A novel proton-selective sensor based on a sugar with hinge flexibility†

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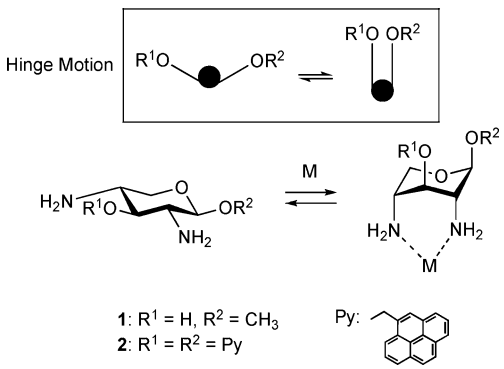
Received 18th June 2007, Accepted 11th July 2007
First published as an Advance Article on the web 2nd August 2007
DOI: 10.1039/b709115j

A hinge sugar, a 2,4-diamino-2,4-dideoxy-β-D-xylopyranoside derivative, turns its four equatorial substituents into axial orientations through a $^4C_1$-to-$^1C_4$ ring flip in response to chelation to a metal ion. This hinge-like motion enables two components attached at the 1- and 3-positions to switch between far and near states. In this study, we examined the effect of *N*-alkylation on the bendability of the hinge molecule and synthesized a 2,4-dipyrenylmethyl derivative as a proton-selective sensor. ^{1}H NMR studies showed that *N*-alkylations of the hinge sugar facilitated $^1C_4$ formation in the presence of an acid, probably because the increased basicity of the amino group promoted the intramolecular hydrogen bond between the 2- and 4-amino substituents, whereas chelation to a metal ion was hampered by the increased bulkiness. In accordance with the above results, *N*,*N*′-dipyrenylmethyl hinge sugar **3** emitted excimer fluorescence (445 nm) owing to the pyrene stacking as a result of the $^1C_4$ formation at lower concentrations of trifuluoroacetic acid (TFA), while no significant changes in fluorescence spectra were observed when metal ions were added. Increase of the monomer fluorescence (375 nm) at higher TFA concentrations was also observed. These observations indicate that **3** could be used as a proton-selective sensor that covers a wide range of proton concentrations through monitoring of the two fluorescence maxima.

Introduction

Chemosensors[1] that function *via* mechanical motion often consist of two components: one that transduces a molecular recognition event into internal molecular motions[2] and one that transduces the motions into a signal. The development of these molecular transducers is one of the most important subjects in the studies of molecular machines and devices, since the transducers are associated with the control or monitoring of molecular motions, the most important aspect in the field.[3] We have previously synthesized a hinge-like molecular transducer **1** from a xylose derivative, which undergoes a hinge motion with regard to the diequatorial-to-diaxial reorientation of the substituents through a ring flip caused by chelation to a metal ion (Scheme 1).[4] On the basis of the molecular transducer **1**, we developed a metal ion sensor **2**, in which two pyrenyl groups at the 1,3-positions of xylose become stacked, resulting in excimer fluorescence when two amino groups at the 2,4-positions chelate to a zinc or cadmium ion.[5] Compound **2** was also found to act as a proton sensor, since protonation of one of the two amino groups produces an ammonium ion, which serves as a strong hydrogen bond donor toward the other amino group, forming an intramolecular hydrogen bond bridge in place of chelation to a metal ion (Scheme 1). As the bendability of the hinge sugar is largely dependent on the amino group basicity, *N*-alkylation is expected to modulate the sensitivity and selectivity of the metal ion sensor. In this study, we synthesized *N*-alkylated hinge sugar derivatives and compared their bendability. Also, *N*,*N*′-dipyrenylmethyl hinge sugar **3** was tested as a metal ion or proton sensor. Compound **3** is intrinsically subject to fluorescence quenching from the amino groups and therefore is expected to recover the fluorescence through coordination to a metal ion or proton.[6]



Scheme 1

Results and discussion

N-Alkylated hinge sugars **3–5** were synthesized through imination–reduction of appropriate aldehydes with **1** and $NaB(CN)H_3$ (Scheme 2). The ring conformations of compounds **3**, **4** and **5** in the absence and presence of zinc(II) ions or protons were estimated from the *J*-values for the vicinal protons in the ^{1}H NMR spectrum (Table 1). The poor solubility of **3** prevented the use of more than 0.5 equivalents of trifluoroacetic acid (TFA) in the ^{1}H NMR experiments, which caused precipitation. The $^1C_4$ populations (%) were computed by a multiple regression analysis with a least-squares fitting of the *J*-values calculated for model

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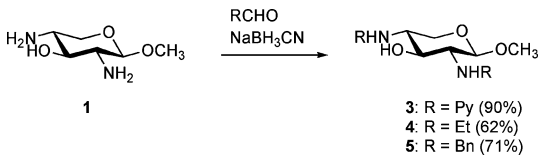
† Electronic supplementary information (ESI) available: NMR spectra for new compounds in the absence and presence of zinc(II) ions or protons. See DOI: 10.1039/b709115j

Table 1 J-Values (Hz) for the vicinal protons and calculated $^1C_4$ populations of xylopyranosides

Entry	Compd	Additive	Equiv.	Solvent	^3J-value/Hz					$^1C_4$
					$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	
1	**1**[a]	None	—	Buffer[c]	8.1	9.6	9.6	5.1	10.7	0%
2	**1**[a]	$Zn(OAc)_2$[b]	2.0	Buffer[c]	5.6	7.5	7.5	4.0	7.5	33%
3	**3**	None	—	$CDCl_3$	7.2	9.0	8.7	4.6	9.6	14%
4	**3**	None	—	DMF-d_7	7.6	9.3	9.3	4.9	10.2	7%
5	**3**	TFA	0.5	$CDCl_3$	6.3	7.7	7.7	3.8	7.9	32%
6	**3**	$Zn(OAc)_2$[b]	2.0	DMF-d_7	7.3	9.5	9.5	5.2	10.4	6%
7	**4**	None	—	Buffer[c]	8.1	9.8	9.8	5.0	10.5	0%
8	**4**	TFA[b]	1.0	D_2O	7.7	9.8	9.5	5.0	9.5	8%
9	**4**	$Zn(OAc)_2$[b]	2.0	Buffer[c]	6.3	8.2	8.2	4.3	8.2	27%
10	**5**	None	—	DMSO-d_6	7.6	9.3	9.4	4.9	10.3	7%
11	**5**	$Zn(OAc)_2$[d]	2.0	DMSO-d_6	7.2	9.1	9.2	4.8	9.5	12%
12	**5**	TFA[b]	1.0	DMSO-d_6	6.6	8.7	8.9	4.6	9.0	18%
13	**5**	TFA	10.0	DMSO-d_6	8.2	10.1	9.9	5.0	10.5	0%

[a] Data from ref. 4. [b] The measurement temperature was 80 °C. [c] 50 mM AcONa-d_3 (pH 7.0). [d] The measurement temperature was 120 °C.



Scheme 2

structures to the observed ones. The calculated J-values were derived by the generalized Karplus equation[7] from the dihedral angles of the computed $^4C_1$, $^1C_4$, $^2S_0$, $^3S_1$ and ^{03}B structures optimized by PC Spartan Plus software[8] using the SYBYL force field. The populations of the skew and boat conformations were negligible for all the J-value sets.

Compounds **3** and **5** were found to be in a conformational equilibrium between $^4C_1$ and $^1C_4$ (entries 3,4,10), while the free amino hinge **1** and N,N'-diethyl hinge **4** exist solely in $^4C_1$ in AcONa-d_3 buffer (entries 1,7). The $^1C_4$ conformers of compounds **3** and **5** are most likely stabilized by an intramolecular hydrophobic interaction between two aromatic groups: the stacking of a pyrene or benzene pair would assist the formation of the $^1C_4$ conformer. The fact that compound **3** has a lower $^1C_4$ population in DMF-d_7 (entry 4) than in the less polar $CDCl_3$ (entry 3) is explainable by a solvent effect: a polar solvent would disturb the stacking interaction. A similar solvent dependence has been observed for methyl 2,4-di-*O*-(1-pyrenecarbonyl)-β-D-xylopyranoside.[5b]

The addition of 0.5 equiv. of TFA significantly increased the $^1C_4$ population of **3** (entry 5). This $^1C_4$ population is comparable to that for **1** with 2 equiv. of zinc ion (entry 2).[4] The driving force of the hinge closure of **3** is attributable to a hydrogen bond bridging between two amino groups, as was discussed for the proton-driven closure of the hinge chemosensor **2**,[5] in which titration with TFA demonstrated that the $^1C_4$ population reached a maximum at 63% with one equivalent of TFA. In the case of **3**, precipitation at higher TFA concentrations prevented the observation of the maximum $^1C_4$ population. In contrast to **3**, N,N'-diethyl hinge sugar **4** showed less hinge closure with the addition of 1.0 equiv. TFA (entry 8). This result suggests that the pyrene stacking assisted the hinge closure of **3** in cooperation with the hydrogen bond between two amino groups. In accordance with the smaller stacking potency of a benzene ring compared with a pyrene group, N,N'-dibenzyl hinge sugar **5** showed a moderate hinge closure ratio at 1.0 equiv. of TFA (entry 12). The observation that the use of excess TFA (10 equiv.) resulted in the complete recovery of the $^4C_1$ conformation (entry 13) is consistent with the similar behavior observed for the proton sensor **2**, attributed to the destabilization of the $^1C_4$ confomer by repulsion between two ammonium ions.

The hinge closure through chelation to zinc ion was slightly suppressed for N,N'-diethyl hinge **4** (entry 9) compared with that of the free amino hinge **1** (entry 2). This supression was unexpected because N-alkylation was expected to enhance the amino group basicity, thereby increasing the nucleophilicity towards the metal ion. Perhaps the bulkiness of the ethyl group principally affected the amino group, attenuating the nucleophilicity. The bulkiness effect is further supported by the experiment with compound **5** (entry 11), in which the bulkier benzyl group resulted in a lower $^1C_4$ population in the presence of zinc ion. Thus it is rational that the even bulkier pyrenylmethyl group prohibited chelation to zinc ion, and therefore the addition of zinc ion had almost no effect on the $^1C_4$ population of **3** (entry 6).

In the previous study for the metal ion sensor **2**, we showed that the addition of zinc(II) or manganese(II) ions caused an increase of excimer fluorescence. However, even when 100 equiv. of manganese(II) ions were added to a chloroform solution of **3**, there was almost no effect on the fluorescence spectrum (Fig. 1A). In the case of zinc(II) ions (Fig. 1B), monomer fluorescence at *ca.* 390 nm was slightly increased, whereas no significant spectral change was observed for excimer region (*ca.* 470 nm). The increase in monomer fluorescence is most likely due to fluorescence recovery from a quenching state through metal coordination to the quenching amino groups. NMR experiments predicted that compound **3** would not be an excimer fluorescence sensor for zinc ion, and this was found to be the case. We suggest that the metal ions are too large to be accommodated in the small groove of the quasi-cyclic bidentate ligand formed by pyrene stacking of compound **3** (Fig. 2).

The addition of TFA to the chloroform solution of **3** gave rise to excimer fluorescence (445 nm), which increased with the addition of TFA up to 50 equiv. but thereafter started to

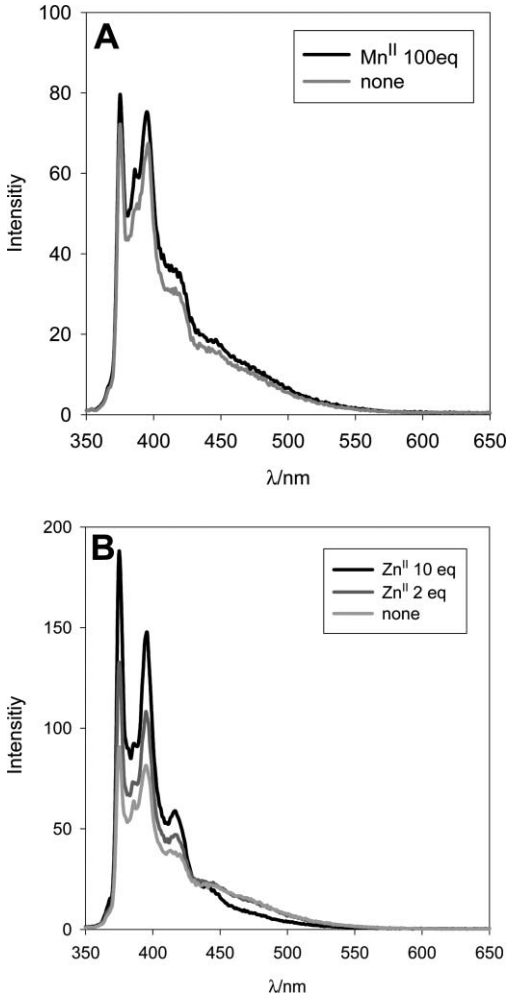


Fig. 1 Fluorescence spectral change of compound **3** (100 μM in $CHCl_3$; excitation at 347 nm) with the addition of $Mn(OAc)_2$ (A) and $ZnCl_2$ (B).

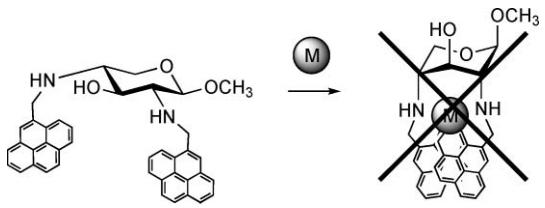


Fig. 2 A hypothetical model indicating the steric congestion caused by metal chelation of compound **3**.

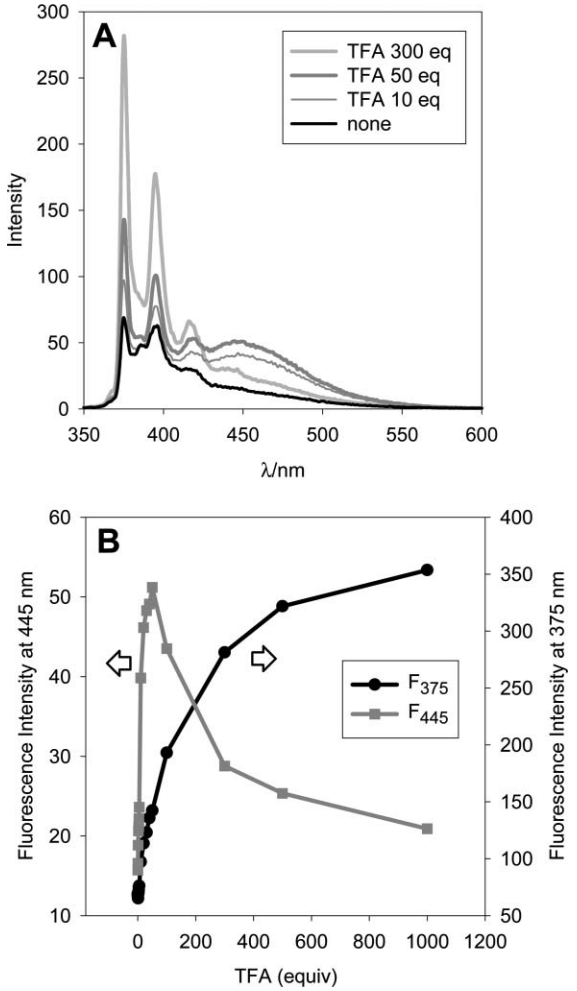


Fig. 3 The changes of fluorescence spectra (A) and fluorescence intensities at 445 and 375 nm (B) of compound **3** (100 μM in $CHCl_3$; excitation at 347 nm) with the addition of TFA.

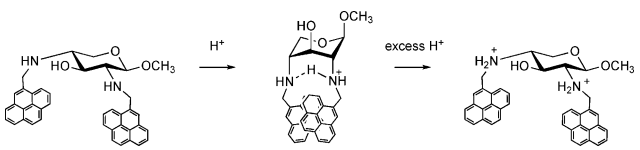


Fig. 4 Conformational changes of compound **3** by the addition of protons.

decrease (Fig. 3A). This up-and-down tendency of the excimer fluorescence intensity with acid titration has been observed with the chemosensor **2**, and therefore the mechanism is suggested to be the same: monoprotonation causes a hydrogen bridge between the two amino groups to stabilize the closed structure, whereas the repulsion between two ammonium ions derived by diprotonation destabilizes the closed structure, turning it into the open-hinge structure (Fig. 4). This proton-selective sensing was predicted from the ^{1}H NMR measurements, and can be explained by the small size of the proton that would be accommodated in the small groove of the bidentate ligand. The different behavior of **3** toward TFA in comparison with that of compound **2** was observed in the monomer fluorescence region (*ca.* 375 nm): it increased significantly with the addition of TFA. There was little change in the same fluorescence region for the previous proton sensor **2**. The significant increase in the monomer fluorescence should be the consequence of fluorescence recovery from a quenching state through protonation of the quenching amino groups. The above results suggest that both monomer fluorescence and excimer fluorescence can be used as indicators of proton concentration. Fig. 3B clearly shows that the excimer fluorescence (445 nm) is sensitive to lower proton concentration, and that the monomer fluorescence (375 nm) covers a wide range of proton concentrations. In addition to being selective for protons, the above profile of the proton sensor **3** demonstrates superiority over the previous proton sensor **2**, in that **3** could be used for a wider range of proton concentrations.

Conclusions

In this paper, we have scrutinized the effect of *N*-alkylation on the bendability of hinge sugars by ^{1}H NMR spectroscopy. As opposed to the expectation that the increased nucleophilicity of the amino group would enhance chelation to a metal ion, the increased bulkiness hampered the chelation. In contrast, the hydrogen bond bridge between the two amino groups was promoted by *N*-alkylation, probably due to the increased basicity resulting in increased bendability of the hinge sugars. We were able to construct a proton-selective sensor **3** using the above properties of an *N*-alkylated hinge sugar.

Experimental

General

All solvents and reagents used were reagent grade and, in cases where further purification was required, standard procedures were followed.[9] Solution transfers where anhydrous conditions were required were performed under dry argon using syringes. Thin-layer chromatography (TLC) was performed on precoated silica gel Merck 60-F254 plates (Art 5715) and visualized by quenching of fluorescence and/or by charring after spraying with 1% $CeSO_4$–1.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$–10% H_2SO_4. Column chromatography was performed on Merck Kieselgel 60 (Art 7734), Wako gel C-300, or Kanto Silica gel 60N (spherical, neutral) with the solvent systems specified.

Optical rotations were determined with a Horiba SEPA-200 polarimeter using a 1 dm length cell. ^{1}H NMR spectra were recorded at 400 MHz (Varian Unity-400) or 270 MHz (JEOL EX-270). Internal tetramethylsilane (δ 0 ppm) was used as a standard in $CDCl_3$, or solvent peaks were used as standards (δ 2.50 ppm in DMSO-d_6). Chemical shifts are expressed in ppm referenced to the solvent as an internal standard. Multiplicities of signals are abbreviated as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, ddd = doublet of doublets of doublets, br = broad signal, m = multiplet. ^{13}C NMR spectra were recorded at 67.8 MHz (JEOL JNM-EX-270) and solvent peaks were used as standards (δ 77.0 ppm in $CDCl_3$). High resolution mass spectra (HRMS) were recorded on Mariner Biospectrometry Workstation ESI-TOF MS.

General fluorescence experiments

Fluorescence spectra were recorded at 35 °C on a Shimadzu RF-5300PC fluorophotometer with excitation at 355 nm, sampling intervals of 2 nm, excitation band widths of 3 nm and an emission band width of 5.0. A cell with 10 mm width and 3 mm depth was used. To a thermostatted (35 °C) solution of **3** (100 μM, 1 mL) in $CHCl_3$ were dropped appropriate amounts of the solution of a metal ion (or TFA) and **3** (100 μM), and fluorescence spectra were recorded for each specified amount of the metal ion.

Synthesis of 3, 4 and 5

Methyl 2,4-di-1-pyrenylmethylamino-2,4-dideoxy-β-D-xyropyranoside, 3. To a stirred solution of **1** (29 mg, 0.18 mmol), 1-pyrenecarboxaldehyde (104 mg, 0.45 mmol) and acetic acid (0.13 mL) in methanol (8 mL) was dropped a solution of $NaB(CN)H_3$ (23 mg, 0.37 mmol) in THF (0.5 mL). After stirring for 12 h at rt, the reaction mixture was diluted with toluene, washed with water and aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$–MeOH 30 : 1) to give **3** as a pale yellow solid (96 mg, 90%): R_f, 0.48 ($CHCl_3$–MeOH 15 : 1); mp 201–203 °C; $[\alpha]_D^{22}$ −16.9 (*c* 0.15 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, Me_4Si) 8.38–7.93 (m, 18H, Ar), 4.77–4.46 (m, 4H, CH_2Ar × 2), 4.32 (d, 1H, $J_{1,2}$ 7.2 Hz, H-1), 4.19 (dd, 1H, $J_{4,5a}$ 4.6, $J_{5a,5b}$ 11.8 Hz, H-5a), 3.63 (s, 3H, OCH_3), 3.34 (dd, 1H, $J_{2,3}$ 9.0, $J_{3,4}$ 8.7 Hz, H-3), 3.26 (dd, 1H, $J_{4,5b}$ 9.6 Hz, H-5b), 2.93 (ddd, 1H, H-4), 2.72 (dd, 1H, H-2), 1.77 (br, 3H, OH, NHCH_2 × 2); δ_C (67.8 MHz, $CDCl_3$, Me_4Si) 133.9, 133.4, 131.2, 130.9, 130.8, 130.8, 129.1, 129.0, 127.8, 127.7, 125.9, 125.8, 125.1, 125.1, 125.0, 124.8, 124.7, 123.3, 123.1, 105.8, 73.7, 65.1, 63.2, 59.8, 56.8, 50.3; HRMS(ESI) Found 591.2657 [M + H]$^+$. Calcd for $C_{40}H_{35}N_2O_3$: 591.2649.

Methyl 2,4-diethylamino-2,4-dideoxy-β-D-xyropyranoside, 4. To a stirred solution of **1** (32 mg, 0.20 mmol), acetaldehyde (33.5 μL, 0.597 mmol) and acetic acid (0.27 mL) in methanol (8 mL) was dropped a solution of $NaB(CN)H_3$ (25 mg, 0.40 mmol) in THF (0.5 mL). Acetaldehyde (22.5 μL, 0.40 mmol) was each added at 3 h, 25 h and 27 h after the start of the reaction. At 46 h, the reaction mixture was neutralized with triethylamine and evaporated. The residue was chromatographed on silca gel ($CHCl_3$–MeOH 5 : 1 to *i*PrOH–H_2O–aq. NH_3 60 : 3 : 1) to give **4** as a syrup (27 mg, 62%): R_f, 0.20 (*i*PrOH–H_2O–aq. NH_3 60 : 3 : 1); $[\alpha]_D^{22}$ −64.9 (*c* 1.15 in MeOH); δ_H (400 MHz, 50 mM AcONa-d_3, pH 7.0) 4.25 (d, 1H, $J_{1,2}$ 8.1 Hz, H-1), 4.09 (dd, 1H, $J_{4,5a}$ 5.0, $J_{5a,5b}$ 11.8 Hz, H-5a), 3.52 (s, 3H, OCH_3), 3.30 (t, 1H, $J_{2,3} = J_{3,4}$ 9.8 Hz, H-3), 3.22 (dd, 1H, $J_{4,5b}$ 10.4 Hz, H-5b), (m, 2H, H-3, H-5b), 2.86–2.78 (m, 2H, H-4, NHC*H*HCH$_3$), 2.73–2.57 (m, 3H, NHCH*H*CH$_3$, NHCH_2CH$_3$), 2.39 (dd, 1H, H-2), 1.06 (q, 6H, *J* 7.1 Hz, 2 × $NHCH_2CH_3$); δ_C (67.8 MHz, CD_3OD) 105.4, 73.0, 64.4, 63.8, 59.6, 55.5, 43.2, 41.7; HRMS(ESI) Found 219.1728 [M + H]$^+$. Calcd for $C_{10}H_{23}N_2O_3$: 219.1710.

Methyl 2,4-di-benzylamino-2,4-dideoxy-β-D-xyropyranoside, 5. To a stirred solution of **1** (29 mg, 0.18 mmol), benzaldehyde (46 μL, 0.45 mmol) and acetic acid (0.13 mL) in methanol (8 mL) was dropped a solution of $NaB(CN)H_3$ (25 mg, 0.39 mmol) in THF (0.5 mL). After stirring for 12 h at rt, the reaction mixture was diluted with ethyl acetate, the solution washed with water and aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silca gel (hexane–ethyl acetate 12 : 7 to $CHCl_3$–MeOH 15 : 1) to give **5** as a syrup (44 mg, 71%): R_f, 0.49 ($CHCl_3$–MeOH 7 : 1); mp 201–203 °C; $[\alpha]_D^{22}$ −33.4 (*c* 1.51 in MeOH); δ_H (500 MHz, DMSO-d_6) 7.33–7.19 (m, 10H, Ar), 5.17 (d, 1H, $J_{3,OH}$ 5.6 Hz, OH), 4.06 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 3.94–3.70 (m, 4H, CH_2Ar × 2), 3.88 (dd, 1H, $J_{4,5a}$ 4.9, $J_{5a,5b}$ 11.4 Hz, H-5a), 3.33 (s, 3H, OCH_3), 3.12 (ddd, 1H, *J* 2,3 9.3, $J_{3,4}$ 9.4 Hz, H-3), 2.98 (dd, 1H, $J_{4,5b}$ 10.3 Hz, H-5b), 2.46 (ddd, 1H, H-4), 2.25 (dd, 1H, H-2), 2.14 (bs, 2H, NH); δ_C (67.8 MHz, $CDCl_3$) 140.4, 140.0, 128.5, 128.4, 128.2, 128.0, 127.1, 127.0, 105.3, 73.3, 65.0, 62.7, 59.1, 56.6, 52.0, 51.9; HRMS(ESI) Found 343.2011 [M + H]$^+$. Calcd for $C_{20}H_{27}N_2O_3$: 343.2022.

Acknowledgements

This work was supported by a grant from the 21st Century COE Program and a Grant-in-Aid for Scientific Research (No. 13680668) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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