** and (*S*)-**10** in the presence of *N*,*N*-diisopropylethylamine to furnish the dipeptide (*S*,*S*)-**11** in 95% yield. In previous reports of the synthesis of (*S*,*S*)-**1**, two steps have been required to construct the DKP structure *via* N-terminal deprotection and intramolecular cyclization of the dipeptide precursor.[7-10] In addition, a long reaction time has been needed for intramolecular cyclization. On the other hand, microwave irradiation has been reported to be efficient for a one-pot conversion of *N*-Boc-dipeptide methyl esters into DKPs with a short reaction time.[11] We therefore attempted a one-pot conversion of (*S*,*S*)-**11** into DKP (*S*,*S*)-**12** using microwave irradiation. As a result, removal of the Boc group followed by intramolecular cyclization of (*S*,*S*)-**11** under microwave irradiation with a single-mode microwave reactor (Initiator™ 60; Biotage AB) at 170 °C in a mixed solvent of water/methanol for 10 min furnished the DKP (*S*,*S*)-**12** in 63% yield. Finally, catalytic hydrogenolysis of (*S*,*S*)-**12** under hydrogen with palladium on carbon (10 wt. % loading) provided rhodotorulic acid [(*S*,*S*)-**1**] in 80% yield. Furthermore, *N*-methylation of the DKP ring of (*S*,*S*)-**12** followed by catalytic hydrogenolysis of the resultant (*S*,*S*)-**13** afforded 1,4-dimethylated rhodotorulic acid [(*S*,*S*)-**2**]. The structures of (*S*,*S*)-**1** and (*S*,*S*)-**2** were confirmed by spectroscopic methods. In general, DKP derivatives have poor solubility in various solvents due to their intermolecular hydrogen bonding through the amide moiety of the DKP ring.[12] Therefore, only a few solvents, including water and dimethylsulfoxide (DMSO), have been found to be capable of dissolving (*S*,*S*)-**1**. However, (*S*,*S*)-**2** was found to be soluble in water, DMSO, methanol, ethanol, chloroform, and ethyl acetate. This enhanced solubility is likely due to the disappearance of intermolecular hydrogen bonding as a result of *N*-methylation.

In conclusion, we have presented the synthesis of rhodotorulic acid [(*S*,*S*)-**1**] and its 1,4-dimethylated derivative [(*S*,*S*)-**2**] using a microwave-assisted cyclization of the corresponding common dipeptide precursor (*S*,*S*)-**11** as a key step. Intriguingly, (*S*,*S*)-**2** was found to be more soluble in various organic solvents than (*S*,*S*)-**1**. Derivatization of (*S*,*S*)-**1** and (*S*,*S*)-**2** toward the synthesis of novel iron-chelating compounds is currently underway and will be reported in due course.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-6200 IR Fourier transform spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker AV500 spectrometer. Chemical shifts are given in δ values (parts per million) using tetramethylsilane (TMS) as an internal standard. Electron spray ionization mass spectra (ESIMS) were recorded on a Waters LCT Premier spectrometer. Elemental combustion analyses were performed using a J-SCIENCE LAB JM10. The microwave-assisted reaction was performed utilizing an automated single-mode microwave synthesizer (Initiator™ 60; Biotage AB). All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Column chromatography was carried out on silica gel [Kanto Chemical 60N (spherical, neutral); 63-210 mm] or [Fuji Silysia Chemical PSQ 60B (spherical)]. Anhydrous THF, CH_2Cl_2, and DMF were used as purchased from Kanto Chemical. *N*-Methylmorpholine (NMM) and *N*,*N*-diisopropylethylamine were distilled prior to use. All other reagents were used as purchased.

Methyl (*S*)-5-[*N*-(Benzyloxy)acetamido]-2-{(*S*)-5-[*N*-(benzyloxy)acetamido]-2-[(*tert*-butoxycarbonyl)amino]pentanamide}pentanoate [(*S*,*S*)-11]

To a solution of (*S*)-**9** (618 mg, 1.62 mmol) and (*S*)-**10** (537 mg, 1.62 mmol) in anhydrous CH_2Cl_2 (6 mL) were added BOP reagent (1.1 g, 2.44 mmol) and *N*,*N*-diisopropylethylamine (552 μL, 3.25 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 24 h. The reaction mixture was treated with 5% citric acid aq (2 mL) and then extracted with $CHCl_3$ (50 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel PSQ 60B: $CHCl_3$–MeOH (100:0 to 10:1)] to afford (*S*,*S*)-**11** (1.0 g, 95%). Colorless oil; $[\alpha]_D^{19}$ +5.6 (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.47–1.88

(m, 8H), 2.09 (s, 3H), 2.11 (s, 3H), 3.41–3.53 (m, 1H), 3.60–3.73 (m, 2H), 3.66 (s, 3H), 4.12–4.27 (m, 1H), 4.32–4.42 (m, 1H), 4.48–4.56 (m, 1H), 4.76–4.88 (m, 4H), 5.22–5.28 (m, 1H), 7.08–7.17 (m, 1H), 7.33–7.42 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.5, 23.0, 23.2, 28.3, 29.1, 30.6, 43.6, 44.7, 51.9, 52.2, 52.3, 76.31, 76.34, 79.6, 128.72, 128.74, 128.96, 129.01, 129.19, 129.24, 134.3, 134.4, 155.8, 172.37, 172.45 (two overlapping singlets), 173.16; ^{13}C NMR (125 MHz, C_6D_6) δ 20.5 (two overlapping singlets), 23.4, 23.7, 28.4, 29.2, 31.1, 43.9, 45.2, 51.7, 52.2, 52.7, 76.1, 76.3, 79.1, 128.77, 128.79, 128.8, 128.9, 129.4, 129.5, 135.1, 135.4, 156.3, 172.1, 172.8, 172.9, 173.1; IR (neat) 3304, 2978, 2935, 1743, 1659, 1499 cm^{-1}; ESI-MS *m/z*: calcd for $C_{34}H_{48}N_4NaO_9$ $[M+Na]^+$, 679.3319; found, 679.3350.

_N,N'_-{[(2_S_,5_S_)-3,6-Dioxopiperazine-2,5-diyl]bis(propane-3,1-diyl)}bis[_N_-(benzyloxy)acetamide] [(_S,S_)-12]

A suspension of (*S,S*)-**11** (611 mg, 0.931 mmol) in a mixed solvent of H_2O (15 mL) with MeOH (5 mL) was irradiated at 170 °C for 10 min utilizing a Biotage Initiator® microwave synthesizer. The reaction mixture was treated with H_2O (20 mL) and then extracted with AcOEt (50 mL x 3). The extract was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel 60N: $CHCl_3$–MeOH (98:2 to 85:15)] to afford (*S,S*)-**12** (305 mg, 63%). Colorless powder (MeOH–Et_2O); mp 149–150 °C (lit.[7] 127–129 °C, lit.[9] 129–131 °C, and lit.[10] 97–99 °C); $[\alpha]_D^{27}$ -20.5 (*c* 1.03, MeOH) {lit.[7] $[\alpha]_D^{25}$ -16.5 (*c* 0.67, MeOH), lit.[9] $[\alpha]_D^{13}$ -16.4 (*c* 1.01, EtOH), and lit.[10] $[\alpha]_D^{20}$ -16.4 (*c* 1.01, EtOH)}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.67–1.85 (m, 8H), 2.03 (s, 6H), 3.63–3.73 (m, 4H), 3.98 (t, *J* = 5.2 Hz, 2H), 4.87 (s, 4H), 7.34–7.43 (m, 10H); ^{13}C NMR (125 MHz, CD_3OD) δ 20.5, 23.6, 32.4, 45.6, 55.7, 77.2, 129.8, 130.0, 130.7, 136.1, 170.2, 174.5; IR (KBr) 3193, 3043, 2953, 2886, 1665, 1455 cm^{-1}; ESI-MS *m/z*: calcd for $C_{28}H_{36}N_4NaO_6$ $[M+Na]^+$, 547.2533; found, 547.2525. Anal. Calcd for $C_{28}H_{36}N_4O_6$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.96; H, 6.91; N, 10.53%.

_N,N'_-{[(2_S_,5_S_)-3,6-Dioxopiperazine-2,5-diyl]bis(propane-3,1-diyl)}bis(_N_-hydroxyacetamide) [Rhodotorulic Acid, (_S,S_)-1]

The mixture of (*S,S*)-**12** (100 mg, 0.191 mmol) and 10% Pd–C (20 mg, 0.019 mmol) in MeOH (3 mL) was stirred at rt for 1 h under hydrogen. The reaction mixture was filtered and concentrated *in vacuo* to afford (*S,S*)-**1** (53 mg, 80%). Colorless powder (H_2O); mp >217 °C (dec) [lit.[7] 217–218 °C, lit.[8] 229–232 °C, lit.[9] 216–218 °C (dec), and lit.[10] 217–218.5 °C (dec)]; $[\alpha]_D^{27}$ -30.2 (*c* 0.16, H_2O) {lit.[8] $[\alpha]_D$ -30.5 (*c* 0.67, AcOH), lit.[9] $[\alpha]_D^{17}$ -30.4 (*c* 0.5, H_2O), lit.[10] $[\alpha]_D^{25}$ -28.8 (*c* 1.00, H_2O)}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.50–1.72 (m, 8H), 1.97 (s, 6H), 3.43–3.52 (m, 4H), 3.79–3.86 (m, 2H), 8.16 (brs, 2H), 9.72 (brs, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 20.2, 22.0, 30.2, 46.7, 53.7, 167.7, 170.0; IR (KBr) 3187, 3086, 2867, 1686, 1594, 1517, 1473, 1448 cm^{-1}; ESI-MS *m/z*: calcd for $C_{14}H_{24}N_4NaO_6$ $[M+Na]^+$, 367.1594; found, 367.1588. Anal. Calcd for $C_{14}H_{24}N_4O_6$: C, 48.83; H, 7.02; N, 16.27. Found: C, 48.53; H, 6.99; N, 16.14%.

***N,N'*-{[(2*S*,5*S*)-1,4-Dimethyl-3,6-dioxopiperazine-2,5-diyl]bis(propane-3,1-diyl)}bis[*N*-(benzyloxy)-acetamide] [(*S,S*)-13]**

NaH (50–72%, 13.6 mg, 0.284 mmol) was added to a solution of (*S*,*S*)-**12** (49.7 mg, 0.0947 mmol) in anhydrous DMF (2 mL) and stirred at 0 °C for 5 min under argon. After adding MeI (17.7 μL, 0.284 mmol), the mixture was stirred at 0 °C for 30 min under argon. The reaction mixture was treated with 1N HCl aq (1 mL) and then extracted with AcOEt (20 mL x 3). The extract was washed with sat. $Na_2S_2O_3$ aq (5 mL) and H_2O (5 mL x 3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The oily residue was purified by silica gel column chromatography [Silica Gel PSQ 60B: $CHCl_3$–MeOH (20:1 to 10:1)] to afford (*S*,*S*)-**13** (43.2 mg, 83%). Colorless oil; $[\alpha]_D^{20}$ +11.4 (*c* 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60–1.92 (m, 8H), 2.09 (s, 6H), 2.89 (s, 6H), 3.58–3.68 (m, 2H), 3.74–3.87 (m, 4H), 4.81 (dd, *J* = 10.5, 13.7 Hz, 4H), 7.34–7.43 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 23.5, 30.5, 32.6, 44.1, 61.7, 76.4, 128.8, 129.1, 129.2, 134.3, 165.7, 172.3; IR (neat) 2937, 2878, 1660, 1454, 1403 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{30}H_{40}N_4NaO_6$ $[M+Na]^+$, 575.2846; found, 575.2815.

***N,N'*-{[(2*S*,5*S*)-1,4-Dimethyl-3,6-dioxopiperazine-2,5-diyl]bis(propane-3,1-diyl)}bis(*N*-hydroxyacet-amide) [1,4-Dimethylated Rhodotorulic Acid, (*S,S*)-2]**

The mixture of (*S*,*S*)-**13** (24.2 mg, 0.0438 mmol) and 10% Pd–C (2.3 mg, 0.00219 mmol) in MeOH (1 mL) was stirred at rt for 2 h under hydrogen. The reaction mixture was filtered and concentrated *in vacuo* to afford (*S*,*S*)-**2** (12 mg, 80%). Colorless prism ($CHCl_3$–Et_2O); mp 134–135.5 °C; $[\alpha]_D^{28}$ +31.0 (*c* 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.67–1.89 (m, 6H), 2.05–2.18 (m, 2H), 2.16 (s, 6H), 2.98 (s, 6H), 3.57–3.67 (m, 2H), 3.77–3.92 (m, 4H), 9.35 (brs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 22.2, 30.9, 32.9, 47.3, 61.9, 166.7, 172.7; IR (KBr) 3351, 3115, 2939, 2868, 1663, 1636, 1600 cm^{-1}; ESI-MS *m*/*z*: calcd for $C_{16}H_{28}N_4NaO_6$ $[M+Na]^+$, 395.1907; found, 395.1920. Anal. Calcd for $C_{16}H_{28}N_4O_6$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.30; H, 7.51; N, 14.91%.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant for the Regional Innovation Cluster Program (Global Type) promoted by MEXT.

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