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Note

Stereoselective Synthesis of the Optically Active Samin Type of Lignan from L-Glutamic Acid

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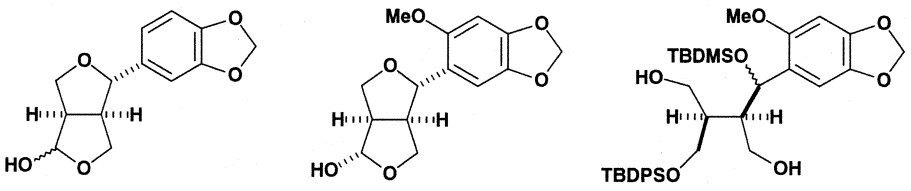
The optically active samin type of lignan, (1*R*,2*S*,5*R*,6*S*)-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ol, was stereoselectively synthesized from L-glutamic acid *via* (2*R*,3*R*)-2-[(1*S* and *R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-3-[(*tert*-butyldiphenylsilyl)oxy]methyl-1,4-butanediol.

Key words: lignan; furofuran lignan; samin

It has been reported that the furofuran type of lignan acted on cAMP metabolism.[1] The samin (**1**) type of lignan, which is a 2-oxidized furofuran lignan, can also be expected to have interesting biological activity. However, only a few reports about the synthesis of samin have been found, presenting the synthesis of an optically active compound from sesamolin,[2] diethyl L-tartrate,[3] and a chiral selenium compound,[4] and the synthesis of a racemate by employing the Ireland-Claisen rearrangement.[5] This report describes the stereoselective synthesis of optically active samin type of lignan **2** from L-glutamic acid. Since we have already synthesized 1,2-oxidized furofuran lignan from L-glutamic acid,[6] this result also shows the possibility for stereoselective synthesis of some types of furofuran lignans from L-glutamic acid. It has been reported that the samin type of lignan was an intermediate for the synthesis of 2-aryloxy furofuran lignan.[3,7] Samin type of lignan **2** can be expected to be a key intermediate in the synthesis of 1-deoxyphrymalolin, which is an important phrymalolin[1] derivative, to examine the effect of a hydroxy group on biological activity. Diol **3**, which had been obtained from L-glutamic acid[6] by 15 steps in 7–8% overall yield, was used as the starting material (Fig.).

Erythro and *threo* diol **3** were treated with boron trifluoride diethyl etherate in dichloromethane to give tetrahydrofuran derivative **4** in 84% and 87% yields, respectively. After desilylation with tetrabutylammonium fluoride (98% yield), resulting diol **5** underwent selective oxidation by dihydridotetrakis(triphenylphosphine)ruthenium (II)[8] to give two lactones: one was desired lactone **6** (39%) and the other was undesired lactone **7** (18%). The hydroxymethyl group at the 4 position of **5** was preferentially oxidized over the hydroxymethyl group at the 3 position in a 2:1 ratio. This selectivity was due to steric hindrance of the phenyl group at the 2 position. Undesired lactone **7** was transformed to diol **5** by diisobutylaluminum hydride and sodium borohydride reduction in 58% yield. Samin type of lignan **2** was obtained from desired lactone **6** by diisobutylaluminum hydride reduction in 70% yield. The presence of NOE between the 2-H and 8β-H positions confirmed that the stereochemistry of the 2 position was *S*. The fact that NOE was observed between 6-H and 4β, 8β-H revealed the stereochemistry at the 6 position as *S* (Scheme).

The samin type of lignan, (1*R*,2*S*,5*R*,6*S*)-6-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ol (**2**), was synthesized from (2*R*,3*R*)-2-[(1*S* and *R*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-(2-methoxy-4,5-methylenedioxyphenyl)methyl]-3-



Samin (1) 2 3

Fig.

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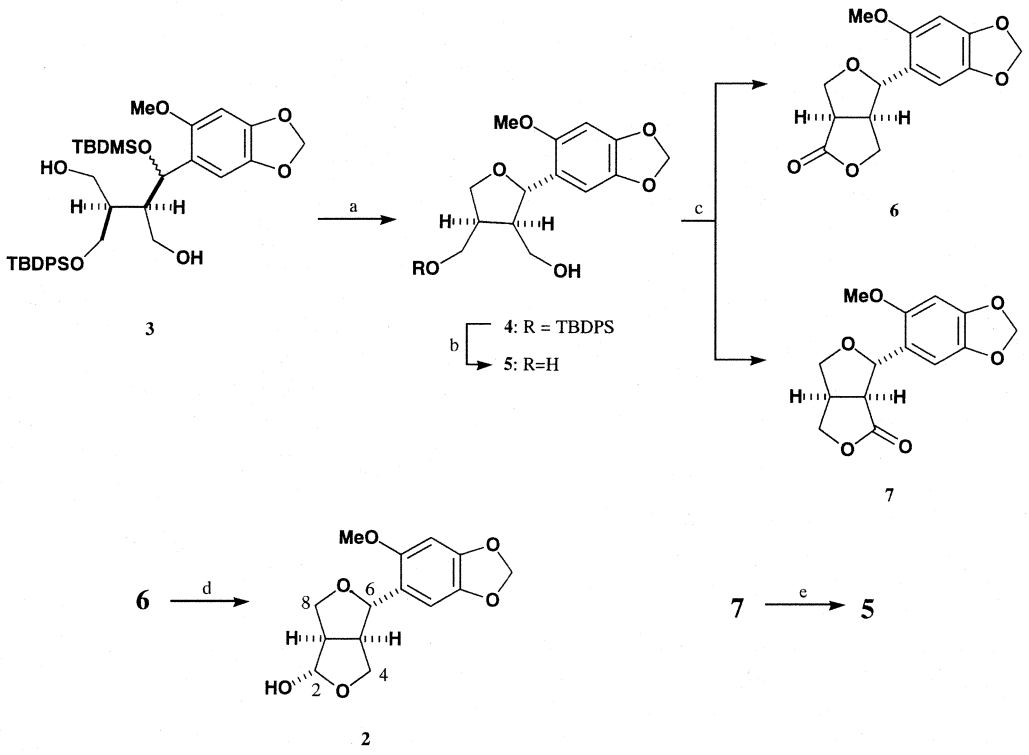

Scheme. Synthesis of Samin Type of Lignan **2**.

(a) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0°C, 30 min (84% yield from *erythro*, 87% yield from *threo*). (b) *n*-Bu_4NF, THF, r.t., 1 h (98% yield). (c) $RuH_2(PPh_3)_4$, acetone, toluene, reflux, 1.5 h (**6**: 39% yield, **7**: 18% yield). (d) DIBAL-H, toluene, −75°C, 1 h (70% yield). (e) (1) DIBAL-H, toluene, −75°C, 1 h; (2) $NaBH_4$, EtOH, r.t., 2 h (58% yield, 2 steps).

[(*tert*-butyldiphenylsilyl)oxy]methyl-1,4-butanediol (**3**), which had been obtained from L-glutamic acid,[6] by 4 steps in 24–28% yield.

Materials and Methods

All melting point (mp) data are uncorrected. NMR data were measured by a JNM-EX400 spectrometer. EIMS and FABMS data were measured with Hitachi M-80B and JEOL HX-110 spectrometers, respectively, and optical rotation was evaluated with HORIBA SEPA-200 equipment. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh), and preparative TLC was conducted with Merck silica gel 60 F_{254} (0.5 mm thickness, 20 × 20 cm).

(2S,3R,4R)-4-[(tert-Butyldiphenylsilyl)oxy]methyl-3-hydroxymethyl-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**4**). To a solution of *erythro* diol **3** (0.20 g, 0.32 mmol) in CH_2Cl_2 (36 ml) was added $BF_3 \cdot OEt_2$ (29 μl, 0.23 mmol) at 0°C, and then the resulting reaction mixture was stirred at 0°C for 30 min before addition of saturated aqueous $NaHCO_3$ solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc / hexane = 1 / 5) gave tetrahydrofuran **4** (0.14 g, 0.27 mmol, 84%) as a colorless oil. Tetrahydrofuran **4** was also obtained from *threo* diol **3** by the same method in 87% yield. $[\alpha]_D^{20} = +9.83$ (*c*1.12, $CHCl_3$). NMR δ_H ($CDCl_3$): 1.07 (9H, s), 2.39 (1H, ddd, J = 13.2, 6.8 Hz), 2.67 (1H, m), 3.09 (1H, dd, J = 4.7, 4.7 Hz), 3.65–3.77 (3H, m), 3.77 (3H, s), 3.82–3.89 (1H, m), 3.91 (1H, dd, J = 8.8, 8.8 Hz), 4.14 (1H, dd, J = 8.8, 7.3 Hz), 4.97 (1H, d, J = 6.8 Hz), 5.90 (2H, s), 6.50 (1H, s), 6.88 (1H, s), 7.40–7.45 (6H, m), 7.65–7.69 (4H, m). NMR δ_C ($CDCl_3$): 19.11, 26.82, 43.61, 52.21, 56.46, 60.97, 62.89, 70.52, 94.52, 101.13, 106.44, 123.31, 127.85, 129.93, 129.95, 132.77, 132.82, 135.54, 135.60, 141.52, 147.23, 151.19. IR ν_{max} ($CHCl_3$): 3472, 3075–2861, 1505, 1485, 1472, 1466, 1428, 1221, 1211, 1192, 1159, 1113, 1082, 1053, 1042, 704 cm^{-1}. EIMS *m/z* (20 eV): 520 (M^+, 29), 199 (94), 191 (46), 165 (100). *Anal.* Found: C, 69.01; H, 6.92%. Calcd. for $C_{30}H_{36}O_6Si$: C, 69.20; H, 6.97%.

(2S,3R,4S)-3,4-Bis(hydroxymethyl)-2-(2-methoxy-4,5-methylenedioxyphenyl)tetrahydrofuran (**5**). To a solution of silyl ether **4** (0.21 g, 0.40 mmol) in THF (10 ml) was added *n*-Bu_4NF (0.47 ml, 1 M in THF, 0.47 mmol). The reaction solution was stirred at room temperature for 1 h before addition of a saturated aqueous NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel column chromatography (EtOAc / hexane = 1 / 2) gave diol **5** (0.11 g, 0.39 mmol, 98%) as a colorless

oil. $[\alpha]_D^{20} = +10.34$ (c0.77, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.26 (1H, ddd, J=14.9, 7.8, 4.9 Hz), 2.64 (1H, m), 3.20–3.64 (2H, br.), 3.69–3.73 (2H, m), 3.78 (3H, s), 3.78–3.80 (2H, m), 3.85 (1H, dd, J=11.7, 8.7 Hz), 4.22 (1H, dd, J=8.5, 7.6 Hz), 4.95 (1H, d, J=7.8 Hz), 5.90 (1H, d, J=1.5 Hz), 5.91 (1H, d, J=1.5 Hz), 6.52 (1H, s), 6.91 (1H, s). NMR δ_C ($CDCl_3$): 43.54, 51.83, 56.59, 60.11, 61.21, 70.04, 76.32, 94.51, 101.16, 106.22, 122.59, 141.66, 147.27, 151.12. IRν_{max} ($CHCl_3$): 3386, 3027–2842, 1505, 1485, 1466, 1428, 1275, 1231, 1192, 1159, 1084, 1042, 1007, 938, 868. EIMS m/z (20 eV): 282 (M^+, 100), 181 (58), 180 (66). HRMS (EI) m/z (M^+): Calcd. for $C_{14}H_{18}O_6$, 282.1101; found, 282.1099.

(1R,5R,6S)-6-(2-Methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one (**6**) and *(1S,5R,8S)-8-(2-methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-one* (**7**). A reaction mixture of diol **5** (94 mg, 0.33 mmol) and $RuH_2(PPh_3)_4$ (59 mg, 0.051 mmol) in toluene (4 ml) and acetone (0.5 ml) was heated under refluxing conditions for 1.5 h. After the concentration, the residue was applied to silica gel column chromatography (EtOAc/hexane=1/2) to give **6** (37 mg, 0.13 mmol, 39%) as colorless crystals, mp 101–103°C, and **7** (17 mg, 0.061 mmol, 18%) as colorless crystals, mp 161–163°C. **6**. $[\alpha]_D^{20} = +59.25$ (c0.27, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.00 (1H, m), 3.34 (1H, m), 3.78 (3H, s), 4.28 (1H, dd, J=8.8, 3.9 Hz), 4.31 (1H, dd, J=8.8, 8.8 Hz), 4.49 (1H, dd, J=8.3, 7.3 Hz), 4.56 (1H, dd, J=8.3, 2.1 Hz), 5.04 (1H, d, J=5.9 Hz), 5.92 (2H, s), 6.53 (1H, s), 6.88 (1H, s). NMR δ_C ($CDCl_3$): 46.31, 48.38, 56.18, 70.42, 71.38, 82.64, 94.44, 101.29, 105.47, 121.19, 133.35, 141.40, 151.30, 178.37. IRν_{max} ($CHCl_3$): 3029–2842, 1771, 1505, 1483, 1466, 1429, 1192, 1173, 1042 cm^{-1}. EIMS m/z (20 eV): 278 (M^+, 100), 193 (18), 180 (28), 165 (52). HRMS (EI) m/z (M^+): Calcd. for $C_{14}H_{14}O_6$, 278.0790; found, 278.0791. **7**. $[\alpha]_D^{20} = +45.19$ (c0.18, $CHCl_3$). NMR δ_H ($CDCl_3$): 3.26 (1H, m), 3.38 (1H, dd, J=9.0, 2.2 Hz), 3.82 (3H, s), 3.84 (1H, dd, J=9.5, 2.2 Hz), 4.22 (1H, dd, J=9.5, 2.2 Hz), 4.35 (1H, dd, J=8.8, 7.8 Hz), 4.46 (1H, dd, J=8.8, 7.3 Hz), 5.49 (1H, d, J=2.2 Hz), 5.92 (2H, s), 6.55 (1H, s), 6.79 (1H, s). NMR δ_C($CDCl_3$): 40.46, 51.55, 56.40, 70.83, 73.34, 80.15, 94.93, 101.27, 106.47, 120.85, 141.02, 147.87, 151.97, 177.29. IRν_{max} ($CHCl_3$): 3023–2857, 1775, 1505, 1485, 1464, 1428, 1194, 1173, 1042. EIMS m/z (20 eV): 278 (M^+, 100), 247 (15), 179 (41), 165 (39). HRMS (EI) m/z (M^+): Calcd. for $C_{14}H_{14}O_6$, 278.0790; found, 278.0799.

Conversion of furofuranone **7** *to diol 5*. To a solution of furofuranone **7** (10 mg, 0.036 mmol) in toluene (5 ml) was added *iso*-Bu_2AlH (0.15 ml, 1 M solution in toluene, 0.15 mmol) at −75°C under N_2 gas. After stirring at −75°C for 1 h, 1 M aqueous HCl solution and EtOAc were added. The organic solution was separated, successively washed with a saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration gave a crude hemiacetal. To a solution of this crude hemiacetal in EtOH was added $NaBH_4$ (9 mg, 0.24 mmol) at 0°C. The reaction mixture was stirred at room temperature for 2 h, and then 1 M aqueous HCl solution was added. After the mixture had been neutralized with a saturated aqueous $NaHCO_3$ solution and concentrated, the residue was dissolved in EtOAc and H_2O. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Concentration followed by silica gel TLC (EtOAc/hexane=1/1) gave diol **5** (6 mg, 0.021 mmol, 58%).

(1R,2S,5R,6S)-6-(2-Methoxy-4,5-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-2-ol (**2**). To a solution of furofuranone **6** (33 mg, 0.12 mmol) in toluene (5 ml) was added *iso*-Bu_2AlH (0.38 ml, 1 M solution in toluene, 0.38 mmol) at −75°C under N_2 gas. After stirring at −75°C for 1 h, 1 M aqueous HCl solution and EtOAc were added. The organic solution was separated, successively washed with a saturated aqueous $NaHCO_3$ solution and brine, and dried (Na_2SO_4). Concentration followed by silica gel TLC (EtOAc/hexane=1/1) gave samin type of lignan **2** (25 mg, 0.084 mmol, 70%) as colorless crystals, mp 114–116°C. $[\alpha]_D^{20} = +121.54$ (c0.54, $CHCl_3$). NMR δ_H ($CDCl_3$): 2.78 (1H, m), 2.99 (1H, m), 3.00 (1H, br. s), 3.60 (1H, dd, J=8.8, 7.3 Hz), 3.76 (3H, s), 4.13 (1H, dd, J=9.0, 2.2 Hz), 4.18 (1H, dd, J=9.0, 6.1 Hz), 4.34 (1H, dd, J=8.8, 8.8 Hz), 4.80 (1H, d, J=6.4 Hz), 5.37 (1H, s), 5.90 (2H, s), 6.51 (1H, s), 6.92 (1H, s). NMR δ_C ($CDCl_3$): 52.22, 53.67, 56.20, 70.51, 71.10, 82.19, 94.38, 101.10, 101.88, 106.05, 122.43, 141.24, 147.14, 151.47. IRν_{max} ($CHCl_3$): 3596, 3025–2861, 1505, 1485, 1466, 1428, 1192, 1159, 1086, 1073, 1042, 1024. EIMS m/z (20 eV): 280 (M^+, 100), 249 (17), 180 (46), 165 (25), 152 (24), 134 (20), 84 (17). HRMS (EI) m/z (M^+): Calcd. for $C_{14}H_{16}O_6$, 280.0946; found, 280.0959.

Acknowledgments

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References

1) Ayres, D. C. and Loike, J. D., Lignans. Cambridge University Press, Cambridge (1990).
2) Fukuda, Y., Isobe, M., Nagata, M., Osawa, T., and Namiki, M., Acidic transformation of sesamolin, the sesame-oil constituent, into an antioxidant bisepoxylignan, sesaminol. *Heterocycles*, **24**, 923–926 (1986).
3) Takano, S., Ohkawa, T., Tamori, S., Satoh, S., and Ogasawara, K., Enantio-controlled route to the furofuran lignans: the total synthesis of (−)-sesamolin, (−)-sesamin, and (−)-acuminatolide, *J. Chem. Soc., Chem. Commun.*, 189–191 (1988).
4) Wirth, T., Kulicke K. J., and Fragale, G., Chiral diselenides in the total synthesis of (+)-samin. *J. Org. Chem.*, **61**, 2686–2689 (1996).
5) Hull, H. M., Jones, R. G., and Knight, D. W., An alternative diastereospecific approach to (±)-samin and 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octane [furanofuran] lignans based on the Ireland-Claisen rearrangement of unsaturated oxa-macrolides. *J. Chem. Soc., Perkin Trans. 1*, 1779–1787 (1998).
6) Yamauchi, S., Yamamoto, N., and Kinoshita, Y., Stereoselective synthesis of optically active methylene lactone, key intermediate for the synthesis of 1,2-oxidized furofuran lignan, from L-glutamic acid. *Biosci. Biotechnol. Biochem.*, **63**, 1605–1613 (1999).
7) Ishibashi, F. and Taniguchi, E., Synthesis and absolute configuration of the insecticidal sesquilignan (+)-haedoxan A. *Phytochemistry*, **49**, 613–622 (1998).
8) Murahashi, S., Naota, T., Ito, K., Maeda, Y., and Taki, H., Ruthenium-catalyzed oxidative transformation of alcohols and aldehydes to esters and lactones. *J. Org. Chem.*, **52**, 4319–4327 (1987).