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Efficient synthesis of 3-hydroxyprolines and 3-hydroxyprolinols from sugars

Jin Hwan Lee, Jae Eun Kang, Min Suk Yang, Kyu Young Kang and Ki Hun Park*

Department of Agricultural Chemistry, Division of Applied Life Science, Gyeongsang National University, Chinju 660-701, South Korea

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Abstract—*trans*-3-Hydroxy-L-proline **1**, *trans*-3-hydroxy-L-prolinol **2**, *cis*-3-hydroxy-D-proline **3**, and *cis*-3-hydroxy-D-prolinol **4** have been prepared in enantiomerically pure form with chirospecific manner. Key intermediates, 2-amino-3-hydroxy-4-pentenoate **9** and **17**, were obtained from D-glucono-δ-lactone and L-gulonic acid γ-lactone via a simultaneous dealkoxyhalogenation.

1. Introduction

3-Hydroxyproline and 3-hydroxyprolinol are an important component or a chiral synthon for biological active compounds such as Mucrorin-D,[1] Telomycin,[2] polyhydroxylated alkaloids,[3] and detoxinine.[4,5] For example, *trans*-3-hydroxy-L-proline **1** was isolated from bovine tendon collagen[6] and then found in antibiotic telomycin.[2] Several syntheses of 3-hydroxyproline and 3-hydroxyprolinol have been described, which are based on reductive cyanation,[7,8] Dieckman-type condensation,[9] a reductive amination of a suitable substituted amino aldehyde,[10] stereoselective cyclocarbamation,[11] diastereoselective amination,[12] and a yeast reduction of pyroglutamate,[13] respectively. However, there is no previous report of synthesis of 3-hydroxyproline derivatives using absolute configurations in sugars. This paper describes the transformation of sugars by homochiral synthetic techniques to obtain optically pure 3-hydroxyprolines (**1**, **3**) and 3-hydroxyprolinols (**2**, **4**).

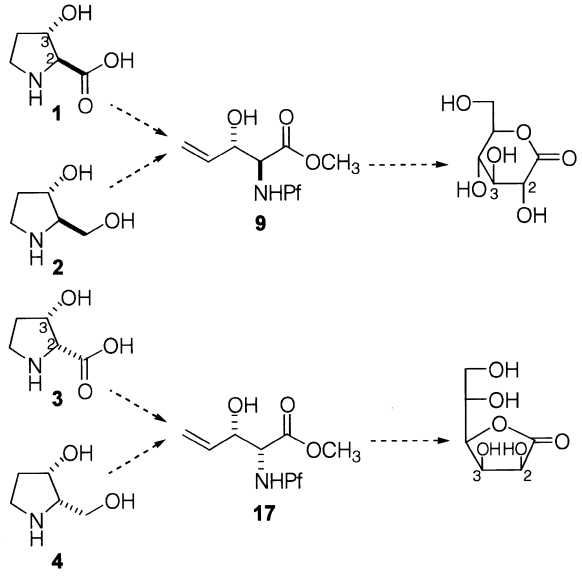
Our approach to synthesis of **1**–**4** envisaged the use of the 2-amino-3-hydroxy-4-pentenoate **9** and **17**, which can be easily obtained from sugar via a simultaneous dealkoxyhalogenation. Generally, Sharpless condition (SeO_2/*t*-BuOOH)[4] and bislactim ether method[14] are accepted to obtain 2-amino-3-hydroxy-4-pentenoate but these synthetic route have a limitation in high yield and selectivity. We now report synthesis optically active 2-amino-3-hydroxy-4-pentenoate **9** and **17** from sugars, and their application to the synthesis of enantiomerically pure *trans*-3-hydroxy-L-proline **1**, *trans*-3-hydroxy-L-prolinol **2**, *cis*-3-hydroxy-D-proline **3**, and *cis*-3-hydroxy-D-prolinol **4** (Scheme 1).

2. Results and discussion

As our chiral source, we chose D-glucono-δ-lactone and L-gulonic acid γ-lactone, which have two stereocenters as required for the target molecules **1**–**4** (Scheme 1). Thus, the stereochemistry of C2 and C3 in D-glucono-δ-lactone was used for compound **1** and **2**, while that of C2 and C3 in L-gulonic acid γ-lactone was for compound **3** and **4**.

2.1. *trans*-3-Hydroxy-L-proline 1 and prolinol 2

The amino group of mannonate **5** was protected with 9-phenyl-9-fluorenyl (Pf) group since this protecting group has been shown to inhibit deprotonation at the α-position of



Scheme 1. Retrosynthesis of compound **1**–**4**.

Keywords: *trans*-3-hydroxy-L-proline; *trans*-3-hydroxy-L-prolinol; *cis*-3-hydroxy-D-proline; *cis*-3-hydroxy-D-prolinol.

* Corresponding author. Fax: +82-55-757-0178; e-mail: khpark@gshp.gsnu.ac.kr

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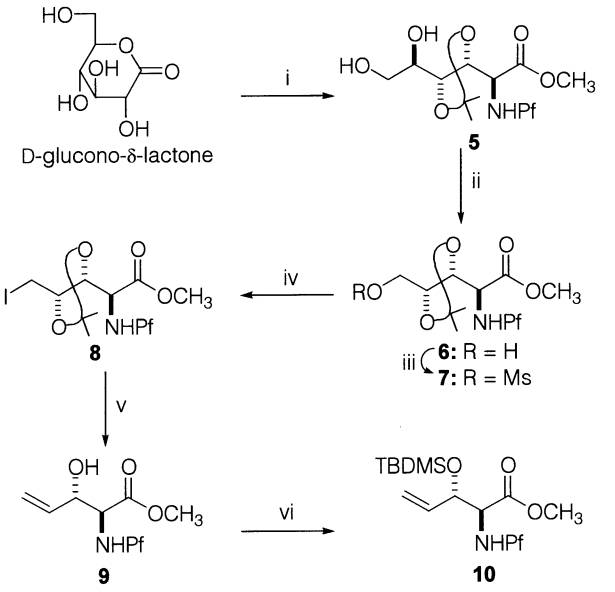
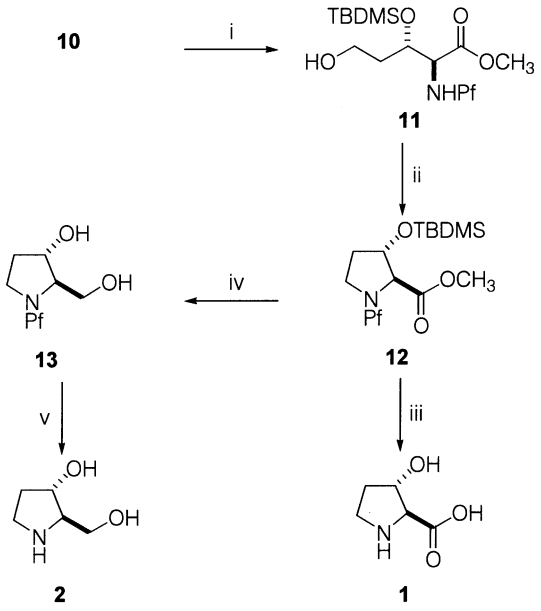


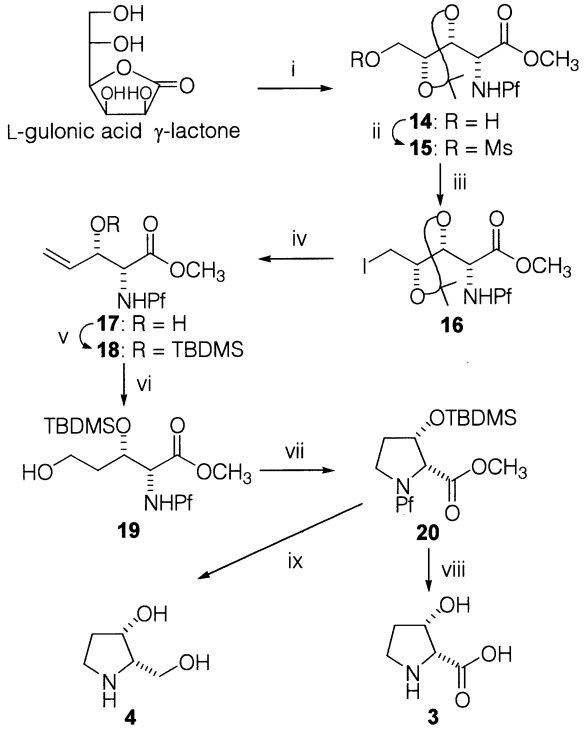
Scheme 2. *Reagents and conditions*: (i) Ref. 16; (ii) $NaIO_4$, $NaBH_4$, EtOH, rt, 98%; (iii) MsCl, Et_3N, THF, 0°C, 98%; (iv) LiI, DMF, 80°C, 95%; (v) *n*-BuLi, THF, −40°C, 85%; (vi) TBDMSCl, imidazole, DMF, rt, 98%.

an α-amino ester and stable on an organometallic conditions.[15] The diol **5** was synthesized in five high yielding steps from D-glucono-δ-lactone as described;[16] the overall yield for this conversion was 70% (Scheme 2).

The diol **5** was oxidized in the presence of $NaIO_4$; this was followed by sodium borohydride reduction of the resulting aldehyde, which led to the formation of alcohol **6** in quantitative yield. After mesylation of alcohol **6**, the resulting mesylate was treated with LiI to give 2,3-isopropylidene iodide **8** in 85% yield. Treatment of 2,3-isopropylidene iodide **8** with *n*-BuLi at −40°C gave the (2*S*,3*S*)-2-amino-3-hydroxy-4-pentenoate **9** {$[\alpha]_D^{20}=-278.2$ (*c* 1.00, $CHCl_3$)} in 85% yield through a simultaneous dealkoxyhalogenation. This is a first report to obtain enantiomerically pure 2-amino-3-hydroxy-4-pentenoic acid derivative. This useful intermediate could be converted to a variety of bioactive β-hydroxy-α-amino acid.



Scheme 3. *Reagents and conditions*: (i) $BH_3(CH_3)_2S$, THF, 0°C, 70%; (ii) MsCl, Et_3N, THF, 0°C, 87%; (iii) H_2, Pd/C, MeOH, 60°C, Dowex 50W-X8, THF–H_2O (2:1), reflux, 76%; (iv) LAH,THF, 0°C, 89%; (v) H_2, Pd/C, MeOH, 60°C, 93%.



Scheme 4. *Reagents and conditions*: (i) Ref. 17; (ii) MsCl, Et_3N, THF, 0°C, 98%; (iii) LiI, DMF, 80°C, 90%; (iv) *n*-BuLi, THF, −40°C, 90%; (v) TBDMSCl, imidazole, DMF, rt, 98%; (vi) $BH_3(CH_3)_2S$, THF, 0°C, 78%; (vii) MsCl, Et_3N, 0°C, 90%; (viii) H_2, Pd/C, MeOH, 60°C, Dowex 50W-X8, THF–H_2O (2:1), reflux, 84%; (ix) LAH, THF, 0°C, H_2, Pd/C, MeOH, 60°C, 75%.

The silyl ether **10** was prepared using TBDMSCl in quantitative yield. Following complete hydroboration with $BH_3(CH_3)_2S$, the resulting organoboranes were oxidized with alkaline hydrogen peroxide to give 5-hydroxypentanoate **11** in 70% yield (Scheme 3). When the alcohol **11** was carried out mesylation in THF, intramolecular amination was occurred simultaneously to produce proline ester **12** in 87% yield. After reduction of Pf group with 10% Pd/C, the remaining TBDMS and methyl ester group were completely hydrolyzed with Dowex 50W-X8 in THF–H_2O (2:1). The mixture was filtered and the resin was washed with methanol, then eluted with 3N aqueous NH_3 to afford the free base form of *trans*-3-hydroxy-L-proline **1** (76% yield) without further purification. On the other hand, the treatment of proline methyl ester **12** with LAH gave the *N*-protected prolinol **13** in 89% yield. In this step, LAH removed TBDMS group as well as reduction of ester group. To remove the remaining Pf group, **13** was treated with 10% Pd/C in methanol. The free base form of *trans*-3-hydroxy-L-prolinol **2** was obtained by ion exchange chromatography (Dowex 50W-X8) as an oil and was pure by NMR and HRMS. ^1H and ^{13}C NMR and optical rotation for **1** and **2** are consistent with those reported.[9,18]

2.2. *cis*-3-Hydroxy-D-proline 3 and prolinol 4

To further demonstrate the versatility of this synthetic strategy, we have prepared the *cis*-3-hydroxy-D-proline **3** and prolinol **4**. The arabinonate **14** was easily obtained form L-gulonic acid γ-lactone as described;[17] the overall yield for this conversion was 74% (Scheme 4).

After mesylation of alcohol **14**, the mesylate **15** was treated with LiI at 80°C to give 2,3-isopropylidene iodide **16** in 90% yield. The iodide **16** was treated with *n*-BuLi in THF at −40°C for 20 min to give the (2*R*,3*S*)-2-amino-3-hydroxy-4-pentenoate 17{$[\alpha]_D^{20}$=+278.9 (*c* 1.25, $CHCl_3$)}. After protection of pentenoate **17** with TBDMSCl, vinyl group in **18** was converted to 5-hydroxypentanoate **19** by $BH_3(CH_3)_2S$ condition. The alcohol **19** was reacted with MsCl in THF to lead mesylation and cyclization simultaneously to obtain proline methyl ester **20** in quantitative yield. After hydrogenation to remove Pf group in **20**, ester and TBDMS group were hydrolyzed with the same procedure for compound **1** to yield *cis*-3-hydroxy-D-proline **3** in 84% yield. The spectroscopic data of **3** is consistent with those reported.[10] The proline methyl ester **20** was treated with LAH and H_2, 10% Pd/C sequentially as same procedure for compound **2** to give *cis*-3-hydroxy-D-prolinol **4** {$[\alpha]_D^{20}$=−23.2 (*c* 0.76, H_2O)}.

3. Conclusions

In summary, we report the first chirospecific synthesis of 2-amino-3-hydroxy-4-pentenoate **9** and **17** via a simultaneous dealkoxyhalogenation. These compounds are an important precursor for the asymmetric synthesis of bioactive β-hydroxy-α-amino acids. Additionally, we have reported the synthesis of enantiomerically pure *trans*-3-hydroxy-L-proline **1**, *trans*-3-hydroxy-L-prolinol **2**, *cis*-3-hydroxy-D-proline **3**, and *cis*-3-hydroxy-D-prolinol **4** with chirospecific manner.

4. Experimental

4.1. General

All non-aqueous reaction was carried out under an inert nitrogen atmosphere. THF was distilled from Na/benzophenone; 2,2-dimethoxypropane, DMF, and methylene chloride were distilled from CaH_2. Column chromatography was carried out using 230–400 mesh silica gel. Final solution before evaporation was washed with brine and dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H and ^{13}C NMR experiments were conducted on Brucker AW-500 spectrometer. HREIMS were obtained on a JEOLJMS-700 mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

4.1.1. Methyl 2-deoxy-3,4-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-D-mannonate 5. This was prepared from D-glucono-δ-lactone as described:[16] mp 69–70°C (lit.,[16] 68–70°C).

4.1.2. Methyl 2-deoxy-3,4-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-D-lyxonate 6. To a solution of diol **5** (6.00 g, 12.26 mmol) in EtOH–H_2O (80:40 mL) was $NaIO_4$ (3.15 g, 14.70 mmol) at room temperature. After stirring for 3 h, the mixture was cooled to 0°C, and then $NaBH_4$ (0.56 g, 14.70 mmol) was added and stirred for 10 min. After evaporation of EtOH, the mixture was poured into excess of H_2O and extracted with EtOAc (100 mL×3). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane–EtOAc (3:1)] to give compound **6** (5.52 g, 98%) as a solid, mp 64–66°C; $[\alpha]_D^{20}$=−150 (*c* 1.16, $CHCl_3$); IR (KBr): 3500, 3050, 1740 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.09 (3H, s), 1.28 (3H, s), 2.63 (1H, d, *J*=8.8 Hz), 3.23 (3H, s), 3.35 (1H, s, OH), 3.76–3.92 (4H, m), 7.09–7.73 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 26.4, 26.8, 51.9, 58.6, 63.8, 72.6, 80.2, 80.3, 109.5, 120.2, 125.5, 125.7, 126.1, 127.4, 127.5, 128.4, 128.5, 128.6, 128.9, 140.4, 141.1, 143.1, 147.9, 174.7 (Found: C, 73.18; H, 6.39; N, 3.02. $C_{28}H_{29}NO_5$ requires C, 73.18; H, 6.36; N, 3.05%).

4.1.3. Methyl 2-deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-lyxonate 7. To a solution of alcohol **6** (5.40 g, 11.75 mmol) in THF (58 mL) were added triethylamine (3.26 mL, 23.50 mmol) and MsCl (1.36 mL, 17.63 mmol) at 0°C. The reaction mixture was stirred for 20 min at room temperature, then was quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL×3). After concentration of combined extracts, the resulting residue was chromatographed on silica gel [hexane–EtOAc (5:1)] to give compound **7** (6.20 g, 98%) as a solid, mp 155–158°C; $[\alpha]_D^{20}$=−204 (*c* 1.00, $CHCl_3$); IR (KBr): 3290, 3010, 1715 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.10 (3H, s), 1.31 (3H, s), 2.62 (1H, dd, *J*=11.0, 9.0 Hz), 3.12 (3H, s), 3.24 (3H, s,), 3.82 (1H, dd, *J*=8.8, 7.3 Hz), 4.00 (1H, m), 4.46 (1H, dd, *J*=10.9, 6.1 Hz), 4.77 (1H, dd, *J*=11.0, 2.4 Hz), 7.11–7.74 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 26.6, 26.8, 51.9, 58.8, 70.3, 72.6, 78.0, 78.2, 110.6, 120.2, 120.3, 125.1, 125.9, 126.1, 127.5, 128.3, 128.5, 128.6, 128.8, 140.1, 141.3, 143.4, 147.9, 148.2, 174.4 (Found: C, 64.73; H, 5.80; N, 2.59. $C_{29}H_{31}NO_7S$ requires C, 64.79; H, 5.81; N, 2.61%).

4.1.4. Methyl 2,5-dideoxy-3,4-*O*-isopropylidene-5-iodo-2-[(9-phenyl-9-fluorenyl)-amino]-D-lyxonate 8. To a solution of mesylate **7** (6.10 g, 11.34 mmol) in dried DMF (38 mL) was added LiI (6.17 g, 46.12 mmol). After stirring of the mixture for overnight at 80°C, saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (40 mL×3). The extract was evaporated and the remaining residue was chromatographed on silica gel [hexane–EtOAc (10:1)] to give compound **8** (6.14 g, 95%) as a solid, mp 60–65°C; $[\alpha]_D^{20}$=−161.8 (*c* 1.2, $CHCl_3$); IR (KBr): 3320, 3040, 1735 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.07 (3H, s), 1.34 (3H, s), 2.63 (1H, m), 3.04 (1H, d, *J*=11 Hz), 3.23 (3H, s), 3.44 (1H, m), 3.67 (1H, dd, *J*=10.2, 3.2 Hz), 7.13–7.71 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 8.8, 27.5, 27.9, 52.2, 59.0, 73.0, 80.0, 82.6, 99.5, 110.6, 120.6, 125.5, 126.3, 126.5, 127.8, 127.9, 128.8, 128.9, 129.0, 129.1, 140.6, 141.6, 144.1, 148.6, 148.7, 174.9 (Found: C, 59.02; H, 4.97; N, 2.49. $C_{28}H_{28}INO_4$ requires C, 59.06; H, 4.96; N, 2.46%).

4.1.5. Methyl (2*S*,3*S*)-3-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 9. A solution of iodinated **8** (6.00 g, 10.54 mmol) in THF (53 mL) was cooled to −40°C, 2.5 M *n*-BuLi (16.90 mL, 42.16 mmol, 400 mmol%) was added dropwise over 30 min via syring pump. The reaction mixture was stirred an additional 20 min at −40°C, then quenched with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with EtOAc (40 mL×3) and combined extracts were concentrated. The resulting residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give compound **9** (3.45 g, 85%) as a solid, mp 120–122°C; $[\alpha]_D^{20}=-278.2$ (*c* 1.00, $CHCl_3$); IR (KBr): 3480, 3045, 1735 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 2.77 (1H, d, *J*=5.5 Hz), 3.28 (3H, s), 4.01 (1H, t, *J*=5.5 Hz), 4.69 (1H, s, NH), 5.15 (1H, d, *J*=10.6 Hz), 5.25 (1H, d, *J*=14.7 Hz), 5.74 (1H, ddd, *J*=16.3, 10.5, 5.5 Hz), 7.20–7.67 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 50.4, 58.8, 71.4, 72.0, 115.2, 118.8, 118.9, 124.0, 124.8, 125.1, 126.2, 126.2, 127.0, 127.2, 127.3, 127.5, 135.6, 139.0, 139.9, 142.9, 146.9, 147.3, 172.7 (Found: C, 77.40; H, 6.05; N, 3.60. $C_{25}H_{23}NO_3$ requires C, 77.90; H, 6.01; N, 3.63%).

4.1.6. Methyl (2*S*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 10. To a solution of compound **9** (3.40 g, 8.82 mmol) in DMF (30 mL) were added imidazole (1.20 g, 17.64 mmol) and TBDMSCl (2.66 g, 17.64 mmol) at room temperature. After stirring of the mixture for 12 h, saturated aqueous $NaHCO_3$ (40 mL) was added and the mixture was extracted with EtOAc (40 mL×3). After concentration of combined extracts, the remaining residue was chromatographed on silica gel [hexane–EtOAc (12:1)] to give compound **10** (4.32 g, 98%) as a solid, mp 95–98°C; $[\alpha]_D^{20}=-208.0$ (*c* 1.46, $CHCl_3$); IR (KBr): 3315, 3040, 1740 cm^{-1}; δ_H (500 MHz; $CDCl_3$) −0.01 (3H, s), 0.03 (3H, s), 0.81 (9H, s), 2.66 (1H, d, *J*=7.9 Hz), 3.21 (3H, s), 4.13 (1H, t, *J*=7.3 Hz), 5.25 (2H, m), 5.74 (1H, ddd, *J*=17.3, 10.3, 7.1 Hz), 7.22–7.71 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −5.2, −4.3, 17.9, 25.6, 51.3, 61.2, 72.7, 76.9, 116.9, 119.9, 119.9, 125.8, 126.1, 126.1, 127.2, 127.3, 127.7, 128.2, 128.3, 128.3, 139.3, 140.2, 141.1, 144.8, 148.5, 148.6, 175.3 (Found: C, 74.54; H, 7.42; N, 2.78. $C_{31}H_{37}NO_3Si$ requires C, 74.51; H, 7.46; N, 2.80%).

4.1.7. Methyl (2*S*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-5-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino] pentanoate 11. To a solution of pentenoate **10** (4.30 g, 8.60 mmol) in THF (43 mL) were added $BH_3(CH_3)_2S$ (12.90 mL, 25.80 mmol) at 0°C. After stirring of the mixture for 10 h at room temperature, the reaction mixture was quenched by sequential addition of water (2.6 mL), 3 M sodium hydroxide (3.25 mL), 30% hydrogen peroxide (5.85 mL). The mixture was extracted with EtOAc (40 mL×3) and combined extracts was concentrated. The residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give compound **11** (3.12 g, 70%) as a solid, mp 64–66°C; $[\alpha]_D^{20}=-81.6$ (*c* 1.73, $CHCl_3$); IR (KBr): 3530, 3060, 1745 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 0.00 (3H, s), 0.07 (3H, s), 0.80 (9H, s), 1.85 (1H, m), 2.01 (1H, m), 2.72 (1H, d, *J*=7.7 Hz), 3.21 (3H, s), 3.45 (2H, m), 3.87 (1H, m), 7.15–7.73 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −5.2, −4.4, 17.7, 25.6, 36.6, 51.5, 59.3, 59.8, 72.7, 74.5, 120.1, 120.2, 125.7, 125.9, 126.1, 127.3, 127.5, 127.9, 128.4, 128.4, 128.7, 140.4, 141.1, 143.9, 148.3, 148.4, 175.6 (Found: C, 71.88; H, 7.59; N, 2.75. $C_{31}H_{39}NO_4Si$ requires C, 71.92; H, 7.59; N, 2.71%).

4.1.8. *trans*-3-*O*-(*tert*-Butyldimethylsilyl)-1-(9-phenyl-9-fluorenyl)-L-proline methyl ester 12. To a solution of alcohol **11** (3.00 g, 5.79 mmol) in THF (29 mL) were added triethylamine (1.57 mL, 11.30 mmol) and MsCl (0.66 mL, 8.46 mmol). The reaction mixture was stirred for 3 h at 0°C, then was quenched with saturated aqueous $NaHCO_3$ (30 mL). The reaction mixture was extracted with EtOAc (20 mL×3). After concentration of combined extracts, the resulting residue was chromatographed on silica gel [hexane–EtOAc (15:1)] to give compound **12** (2.52 g, 87%) as a oil, $[\alpha]_D^{20}=+272.6$ (*c* 2.5, $CHCl_3$); IR (neat): 3030, 2910, 1725 cm^{-1}; δ_H (500 MHz; $CDCl_3$) −0.11 (3H, s), 0.00 (3H, s), 0.82 (9H, s), 1.73 (1H, m), 2.16 (1H, m), 2.97 (1H, d, *J*=1.0 Hz), 3.33 (1H, m), 3.40 (1H, m), 3.44 (3H, s), 4.17 (1H, m), 7.22–7.85 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −5.1, 17.7, 25.6, 34.5, 47.0, 51.2, 69.7, 76.0, 119.7, 119.8, 126.9, 127.0, 127.0, 127.2, 127.6, 127.6, 128.1, 128.2, 128.4, 139.4, 141.7, 142.9, 145.9, 148.4, 175.3 (Found: C, 74.54; H, 7.49; N, 2.78. $C_{31}H_{37}NO_3Si$ requires C, 74.51; H, 7.46; N, 2.80%).

4.1.9. *trans*-3-Hydroxy-1-(9-phenyl-9-fluorenyl)-L-prolinol 13. To an ice-cooled solution of LAH (0.08 g, 2.10 mmol) in THF (7 mL) was added a solution of proline methyl ester **12** (0.70 g, 1.40 mmol) in THF (4 mL). The reaction mixture was warmed to room temperature, stirred for 7 h, then quenched by the sequential addition of water (0.8 mL), 15% aqueous NaOH (0.8 mL), and water (2.4 mL). The mixture was filtered and evaporated. The resulting residue was chromatographed on silica gel [hexane–EtOAc (2:1)] to give compound **13** (0.45 g, 89%) as a solid, mp 150–160°C; $[\alpha]_D^{20}=+18.6$ (*c* 1.00, $CHCl_3$); IR (KBr): 3480, 3040, 2890 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.64 (1H, m), 1.92 (1H, m), 2.32 (1H, m), 2.51 (1H, dd, *J*=10.5, 5.6 Hz), 3.05 (1H, d, *J*=10.1 Hz), 3.27 (2H, m), 4.03 (1H, s), 7.18–7.74 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 31.7, 47.2, 61.5, 66.3, 75.1, 118.5, 118.7, 124.3, 125.0, 125.9, 125.9, 126.3, 126.4, 126.9, 127.1, 127.4, 137.4, 1405, 141.3, 145.0, 147.4 (Found: C, 80.61; H, 6.51; N, 3.90. $C_{24}H_{23}NO_2$ requires C, 80.64; H, 6.49; N, 3.92%).

4.1.10. Methyl 2-deoxy-3,4-*O*-isopropylidene-2-[(9-phenyl-9-fluorenyl)-amino]-D-arabinonate 14. This was prepared from L-gulonic acid γ-lactone as described:[17] mp 57–58°C (lit.,[17] 56–58°C).

4.1.11. Methyl 2-deoxy-3,4-*O*-isopropylidene-5-*O*-methanesulfonyl-2-[(9-phenyl-9-fluorenyl)-amino]-D-arabinonate 15. To a solution of alcohol **14** (5.40 g, 11.75 mmol) in THF (58 mL) were added triethylamine (3.26 mL, 23.50 mmol) and MsCl (1.42 mL, 17.63 mmol), at 0°C. After stirring of the mixture for 15 min at room temperature, saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (60 mL×3). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane–EtOAc (5:1)] to give compound **15** (6.19 g, 98%) as a solid, mp 55–60°C; $[\alpha]_D^{20}=+230.2$ (*c* 1.00, $CHCl_3$); IR (KBr): 3310,

3030, 1730 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.35 (3H, s), 1.46 (3H, s), 2.65 (1H, s), 2.99 (3H, s), 3.33 (3H, s), 3.75 (1H, m), 3.87 (1H, dd, J=11.5, 5.2 Hz), 4.20 (1H, dd, J=11.5, 2.7 Hz), 4.47 (1H, m), 7.20–7.67 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 27.0, 27.1, 37.7, 51.9, 55.2, 68.4, 72.9, 74.6, 77.6, 110.3, 120.0, 120.2, 125.3, 126.6, 126.7, 127.4, 127.5, 128.1, 128.5, 128.6, 128.8, 140.3, 141.0, 143.7, 147.8, 148.4, 173.5 (Found: C, 64.82; H, 5.80; N, 2.59. $C_{29}H_{31}NO_7S$ requires C, 64.79; H, 5.81; N, 2.61%).

4.1.12. Methyl 2,5-dideoxy-3,4-*O*-isopropylidene-5-iodo-2-[(9-phenyl-9-fluorenyl)-amino]-D-arabinonate 16. To a solution of mesylate **15** (6.00 g, 11.16 mmol) in DMF (40 mL) was added LiI (6.17 g, 46.12 mmol). After stirring of the mixture for overnight at 80°C, saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was extracted with EtOAc (50 mL×3). After evaporation of combined extracts, the resulting residue was chromatographed on silica gel [hexane–EtOAc (10:1)] to give compound **16** (5.72 g, 90%) as a solid, mp 59–64°C; $[\alpha]_D^{20}$=+200.7 (c 1.25, $CHCl_3$); IR (KBr): 3340, 3020, 1730 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 1.37 (3H, s), 1.50 (3H, s), 2.64 (1H, m), 2.89 (1H, dd, J=10.8, 5.8 Hz), 3.01 (1H, dd, J=10.8, 4.0 Hz), 3.33 (1H, s), 3.60 (1H, dd, J=7.6, 3.0 Hz), 4.13 (1H, m), 7.21–7.69 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 5.9, 27.2, 51.8, 55.3, 72.8, 75.4, 81.8, 109.7, 119.9, 120.1, 125.4, 126.1, 126.9, 127.3, 127.4, 128.1, 128.3, 128.4, 128.5, 128.7, 140.2, 141.1, 143.9, 147.8, 148.6, 173.6 (Found: C, 59.02; H, 4.99; N, 2.47. $C_{28}H_{28}INO_4$ requires C, 59.06; H, 4.96; N, 2.46%).

4.1.13. Methyl (2*R*,3*S*)-3-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 17. A solution of iodinated **16** (5.30 g, 9.31 mmol) in THF (50 mL) was cooled to −40°C, 2.5 M *n*-BuLi (14.90 mL, 37.24 mmol, 400 mmol%) was added dropwise over 30 min via syring pump. The reaction mixture was stirred an additional 20 min at −40°C, then quenched with saturated aqueous NH_4Cl (40 mL). The mixture was extracted with EtOAc (50 mL×3) and combined extracts were concentrated. The remaining residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give compound **17** (3.23 g, 90%) as a solid, mp 117–120°C; $[\alpha]_D^{20}$=+278.9 (c 1.25, $CHCl_3$); IR (KBr): 3490, 3020, 1720 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 2.51 (1H, d, J=7.8 Hz), 3.20 (3H, s), 3.89 (1H, dd, J=7.7, 6.9 Hz), 5.04 (1H, dt, J=10.4, 1.1 Hz), 5.16 (1H, dt, J=17.1, 1.3 Hz), 5.49 (1H, m), 7.23–7.39 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) 51.5, 61.0, 72.5, 74.3, 117.7, 120.1, 120.1, 125.3, 125.9, 126.2, 127.4, 127.5, 128.4, 128.5, 128.6, 128.7, 136.1, 140.1, 141.2, 143.8, 148.1, 148.1, 174.3 (Found: C, 77.88; H, 6.03; N, 3.60. $C_{25}H_{23}NO_3$ requires C, 77.90;H, 6.01; N, 3.63%).

4.1.14. Methyl (2*R*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-2-[(9-phenyl-9-fluorenyl)-amino]-4-pentenoate 18. To a solution of pentenoate **17** (3.20 g, 8.30 mmol) in DMF (28 mL) were added imidazole (1.13 g, 16.60 mmol) and TBDMSCl (2.50 g, 16.60 mmol) at room temperature. After stirring of the mixture for 12 h, saturated aqueous $NaHCO_3$ (40 mL) was added and the mixture was extracted with EtOAc (50 mL×3). After concentration of combined extracts, the residue was chromatographed on silica gel [hexane–EtOAc (10:1)] to give compound **18** (4.06 g, 98%) as a oil, $[\alpha]_D^{20}$=−109.2 (c 3.00, $CHCl_3$); IR (neat): 3340, 3040, 1730 cm^{-1}; δ_H (500 MHz; $CDCl_3$) −0.06 (3H, s), 0.00 (3H, s), 0.91 (9H, s), 2.84 (1H, s), 3.11 (1H, s), 3.32 (3H, s), 4.20 (1H, m), 5.25 (1H, dt, J=10.4, 1.3 Hz), 5.31 (1H, dt, J=17.2, 1.6 Hz), 6.03 (1H, ddd, J=17.0, 10.4, 6.4 Hz), 7.31–7.79 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −4.8, −4.5, 18.4, 26.1, 51.5, 61.1, 73.2, 76.5, 116.6, 120.2, 120.3, 125.8, 126.6, 126.8, 127.5, 127.7, 128.2, 128.6, 128.7, 137.9, 140.7, 141.4, 145.0, 149.2, 149.5, 174.4 (Found: C, 74.48; H, 7.49; N, 2.76. $C_{31}H_{37}NO_3Si$ requires C, 74.51;H, 7.46; N, 2.80%).

4.1.15. Methyl (2*R*,3*S*)-3-(*tert*-butyldimethylsilyl)oxy-5-hydroxy-2-[(9-phenyl-9-fluorenyl)-amino] pentanoate 19. To a solution of compound **18** (4.00 g, 8.00 mmol) in THF (41 mL) were added $BH_3(CH_3)_2S$ (12.00 mL, 24.00 mmol) at 0°C. After stirring of the mixture for 10 h at room temperature, the reaction mixture was quenched by sequential addition of water (2.5 mL), 3 M sodium hydroxide (3.15 mL), 30% hydrogen peroxide (5.35 mL). The mixture was extracted with EtOAc (40 mL×3). After evaporation of combined extracts, the residue was chromatographed on silica gel [hexane–EtOAc (4:1)] to give compound **19** (3.23 g, 78%) as a solid, mp 117–120°C; $[\alpha]_D^{20}$=+381.0 (c 1.26, $CHCl_3$); IR (KBr): 3490, 3030, 1720 cm^{-1}; δ_H (500 MHz; $CDCl_3$) −0.25 (3H, s), 0.00 (3H, s), 0.91 (9H, s), 1.76 (1H, m), 2.24 (1H, m), 2.82 (1H, d, J=4.6 Hz), 3.44 (3H, s), 3.77 (2H, m), 3.90 (1H, m), 7.29–7.85 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −5.3, −5.2, 17.8, 25.7, 34.8, 51.3, 59.1, 59.8, 60.0, 73.0, 119.9, 120.1, 125.4, 126.1, 126.2, 127.3, 127.5, 128.0, 128.4, 128.6, 128.7, 140.4, 141.4, 144.0, 148.6, 149.1, 174.6 (Found: C, 71.88; H, 76.2; N, 2.73. $C_{31}H_{39}NO_4Si$ requires C, 71.92; H, 7.59; N, 2.71%).

4.1.16. *cis*-3-*O*-(*tert*-Butyldimethylsilyl)-1-(9-phenyl-9-fluorenyl)-D-proline methyl ester 20. To a solution of alcohol **19** (2.40 g, 4.63 mmol) in THF (23 mL) were added triethylamine (1.29 mL, 9.26 mmol) and MsCl (0.54 mL, 7.0 mmol). The reaction mixture was stirred for 3 h at 0°C, then was quenched with saturated aqueous $NaHCO_3$ (30 mL). The organic phase was separated, and the aqueous phase was treated with EtOAc (40 mL×3). The extract was concentrated and the resulting residue was chromatographed on silica gel [hexane–EtOAc (15:1)] to give compound **20** (2.08 g, 90%) as a oil, $[\alpha]_D^{20}$=−248.7 (c 1.73, $CHCl_3$); IR (neat): 3020, 2910, 1730 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 0.00 (3H, s), 0.04 (3H, s), 0.88 (9H, s), 1.91 (1H, m), 2.17 (1H, m), 2.84 (1H, m), 3.37 (2H, m), 3.51 (3H, s), 4.14 (1H, m), 7.20–7.81 (13H, m, Pf); δ_C (125 MHz; $CDCl_3$) −4.9, 17.9, 25.6, 33.1, 46.1, 50.9, 65.0, 73.6, 76.5, 119.8, 120.0, 126.3, 126.6, 127.3, 127.3, 127.5, 127.6, 128.3, 128.3, 128.4, 140.0, 141.2, 142.8, 146.8, 148.2, 173.7 (Found: C, 74.47; H, 7.49; N, 2.79. $C_{31}H_{37}NO_3Si$ requires C, 74.51; H, 7.46; N, 2.80%).

4.1.17. *trans*-3-Hydroxy-L-proline 1. The protected proline **12** (0.70 g, 1.40 mmol) and 10% Pd/C (0.07 g) were stirred in CH_3OH (14 mL) under an atmosphere of hydrogen at 60°C for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. A solution of remaining residue and Dowex 50W-X8 (0.18 g) in THF–H_2O (4:2 mL) was refluxed for overnight, cooled to room

temperature. The mixture was filtered, and then the insoluble material was washed with CH_3OH (50 mL). The remaining residue was eluted with 3N NH_4OH. The ammoniacal solution was evaporated, then co-evaporation with toluene to give the compound **1** (0.14 g, 76%) as a solid, mp 231–234°C (decomp.); $[\alpha]_D^{20}=-23.3$ (*c* 0.92, H_2O); {lit.,[9] $[\alpha]_D^{20}=-18.8$ (*c* 0.14, H_2O), mp 232°C}; IR (KBr): 3410, 2920 cm^{-1}; δ_H (500 MHz; D_2O) 2.04 (2H, m), 3.48 (1H, m), 3.58 (1H, m), 4.06 (1H, s), 4.67 (1H, m); δ_C (125 MHz; D_2O) 30.1, 42.8, 67.6, 72.5, 170.2; MS: *m/z* 131 (M^+); [found (HRMS): (M^+), 131.0567. Calcd for $C_5H_9NO_3$: 131.0582].

4.1.18. *trans*-3-Hydroxy-L-prolinol 2. The *N*-protected prolinol **13** (0.30 g, 0.84 mmol) and 10% Pd/C (0.03 g) were stirred in CH_3OH (4 mL) under an atmosphere of hydrogen at 60°C for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The remaining oil was subjected to ion-exchange chromatography (Dowex 50W-X8, eluting with 3N NH_3 in water), and free base **2** was obtained as an oil in 93% yield, $[\alpha]_D^{20}=+45.8$ (*c* 0.5, H_2O); {lit.,[18] $[\alpha]_D^{20}=+46.5$ (*c* 1.0, H_2O)}; IR (neat): 3450, 2895 cm^{-1}; δ_H (500 MHz; D_2O) 1.78 (1H, m), 2.02 (1H, m), 3.03 (3H, m), 3.55 (1H, m), 3.64 (1H, m), 4.14 (1H, m); δ_C (125 MHz; D_2O) 34.0, 44.3, 62.2, 67.4, 73.6; MS: *m/z* 117 (M^+); [Found (HRMS): (M^+), 117.0792. Calcd for $C_5H_{11}NO_2$: 117.0790].

4.1.19. *cis*-3-Hydroxy-D-proline 3. The protected proline **20** (0.70 g, 1.40 mmol) and 10% Pd/C (0.07 g) were in CH_3OH (14 mL) under an atmosphere of hydrogen at 60°C 3 h. The reaction mixture was filtered through Celite, and the filtrate concentrated. A solution of remaining residue and Dowex 50W-X8 (0.17 g) in THF–H_2O (4:2 mL) was refluxed for overnight, cooled to room temperature. The mixture was filtered, and then the insoluble material was washed with CH_3OH (50 mL). The remaining residue was eluted with 3N NH_4OH. The ammoniacal solution was evaporated, then co-evaporation with toluene to give the compound **3** (0.15 g, 84%) as a solid, mp 210–217°C (decomp.); $[\alpha]_D^{20}=+96.3$ (*c* 0.92, H_2O); {lit.,[10] $[\alpha]_D^{20}=+89.0$} (*c* 0.7, H_2O), mp 225–235°C (decomp.)}; IR (KBr): 3400, 2910 cm^{-1}; δ_H (500 MHz; D_2O) 2.12 (1H, m), 2.21 (1H, m), 3.47 (1H, m), 3.57 (1H, m), 4.13 (1H, d, *J*=4.1 Hz), 4.72 (1H, m); δ_C (125 MHz; D_2O) 32.3, 42.9, 66.7, 70.0, 169.7; MS: *m/z* 131 (M^+); [Found (HRMS): (M^+), 131.0580. Calcd for $C_5H_9NO_3$: 131.0582].

4.1.20. *cis*-3-Hydroxy-D-prolinol 4. To an ice-cooled solution of LAH (0.08 g, 2.10 mmol) in THF (7 mL) was added a solution of proline **20** (0.70 g, 1.40 mmol) in THF (10 mL). The reaction mixture was warmed to room temperature, stirred for 7 h and then quenched by sequential addition of water (0.8 mL), 15% aqueous NaOH (0.8 mL), and water (2.4 mL). The mixture was filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel [hexane–EtOAc (2:1)] to give compound. The *N*-protected prolinol and 10% Pd/C (0.03 g) were stirred in CH_3OH (4 mL) under an atmosphere of hydrogen at 60°C for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated. The remaining oil was subjected to ion-exchange chromatography (Dowex 50W-X8, eluting with 3N NH_3 in water), and free base **4** was obtained as an oil in 75% yield, $[\alpha]_D^{20}=-23.2$ (*c* 0.76, H_2O); IR (neat): 3310, 2890 cm^{-1}; δ_H (500 MHz; D_2O) 1.93 (1H, m), 2.14 (1H, m), 3.14 (1H, m), 3.30 (2H, m), 3.78 (1H, m), 3.38 (1H, dd, *J*=11.7, 5.5 Hz), 4.46 (1H, s); δ_C (125 MHz; D_2O) 33.8, 43.5, 59.3, 64.8, 71.2; MS: *m/z* 117 (M^+); [Found (HRMS): (M^+), 117.0804. Calcd for $C_5H_{11}NO_2$: 117.0790].

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References

1. Tschesche, R.; Samuel, T. D.; Uhlendorf, J.; Fehlaber, H. W. *Chem. Ber.* **1972**, *105*, 3106–3114.
2. Sheeban, J. C.; Mania, D.; Nakamura, S.; Stock, J. A.; Maeda, K. *J. Am. Chem. Soc.* **1968**, *90*, 462–470.
3. (a) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1998**, *44*, 2637–2647. (b) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119–136. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872.
4. Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133–4136.
5. Mulzer, J.; Meier, A.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1996**, *61*, 566–572.
6. Ogle, J.; Arlinghaus, R.; Logan, M. *Arch. Biochem. Biophys.* **1961**, *94*, 85–93.
7. Kubo, A.; Nakai, T.; Koizumi, Y.; Kitahara, Y.; Saito, N.; Micami, Y.; Yazawa, K.; Uno, J. *Heterocycles* **1996**, *42*, 195–211.
8. Durand, J.-O.; Larchevêque, M.; Petit, Y. *Tetrahedron Lett.* **1998**, *39*, 5743–5746.
9. Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 119–128.
10. Jurczak, J.; Prokowicz, P.; Golebiowski, A. *Tetrahedron Lett.* **1993**, *34*, 7107–7110.
11. Dell'Uomo, N.; Cristina Di Giovanni, M.; Misiti, D.; Zappia, G.; Delle Monache, G. *Tetrahedron: Asymmetry* **1996**, *7*, 181–188.
12. Poupardin, O.; Greck, C.; Genêt, J.-P. *Synlett* **1998**, 1279–1281.
13. Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1313–1317.
14. Schöllkopf, U.; Bardenhagen, J. *Liebigs Ann. Chem.* **1987**, 393–397.
15. Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236–239.
16. Kim, J. H.; Lee, W. S.; Yang, M. S.; Park, K. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2877–2880.
17. Lee, B. W.; Jeong, I. Y.; Yang, M. S.; Choi, S. U.; Park, K. H. *Synthesis* **2000**, *9*, 1305–1309.
18. Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, J. M. *J. Chem. Soc. Chem. Commun.* **1985**, 738–740.