Biosci. Biotechnol. Biochem., **71** (3), 741–745, 2007

Synthesis of Amino Tetrahydrofuran Lignan *via* an *N*,*O*-Heterocyclic Compound as an Intermediate

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Received October 18, 2006; Accepted November 16, 2006; Online Publication, March 7, 2007
[doi:10.1271/bbb.60575]

Tetrahydrofuran aminolignans bearing an amino group at the 8 position were synthesized *via* an *N*,*O*-heterocyclic compound that had been obtained by silylnitronate cycloaddition.

Key words: lignan; silylnitronate cycloaddition; aminolignan

Lignans are widely biosynthesized by plants, and many types of biological activity have been reported from many kinds of lignans[1,2] In the case of the cytotoxic lignan, podophyllotoxin, research on its structure-activity relationship has been performed, and podophyllotoxin derivatives containing nitrogen which had strong cytotoxic activity[3] have been synthesized. The biologically active dibenzocyclooctene derivatives containing a nitrogen atom have also been synthesized.[4] Derivatives of natural products containing nitrogen are interesting for biological research. Although the synthetic study of many kinds of lignans has also been reported,[5] there are no reports on a convenient synthesis of aminolignans except for podophyllotoxin. Synthetic study is important to develop research on the biological activity of aminolignans.

In our previous study, some tetrahydrofuran lignans of the oxidized type have been synthesized.[6–11] In this study, tetrahydrofuran aminolignans **1** and **2** were adopted as targets (Fig. 1). Tetrahydrofuran lignans having many kinds of biological activity are in one of the important groups of natural lignans and oxidized tetrahydrofuran lignans are known. These target compounds have an amino group at the 8 position. The synthesis of tetrahydrofuran lignans bearing an NH_2 group attached to a primary or secondary carbon would not be difficult to achieve by transformation from a hydroxy group. However, a compound bearing an NH_2 group attached to the tertiary carbon would be difficult. To obtain the tetrahydrofuran aminolignan structure of **1** and **2**, silylnitronate cycloaddition (Scheme 1)[12] was employed as the key reaction, giving *N*,*O*-heterocyclic compound **4**. The reduction of this *N*,*O*-heterocyclic compound **4** was considered likely to give the target compounds. The previous study has described the production of an *N*,*O*-heterocyclic compound without a 1-substituent.[12–15] To lead to the lignan structure, the presence of a 1-substituent is important, this being the reason for compound **3** being selected as a cyclization substrate. The reaction conditions for silylnitronate cycloaddition of olefin **3** bearing a hydroxymethyl group needs to be considered in this study. This article describes a convenient synthesis of an aminolignan bearing an amino group attached to the 8 position of a tetrahydrofuran lignan.

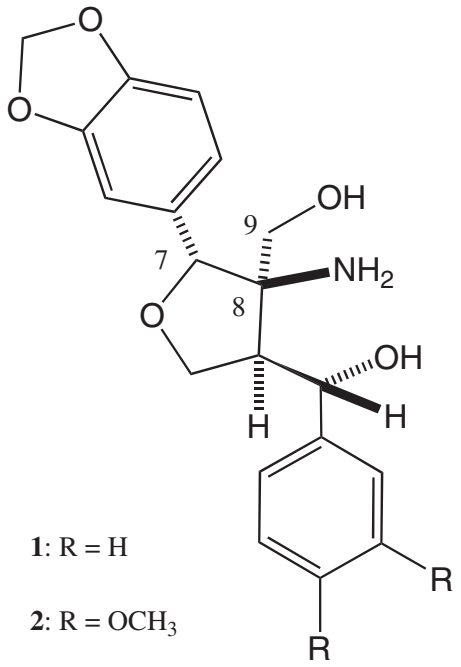

Fig. 1. Target Tetrahydrofuran Aminolignans **1** and **2** Bearing an NH_2 Group at the 8 Position.

Results and Discussion

Substrate **8** for the silyl nitronate cycloaddition

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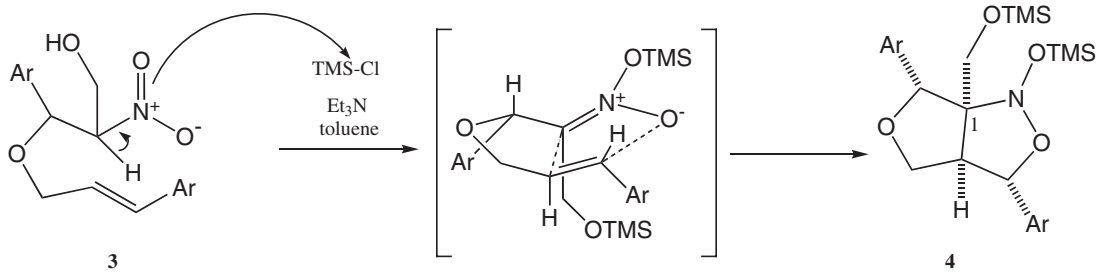
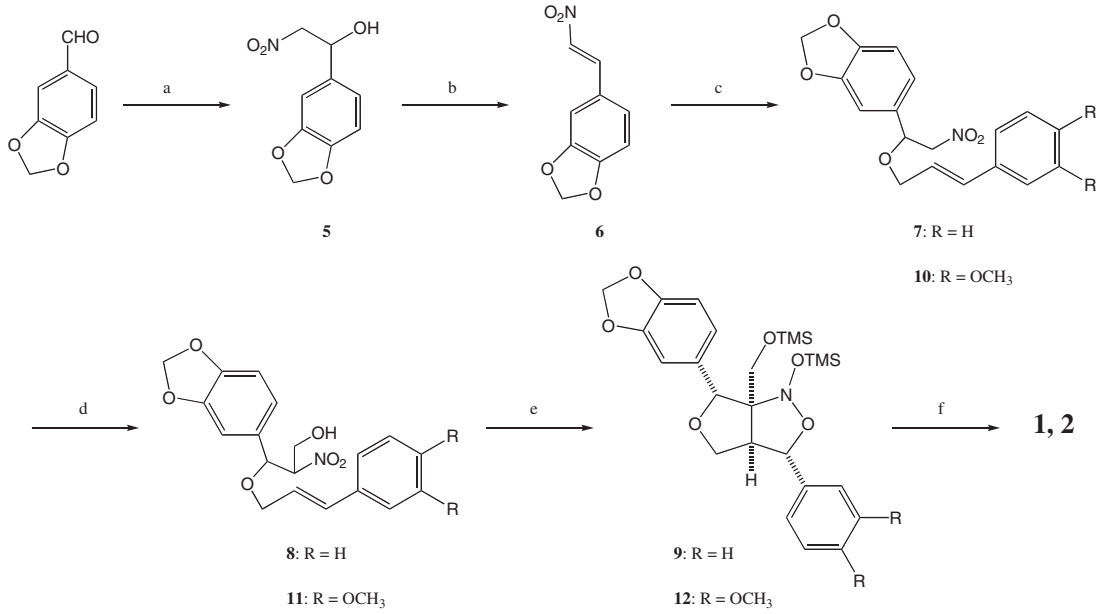


3 4

Scheme 1. Intramolecular Silyl Nitronate Cycloaddition Giving 1-Substituted 4,8-Diaryl-2-aza-3,7-dioxabicyclo[3.3.0]octane.



5 **6** **7**: R = H **10**: R = OCH_3

8: R = H **9**: R = H

11: R = OCH_3 **12**: R = OCH_3

Scheme 2. Synthesis of Tetrahydrofuran Aminolignans **1** and **2**.

(a) NaOH, CH_3NO_2, NaOH, aq. MeOH, 10–15 °C, 1 h (67% yield); (b) $KHSO_4$, toluene, reflux, 1 h (74% yield); (c) NaH, cinnamyl alcohol or 3′,4′-dimethoxycinnamyl alcohol, THF, −75 °C, 2 h (**7**, 88% yield; **10**, 62% yield); (d) $(CH_2O)_n$, KF, DMSO, r.t., 3 h (*R*f 0.16-**8**, 12% yield; *R*f 0.06-**8**, 36% yield; **11**, 46% yield); (e) Method 1, TMSCl, Et_3N, toluene, r.t., 48 h (from *R*f 0.06-**8**, 0–68% yield; from *R*f 0.16-**8**, 0% yield); Method 2, *N*,*O*-bis(trimethylsilyl)acetamide, Et_3N, CH_3CN, toluene, 85 °C, 24 h (from *R*f 0.06-**8**, 100% yield; from *R*f 0.16-**8**, 100% yield; from **11**, 79% yield); (f) $Mo(CO)_6$, $NaBH_4$, aq. CH_3CN, reflux, 10 min (**1**, 73% yield; **2**, 100% yield).

reaction was prepared from piperonal (Scheme 2). After piperonal had been exposed to a condensation reaction with nitromethane by using sodium hydroxide (67% yield), resulting alcohol **5** was subjected to dehydroxylation by treatment with $KHSO_4$ in refluxing toluene to give alkene **6**[16] in 74% yield. The 1,4-addition of cinnamyl alcohol to nitroalkene **6** was achieved by using NaH, giving nitro compound **7** in 88% yield. Substrate **8** for the silylnitronate cycloaddition reaction was obtained as two separable diastereomers (*R*f 0.06, silica gel, EtOAc/hexane = 1/6; and *R*f 0.16, silica gel, EtOAc/hexane = 1/6) by the condensation reaction of nitro compound **7** with paraformaldehyde using KF in DMSO in 48% yield. Due to its instability, this substrate was immediately used for the next intramolecular cyclization reaction.

The intramolecular silylnitronate cycloaddition reaction of one of the diastereomers of **8** (*R*f 0.06) was initially attempted by using chlorotrimethylsilane and triethylamine in toluene. *N*,*O*-heterocyclic compound **9** was sometimes obtained in 68% maximum yield, although there was little reproducibility. In most cases, decomposed products containing piperonal were yielded, giving no desired product. The other diastereomer of **8** (*R*f 0.16) did not produce *N*,*O*-heterocyclic compound **9** by this method. It was assumed that the instability of the trimethylsilyl ether of the cyclization intermediate or desired compound caused decomposition. However, the adoption of chlorotriethylsilane did not improve the yield, while the use of the other bases, pyridine and *N*,*N*,-diisopropylethylamine, did not give desired *N*,*O*-heterocyclic compound **9**. On the presumption that the hydrochloric acid salt of the base would decompose the intermediate or desired cyclic compound, *N*,*O*-bis(trimethylsilyl)acetamide was employed instead of chlorotrimethylsilane[17] as an alternative method. This attempt succeeded, namely, the important synthetic intermediate, *N*,*O*-heterocyclic compound **9**, was obtained in a

quantitative yield by a treatment with *N*,*O*-bis(trimethylsilyl)acetamide and triethylamine in heated toluene–CH_3CN (10:1). Compound **9** having the same stereochemistry was obtained from both diastereomers of **8**. The steric configuration of **9** was determined by a differential NOE experiment. The presence of NOE between both benzylic positions revealed the *cis* form, no production of the *trans* form being apparent. The silylnitronate cycloaddition which gave a 4,8-diaryl-2-aza-3,7-dioxabicylo[3.3.0]octane structure bearing the 1-substituent was achieved stereoselectively by treatment of the acyclic substance with *N*,*O*-bis(trimethylsilyl)acetamide and triethylamine. Finally, reduction with $Mo(CO)_6$ and $NaBH_4$[18,19] gave aminolignan **1** in 71% yield. Aminolignan **2** was also obtained by the same synthetic method. In this synthetic process, substrate **11** for cyclization was obtained as a single isomer. The production of many by-products was observed in the reaction of **10** with formaldehyde.

Aminolignans **1** and **2** were synthesized by 7 steps in 15% and 11% overall yields, respectively. As the key reaction, silyl nitronate cycloaddition was employed, giving the important intermediate, *N*,*O*-heterocyclic compound **4**. This is first example of silylnitronate cycloaddition giving 4,8-diaryl-2-aza-3,7-dioxabicylo[3.3.0]octane bearing the 1-substituent. This is also a convenient new synthetic method for producing an amino tetrahydrofuran lignan, in which the amino group is attached to the tertiary carbon (8 position).

Experimental

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer, and EIMS data were measured with a JMS-MS700V spectrometer. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh). The numbering of compounds follows the IUPAC nomenclatural rules.

*1-(3,4-Methylenedioxyphenyl)-2-nitro-1-ethanol (**5**).* To an ice-cooled solution of piperonal (54.0 g, 0.36 mol) in methanol (300 ml) was added an aqueous solution of sodium hydroxide (17.3 g, 0.43 mol) in H_2O (35 ml) and nitromethane (25.0 ml, 0.46 mol) at 10–15 °C. The reaction solution was stirred at 10–15 °C for 1 h, and then a sat. aq. NH_4Cl solution was added. After the resulting mixture was filtered, the crude crystals were washed with water, dried, and then recrystallized from benzene to give nitro compound **5** (50.3 g, 0.24 mol, 67%) as yellowish crystals, mp 85–86 °C. NMR δ_H ($CDCl_3$): 2.81 (1H, d, J = 3.4 Hz, OH), 4.46 (1H, dd, J = 13.3, 3.2 Hz, C*H*HNO_2), 4.57 (1H, dd, J = 13.3, 9.3 Hz, CH*H*NO_2), 5.37 (1H, m, ArC*H*OH), 5.98 (2H, s, OCH_2O), 6.80–6.89 (3H, m, ArH). NMR δ_C ($CDCl_3$): 70.8, 81.2, 101.4, 106.3, 108.6, 119.6, 132.0, 148.1, 148.2. *Anal.* Found: C, 51.14; H, 4.25; N, 6.72%. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63%.

*(E)-1-(3,4-Methylenedioxyphenyl)-2-nitroethene (**6**).* A reaction mixture of benzyl alcohol **5** (4.43 g, 0.021 mmol) and $KHSO_4$ (2.85 g, 0.021 mol) in toluene (80 ml) was heated under refluxing for 1 h before addition of H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by recrystallization (MeOH) gave alkene **6** (3.09 g, 0.016 mol, 74%) as yellowish crystals, mp 140–141 °C. NMR δ_H (acetone-d_6): 6.13 (2H, s, OCH_2O), 6.97 (1H, d, J = 8.3 Hz, ArH), 7.33–7.39 (2H, m, ArH), 7.87 (1H, d, J = 13.7 Hz, 1-H), 8.01 (1H, d, J = 13.7 Hz, 2-H). NMR δ_C ($CDCl_3$): 103.6, 108.5, 110.1, 126.0, 128.5, 137.3, 140.2, 150.2, 152.7. *Anal.* Found: C, 55.86; H, 3.68; N, 7.24%. Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25%.

*1-Cinnamyloxy-1-(3,4-methylenedioxyphenyl)-2-nitroethane (**7**).* To a suspension of NaH (0.20 g, 60% in mineral oil, 5.00 mmol), which was washed with hexane, in THF (10 ml) was added a solution of cinnamyl alcohol (0.70 g, 5.22 mmol) in THF (20 ml) at 10–15 °C, and then the mixture was stirred for 1 h at room temperature. After the solution was cooled to −75 °C, alkene **6** (0.50 g, 2.59 mmol) in THF (20 ml) was added. The reaction mixture was stirred for 2 h at −78 °C, and then sat. aq. NH_4Cl was added. The aqueous solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave nitro compound **7** (0.75 g, 2.29 mmol, 88%) as a yellowish oil. NMR δ_H ($CDCl_3$): 3.97 (1H, dd, J = 12.5, 6.6 Hz, ArCH=CHC*H*HO), 4.14 (1H, ddd, J = 12.5, 5.4, 1.5 Hz, ArCH=CHCH*H*O), 4.37 (1H, dd, J = 12.7, 3.4 Hz, C*H*HNO_2), 4.63 (1H, dd, J = 12.7, 9.8 Hz, CH*H*NO_2), 5.09 (1H, dd, J = 9.8, 3.4 Hz, ArCH), 5.98 (2H, s, OCH_2O), 6.18 (1H, m, ArCH=C*H*), 6.50 (1H, d, J = 15.6 Hz, ArC*H*=CH), 6.81–6.87 (3H, m, ArH), 7.22–7.36 (5H, m, ArH). NMR δ_C ($CDCl_3$): 69.4, 77.0, 80.3, 101.4, 106.9, 108.6, 120.8, 124.9, 126.5, 127.8, 128.5, 130.0, 133.1, 136.4, 148.3, 148.4. *Anal.* Found: C, 66.32; H, 5.29; N, 4.17%. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28%.

*1-[(E)-3-(3,4-Dimethoxyphenyl)-2-propenyloxy]-1-(3,4-methylenedioxyphenyl)-2-nitroethane (**10**).* 62% yield, a yellowish oil. NMR δ_H ($CDCl_3$): 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.89–3.98 (1H, overlapped, ArCH=CHC*H*H), 4.13 (1H, m, ArCH=CHCH*H*O), 4.37 (1H, dd, J = 12.7, 3.4 Hz, C*H*HNO_2), 4.62 (1H, dd, J = 12.7, 10.4 Hz, CH*H*NO_2), 5.09 (1H, dd, J = 9.8, 3.4 Hz, ArCHOR), 5.98 (2H, s, OCH_2O), 6.05 (1H, m, ArCH=C*H*), 6.44 (1H, d, J = 15.6 Hz, ArC*H*=CH), 6.79–6.92 (6H, m, ArH). NMR δ_C ($CDCl_3$): 55.8, 55.9, 69.5, 76.9, 80.4, 101.4, 106.9, 108.6, 108.9, 111.1, 119.8, 120.8, 121.9, 122.9, 129.5, 130.1, 133.1, 148.4, 149.0, 149.1. *Anal.* Found: C, 61.85; H, 5.47; N, 3.59%. Calcd. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62%.

*3-Cinnamyloxy-3-(3,4-methylenedioxyphenyl)-2-nitro-1-propanol (**8**).* A reaction mixture of nitro compound **7** (1.00 g, 3.05 mmol), KF (0.18 g, 3.10 mmol), and paraformaldehyde (0.60 g) in DMSO (20 ml) was stirred at room temperature for 3 h, and then sat. aq. NH_4Cl and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc/hexane = 1/6) gave hydroxymethyl nitro compound **8** (*R*f 0.16, silica gel, EtOAc/hexane = 1/6, 0.13 g, 0.36 mmol, 12%) as a yellowish oil and **8** (*R*f 0.06, silica gel, EtOAc/hexane = 1/6, 0.39 g, 1.09 mmol, 36%) as a yellowish oil. Because both diastereomers were unstable, these compounds were immediately used for the next reaction. *R*f (0.16)-**8**, NMR δ_H ($CDCl_3$): 2.38 (1H, br. s, OH), 3.95 (1H, ddd, J = 12.5, 6.8, 1.5 Hz, ArCH=CHC*H*H), 4.10 (1H, m, HOC*H*H), 4.15 (1H, ddd, J = 12.5, 5.5, 1.5 Hz, ArCH=CHCH*H*), 4.30 (1H, m, HOCH*H*), 4.67 (1H, m, $CHNO_2$), 4.99 (1H, d, J = 6.8 Hz, ArCHOR), 5.98 (2H, s, OCH_2O), 6.17 (1H, m, ArCH=C*H*), 6.51 (1H, d, J = 15.6 Hz, ArC*H*=CH), 6.75–6.89 (3H, m, ArH), 7.23–7.42 (5H, m, ArH). NMR δ_C ($CDCl_3$): 60.4, 69.8, 78.9, 92.4, 101.4, 107.0, 108.5, 121.0, 124.4, 126.5, 127.8, 128.5, 128.6, 129.7, 133.6, 136.2, 148.2. *R*f (0.06)-**8**. NMR δ_H ($CDCl_3$): 1.99 (1H, br. s, OH), 3.71 (2H, m, HOCH_2), 3.90 (1H, dd, J = 12.2, 6.8 Hz, ArCH=CHC*H*HO), 4.10 (1H, dd, J = 12.2, 5.1 Hz, ArCH=CHCH*H*O), 4.77 (1H, ddd, J = 9.8, 6.3, 3.4 Hz, $CHNO_2$), 4.89 (1H, d, J = 9.8 Hz, ArCHOR), 6.00 (2H, s, OCH_2O), 6.12 (1H, m, ArCH=C*H*), 6.46 (1H, d, J = 16.1 Hz, ArC*H*=CH), 6.69–6.90 (3H, m, ArH), 7.22–7.36 (5H, m, ArH). NMR δ_C ($CDCl_3$): 61.1, 69.2, 78.1, 93.1, 101.4, 107.3, 108.6, 121.6, 124.8, 126.6, 127.8, 128.5, 133.2, 136.4, 148.5.

*1-[(E)-3-(3,4-Dimethoxyphenyl)-2-propenyloxy]-1-(3,4-methylenedioxyphenyl)-2-nitro-1-propanol (**11**).* 46% yield, a yellowish oil. NMR δ_H ($CDCl_3$): 1.98 (1H, br. s), 3.70–3.73 (2H, m, HOCH_2), 3.86–3.92 (1H, overlapped, ArCH=CHC*H*HO), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 4.08 (1H, ddd, J = 12.5, 5.6, 1.0 Hz, ArCHCHCH*H*O), 4.76 (1H, ddd, J = 9.8, 6.4, 3.4 Hz, $CHNO_2$), 4.88 (1H, d, J = 9.8 Hz, ArCHOR), 5.99 (2H, s, OCH_2O), 5.94–6.03 (1H, overlapped, ArCH=C*H*), 6.39 (1H, d, J = 15.9 Hz, ArC*H*=CH), 6.79–6.91 (6H, m, ArH). NMR δ_C ($CDCl_3$): 55.9, 56.0, 61.2, 69.5, 78.2, 93.2, 101.5, 107.4, 108.7, 109.0, 111.2, 120.0, 121.7, 122.9, 129.6, 129.6, 133.2, 148.6, 149.1.

(1R,4S*,5R*,8R*)-8-(3,4-Methylenedioxyphenyl)-4-phenyl-2-(trimethylsilyloxy)-1-(trimethylsilyloxy)methyl-2-aza-3,7-dioxabicyclo[3.3.0]octane (**9**).* Method 1: A reaction mixture of a solution of hydroxymethyl nitro compound **8** (*R*f 0.06, 1.56 g, 4.37 mmol), TMSCl (3.12 ml, 24.4 mmol), and Et_3N (2.80 ml, 20.1 mmol) in toluene (20 ml) was stirred at room temperature for 48 h under N_2 gas, and then H_2O and EtOAc were added. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (5% EtOAc/hexane) gave *N*,*O*-hetero compound **9** (1.50 g, 2.99 mmol, 68%) as colorless crystals, mp 108–110 °C (*iso*-Pr_2O). Method 2: A reaction solution of hydroxymethyl nitro compound **8** (*R*f 0.06, 0.30 g, 0.84 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (0.80 ml, 3.27 mmol), and Et_3N (0.08 ml, 0.57 mmol) in toluene (5 ml) and MeCN (0.5 ml) was stirred at 85 °C for 24 h under N_2 gas. After additions of H_2O and EtOAc, the organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (5% EtOAc/hexane) gave **9** (0.42 g, 0.84 mmol, 100%). From diastereomer **8** (*R*f 0.16), **9** was also obtained in 100% yield. NMR δ_H ($CDCl_3$): −0.10 (9H, s, $Si(CH_3)_3$), 0.14 (9H, s, $Si(CH_3)_3$), 3.38 (1H, d, J = 10.1 Hz, TMSOC*H*H), 3.46 (1H, m, 5-H), 3.69 (1H, d, J = 10.1 Hz, TMSOCH*H*), 4.20 (1H, d, J = 8.3 Hz, 6-*H*H), 4.46 (1H, dd, J = 8.3, 5.9 Hz, 6-H*H*), 5.03 (1H, s, 8-H), 5.27 (1H, d, J = 5.4 Hz, 4-H), 5.91 (1H, d, J = 14.2 Hz, OC*H*HO), 5.96 (1H, d, J = 14.2 Hz, OCH*H*O), 6.77 (1H, d, J = 7.8 Hz, ArH), 6.91 (1H, d, J = 8.8 Hz, ArH), 7.00 (1H, s, ArH), 7.25–7.36 (3H, m, ArH), 7.52–7.54 (2H, m, ArH). NMR δ_C ($CDCl_3$): −1.09, −0.46, 56.5, 60.9, 73.6, 84.0, 89.4, 92.9, 100.7, 107.2, 107.5, 119.2, 127.3, 127.5, 128.1, 132.6, 141.9, 146.5, 147.0. *Anal.* Found: C, 59.90; H, 6.90; N, 2.81%. Calcd. for $C_{25}H_{35}NO_6Si_2$: C, 59.85; H, 7.03; N, 2.79%.

(1R,4S*,5R*,8R*)-4-(3,4-Dimethoxyphenyl)-8-(3,4-methylenedioxyphenyl)-2-(trimethylsilyloxy)-1-(trimethylsilyloxy)methyl-2-aza-3,7-dioxabicyclo[3.3.0]octane (**12**).* 79% yield, colorless crystals, mp 105 °C (*iso*-Pr_2O). NMR δ_H ($CDCl_3$): −0.08 (9H, s, $Si(CH_3)_3$), 0.17 (9H, s, $Si(CH_3)_3$), 3.40 (1H, d, J = 10.1 Hz, TMSOC*H*H), 3.41 (1H, m, 5-H), 3.71 (1H, d, J = 10.1 Hz, TMSOCH*H*), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.19 (1H, d, J = 8.4 Hz, 6-*H*H), 4.42 (1H, dd, J = 8.4, 5.5 Hz, 6-H*H*), 5.04 (1H, s, 8-ArCH), 5.20 (1H, d, J = 6.2 Hz, 4-ArCH), 5.93 (1H, d, J = 5.8 Hz, OCH*H*O), 5.94 (1H, d, J = 5.8 Hz, OCH*H*O), 6.77 (1H, d, J = 8.1 Hz, ArH), 6.81 (1H, d, J = 8.2 Hz, ArH), 6.92 (1H, d, J = 7.8 Hz, ArH), 6.97–7.00 (2H, m, ArH), 7.24 (1H, d, J = 1.8 Hz, ArH). NMR δ_C ($CDCl_3$): −1.13, −0.39, 55.8, 55.9, 56.6, 60.8, 73.2, 83.7, 89.2, 93.3, 100.7, 107.2, 107.4, 110.4, 110.9, 119.2, 119.8, 132.4, 134.0, 146.5, 147.0, 148.7, 149.0. EIMS m/z: 561 (M^+, 73), 239 (100). HRMS (EI) m/z (M^+): calcd. for $C_{27}H_{39}NO_8Si_2$, 561.2214; found, 561.2213.

(2R,3R*,4R*)-3-Amino-3-hydroxymethyl-4-[(S*)-(hydroxy)(phenyl)methyl]-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (**1**).* To a solution of 2-aza-3,7-dioxabicyclo[3.3.0]octane **9** (1.00 g, 1.99 mmol) in MeCN (20 ml) and H_2O (1 ml) were added $Mo(CO)_6$ (0.20 g, 0.76 mmol) and $NaBH_4$ (0.30 g, 7.93 mmol). After the reaction mixture was heated under refluxing for 10 min, the mixture was cooled by ice for 1 h. The resulting

solid inorganic by-products were filtered off. Concentration of the filtrate, followed by silica gel column chromatography (EtOAc) gave aminolignan **1** (0.50 g, 1.46 mmol, 73%) as colorless crystals, mp 132–134 °C ($CHCl_3$). NMR δ_H (C_5D_5N): 2.97 (1H, ddd, J = 10.0, 10.0, 7.8 Hz, 4-H), 3.61 (1H, d, J = 10.5 Hz, C*H*HOH), 3.68 (1H, d, J = 10.5 Hz, CH*H*OH), 3.79 (1H, dd, J = 10.7, 8.8 Hz, 5-*H*H), 3.89 (1H, dd, J = 10.7, 8.8 Hz, 5-H*H*), 5.04 (1H, s, 2-H), 5.21 (1H, d, J = 9.8 Hz, ArC*H*OH), 5.93 (2H, s, OCH_2O), 6.90 (1H, d, J = 8.3 Hz, ArH), 7.09 (1H, dd, J = 8.3, 1.5 Hz, ArH), 7.27 (1H, d, J = 1.5 Hz, ArH), 7.30–7.34 (1H, m, ArH), 7.38–7.57 (2H, m, ArH), 7.62–7.64 (2H, m, ArH). NMR δ_C (C_5D_5N): 55.0, 65.7, 68.9, 70.3, 72.0, 91.8, 101.4, 107.7, 108.1, 120.2, 127.3, 127.9, 128.7, 134.0, 145.2, 147.3, 147.9. *Anal.* Found: C, 66.23; H, 6.18; N, 4.05%. Calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08%.

(2R,3R*,4R*)-3-Amino-3-hydroxymethyl-4-[(S*)-(hydroxy)(3,4-dimethoxyphenyl)methyl]-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (**2**).* 100% yield, colorless crystals, mp 130–131 °C (acetone). NMR δ_H (C_5D_5N): 3.05 (1H, ddd, J = 10.0, 10.0, 7.9 Hz, 4-*H*H), 3.62 (1H, d, J = 10.5 Hz, C*H*HOH), 3.70 (1H, d, J = 10.5 Hz, CH*H*OH), 3.74 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.88–3.97 (2H, m, 5-H_2), 5.07 (1H, s, 2-H), 5.23 (1H, d, J = 9.7 Hz, ArC*H*OH), 5.95 (2H, s, OCH_2O), 6.91 (1H, d, J = 7.9 Hz, ArH), 6.96 (1H, d, J = 8.2 Hz, ArH), 7.12 (1H, dd, J = 7.9, 1.3 Hz, ArH), 7.18 (1H, dd, J = 8.2, 1.9 Hz, ArH), 7.29 (1H, d, J = 1.3 Hz, ArH), 7.37 (1H, d, J = 1.9 Hz, ArH). NMR δ_C (C_5D_5N): 55.0, 55.8, 55.9, 65.6, 69.0, 70.4, 72.0, 91.9, 101.4, 107.8, 108.1, 111.3, 112.2, 119.5, 120.3, 134.0, 137.8, 147.4, 148.0, 149.5. EIMS m/z: 403 (M^+, 81), 235 (97), 167 (100), 139 (71). HRMS (EI) m/z (M^+): calcd. for $C_{21}H_{25}NO_7$, 403.1632; found, 403.1635.

Acknowledgments

We measured the 400 MHz NMR and MS data at INCS of Ehime University. We are grateful to Marutomo Co. for financial support.

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