Synthesis of 1,2-Oxygenated 6-arylfurofuran Lignan: Stereoselective Synthesis of (1S,2S,5R,6S)-1-hydroxysamin

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(1S,2S,5R,6S)-6-(3,4-Methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-1,2-diol (1-hydroxysamin) was synthesized, starting from olefin 8. Stereoselective α-hydroxylation was achieved after converting 8 to aldehyde 13. Resulting unstable α-hydroxy aldehyde 14 was then transformed to (++)-1-hydroxysamin (I). This is a new efficient synthetic route to 1,2-oxygenated 6-arylfurofuran lignans.

Key words: lignan; furofuran lignan

Furofuran lignan, which is one of the largest groups of lignans, has interesting biological characteristics such as antioxidative activity, antitumour activity, cytotoxic activity, and an inhibitor of cAMP phosphodiesterase. The synthetic study of this furofuran lignan is important for further research into its biological activity, and many synthetic routes has been developed. Our synthetic study has been focused on the 1,2-oxygenated 6-arylfurofuran lignans, because only a few synthetic route to this type of lignan have been reported. This study is expected to contribute to biological research into the structure-activity relationship of furofuran lignan and to discover new biological activities of 1,2-oxygenated 6-arylfurofuran lignan. The method used to stereoselectively introduce the three substituents on a furofuran ring is also important. This present report describes the stereoselective synthesis of (1S,2S,5R,6S)-1-hydroxysamin (I) in fewer steps than previously described. This 1-hydroxysamin type of lignan is a useful compound for biological testing and an important intermediate for the synthesis of the 6-aryl-2-aryloxy-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane type of lignan (Fig.).

Although some synthetic methods for optically active samin are known, only one stereoselective synthetic route to optically active 1-hydroxysamin (I) has been reported. However, the long pathway for this synthetic method inhibits the production of many synthetic analogues of 1,2-oxygenated 6-arylfurofuran lignan. The many processes for protecting and deprotecting the hydroxy groups result in a lengthy procedure for the synthesis of oxidized lignan. To develop more efficient synthetic method, direct stereoselective introduction of the tertiary hydroxy group by an oxidant was planned. Thus, enol ether or enolate was adopted as a substrate for this oxidation reaction (Fig.). This oxidant would attack from the opposite side of the substituent at the 3 position, and the resulting product could then be converted to 1-hydroxysamin.

It was assumed that the substrate for this oxidation could be obtained from olefin 7. Scheme 1 shows the retrosynthetic analysis of 1-hydroxysamin (I). 1-Hydroxysamin (I) could be obtained from α-hydroxyaldehyde 4 by deprotection. Aldehyde 5 could be converted to α-hydroxyaldehyde 4 by stereoselective oxidation to an enol ether or enolate from 5. Aldehyde 5 would be obtained from lactone 6 by carbon-carbon bond formation at the α position, reduction, intramolecular cyclization, and subsequent oxidation. Olefin 7 could be transformed to lactone 6 by successive oxidation. This olefin 7 could be stereoselectively prepared from (S)-4-benzyl-2-oxazolidinone and 4-pentenoic acid by Mailoli’s
**Results and discussion**

Olefin 8, which was stereoselectively prepared from (S)-4-benzyl-2-oxazolidinone and 4-pentenoic acid in 4 steps in 56% overall yield, was selected as the starting material. Successive oxidation of 8 by osmium tetroxide, sodium periodate, and silver carbonate-celite gave lactone 9 in 92% yield. Although the aldol condensation of 9 with formaldehyde did not proceed, the reaction with methyl chloroformate gave 10 in 90% conversion yield. Stereoselectivity in this condensation reaction was not necessary, because product 2R-10 was obtained as a single isomer. The observation of NOE between 4-H and the methylene protons of a silyloxymethyl group showed the 3R,4S configuration. Another correlation between 2-H and 4-H confirmed the configuration at the 2 position to be R. At this stage, the carbon-carbon formation required for the synthesis of 1-hydroxysamin was achieved. Lithium aluminum hydride reduction of lactone 10 afforded desired triol 11 (63%) and corresponding hemiacetal (22%). This hemiacetal was transformed to triol 11 by sodium borohydride reduction (57%). The total yield of triol 11 from lactone 10 was 76%. Cyclization of triol 11 to tetrahydrofuran ring 12 was achieved by SN1 intramolecular etherification, using a catalytic amount of 10-camphorsulfonic acid. This cyclization gave desired 2S,5R as a diastereomeric mixture of 4R/S (1/1) in 83% yield. No undesired 2R isomer was apparent. Pyridinium chlorochromate oxidation of 12 furnished aldehyde 13 as a 2/3 diastereomeric mixture in 72% yield. Since this aldehyde could be converted to an enolate or enol ether, it was used for the next step without separation of the 4R/S diastereomers.

The next stage involved stereoselective α-hydroxylation to aldehyde 13, which is the key reaction for the synthesis of 1-hydroxysamin. Direct α-hydroxylation of aldehyde 13, using 2-sulfonyloxaziridine and MoOPH with a base, did not give α-hydroxylaldehyde 14 and resulted in recovery of the aldehyde. Oxidation via an acetyl enol ether also resulted in recovery of aldehyde. The conversion of 13 to 14 was achieved via triisopropylsilyl enol ether, which was prepared by treating 13 with triisopropylsilylefluoromethanesulfonate, 1,8-diazabicyclo[5.4.0]undec-7-ene, and 4-dimethylaminopyridine in a quantitative yield. After the unstable silyl enol ether had been subjected to osmium oxidation, the crude product was treated with N,N′-dimethylethlenediamine followed by silica gel column chromatography to convert the dimers of α-hydroxaldehyde 14 to a monomer. It is well known that a hydroxy aldehyde is easily dimerized. Resulting unstable α-hydroxaldehyde 14 was therefore immediately treated with tetrabutylammonium fluoride to cleave the silyl ether, giving (1S,2S,5R,6S)-1-hydroxysamin 1 as a single isomer in 78% yield: [α]D20 +74.5, c 0.51 in CHCl3; lit. [α]D20 +74.8, c 0.21 in CHCl3. The NMR data agreed with previously described data.

This new stereoselective synthetic method for (1S,2S,5R,6S)-1-hydroxysamin (1) involved 14 steps from (S)-4-benzyl-2-oxazolidinone and 4-pentenoic acid to provide 12% overall yield. This is a more efficient synthetic method than that previously described (25 steps, 0.3% overall yield). Since the transformation of the hemiacetal portion in the 1-hydroxysamin type of lignan to an acetal is possible, this method also provides a new synthetic route to the optically active 6-aryl-2-aryloxy-1-hydroxy-3,7-dioxabicyclo[3.3.0]octane type of lignan.

**Experimental**

All melting point (mp) data are uncorrected. NMR
Scheme 2. Synthesis of \((1S,2S,5R,6S)-1\)-Hydroxysamin (1).

Reagents and conditions (yield): (a) (1) OsO₄, NMO, acetone, tert-BuOH, H₂O, r.t., 24 h; (2) NaIO₄, MeOH, r.t., 3 h; (3) Ag₂CO₃-Celite, toluene, reflux, 1 h (92% 3 steps); (b) LHMDS, ClCO₂CH₃, THF, 75°C, 2 h (90% conversion yield); (c) (1) LiAlH₄, THF, r.t., 3 h; (2) NaBH₄, EtOH, 3 h (100%); (d) CSA, CH₂Cl₂, r.t., 24 h (83%); (e) PCC, CH₂Cl₂, r.t., 5 h (72%); (f) (1) TIP-OSO₂Tf, DBU, DMAP, CH₂Cl₂, r.t., 2 h (100%); (2) OsO₄, NMO, acetone, tert-BuOH, H₂O, r.t., 24 h, and then (CH₃NHCH₂)₂, benzene, reflux, 0.5 h, SiO₂ (71%); (g) n-Bu₄NF, THF, r.t., 1 h (78%).

Synthesis of Optically Active 1-Hydroxysamin

data were measured by a JNM-EX400 spectrometer, while IR spectra were determined with a Shimadzu FTIR-8100 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. [α]D values are in units of 10⁻¹ deg cm²g⁻¹. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh).

\((3R,4S)-3-(\text{tert-Butyldiphenylsilyloxy})\text{methyl}-4-(3,4-\text{methylenedioxyphenyl})-4\text{-butanolide}
\) (9). A reaction solution of olefin 8 (5.51 g, 0.012 mol), 4-methylmorpholine N-oxide (1.63 g, 0.014 mol), and OsO₄ (2% H₂O solution, 1 ml) in acetone (20 ml), tert-butyl alcohol (5 ml), and H₂O (5 ml) was stirred at room temperature for 24 h before addition of NaHSO₃. After the mixture was filtered, the filtrate was concentrated. The resulting residue was dissolved in H₂O and EtOAc. The organic solution was separated, washed with brine, and dried (Na₂SO₄). Evaporation gave a crude glycol. A reaction mixture of this crude glycol and NaIO₄ (2.73 g, 0.013 mol) in MeOH (10 ml) was stirred at room temperature for 3 h. After the mixture was filtered, the residue was dissolved in H₂O and EtOAc. The organic solution was separated, washed with brine, and dried (Na₂SO₄). After evaporation, the residue was applied to silica gel column chromatography (EtOAc-hexane 1:5) to give a hemiacetal (5.24 g). A reaction mixture of this hemiacetal (5.24 g, 0.011 mol) and Ag₂CO₃-Celite (12.1 g, 1 mmol/g, 0.012 mol) in toluene (30 ml) was heated under reflux for 1 h before filtration. The filtrate was concentrated, and the resulting residue was applied to silica gel column chromatography (EtOAc-hexane 3:1) to give lactone 9 (5.22 g, 92% from olefin 8) as a colorless oil. \([\alpha]_{D}^{20} +9.7\) (c 1.03, CHCl₃). IR \(\nu_{\text{max}}\) (CHCl₃) cm⁻¹: 2987, 1777, 1449, 1113, 1042. NMR \(\delta\)H(CDCl₃): 1.08 (9H, s, C(C₆H₃)₃), 2.64 (1H, dd, \(J=17.6, 8.3\) Hz, 2-CH₂H), 2.70 (1H, dd, \(J=17.6, 9.3\) Hz, 2-CH₃H), 3.68 (1H, dd, \(J=10.7, 4.4\) Hz, CCHOTBDPS), 3.73 (1H, dd, \(J=10.7, 4.9\) Hz, CHCHOTBDPS), 5.29 (1H, d, \(J=6.8\) Hz, 4-H), 5.95 (2H, s, OCH₂O), 6.62 (1H, d, \(J=7.8\) Hz, ArH), 6.69 (1H, s, ArH), 6.73 (1H, d, \(J=7.8\) Hz, ArH), 7.37–7.46 (6H, m, ArH), 7.61–7.62 (4H, m, ArH). NMR \(\delta\)C(CDCl₃): 19.3, 26.9, 31.2, 46.4, 62.1, 82.8, 101.3, 106.2, 108.2, 119.6, 127.9, 130.0, 132.4, 132.8, 135.5, 135.6, 147.8, 148.1, 176.1. MS \(m/z\) (EI, 20 eV): 417 (M+–C(CH₃)₃, 32), 387 (100), 199 (42). Anal. Found: C, 70.87; H, 6.61%. Calcd. for C₂₈H₃₀O₅Si: C, 70.86; H, 6.37%.

\((2R,3R,4S)-3-(\text{tert-Butyldiphenylsilyloxy})\text{methyl}-2\text{-methoxycarbonyl}-4-(3,4-\text{methylenedioxyphenyl})-4\text{-butanolide}
\) (10). To a solution of LHMDS (1 m in THF; 17.6 ml, 0.018 mol) in THF (150 ml) was
added a solution of lactone 9 (5.60 g, 0.012 mol) in THF (50 ml) at −75°C. After the solution was stirred at −75°C for 30 min, a solution of methyl chloroformate (1.36 ml, 0.018 mol) in THF (20 ml) was added. The reaction solution was stirred at −75°C for 2 h before additions of sat. aq. NH₄Cl solution and EtOAc. The organic solution was separated, washed with brine, dried (Na₂SO₄), and evaporated. The residue was applied to silica gel column chromatography (EtOAc-hexane 1:1) to give 10 (3.04 g) and recovered lactone 9 (2.71 g). The conversion yield was 90%. [α]D²⁰ + 1.8 (c 1.09, CHCl₃). IR νmax(CHCl₃) cm⁻¹: 2984, 1782, 1742, 1507, 1462, 1159, 1113, 1042. NMR δ(CHCl₃): 1.08 (9H, s, C(CH₃)₃), 2.96 (1H, m, 3-H), 3.65 (1H, dd, J = 11.2, 3.7 Hz, CH/HOTBPS), 3.74 (1H, dd, J = 11.2, 3.4 Hz, CH/HOTBPS), 3.81 (3H, s, CH₃O), 3.98 (1H, d, J = 11.2 Hz, 2-H), 5.21 (1H, d, J = 9.8 Hz, 4-H), 5.96 (2H, s, OCH₂CH₂), 6.61 (1H, dd, J = 8.1, 1.5 Hz, ArH), 6.72 (1H, d, J = 8.1 Hz, ArH), 6.73 (1H, d, J = 1.5 Hz, ArH), 7.36–78.48 (6H, m, ArH), 7.58–7.63 (4H, m, ArH). NMR δ(CDC1₃): 19.3, 26.9, 49.1, 50.6, 53.0, 59.5, 77.2, 81.3, 101.4, 106.7, 108.2, 120.7, 127.9, 128.0, 130.4, 130.5, 132.4, 132.5, 135.5, 135.6, 148.2, 148.3, 167.7, 170.7. MS m/z (EI, 70 eV): 475 (M⁺-CO₂CH₃, 82), 150 (84), 135 (91), 105 (100). Anal. Found: C, 67.87; H, 6.29%. Calcd. for C₉H₁₀O₃Si: C, 67.65; H, 6.06%.

(1S,2R)-2-(tert-Butyldiphenylsiloxy)methyl-3-hydroxy-1-(3,4-methylenedioxyphenyl)-1,4-butanediol (11). To an iced-cooled suspension of LiAlH₄ (0.07 g, 1.84 mmol) in THF (10 ml) was added a solution of lactone 10 (0.50 g, 0.94 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 3 h before addition of sat. aq. MgSO₄ solution and K₂CO₃. After the mixture was filtered, the filtrate was concentrated. The residue was purified by silica gel column chromatography (EtOAc-hexane 1:1) to give triol 11 (0.55 g, 1.08 mmol) and CSA (10 mg, 0.043 mmol) in CH₂Cl₂ (10 ml) was stirred at room temperature for 24 h before addition of a few drops of Et₃N. After concentration, the residue was applied to silica gel column chromatography (EtOAc-hexane 1:5) to give hydroxymethyltetrahydrofuran 12 (0.44 g, 83%) in a 1/1 diastereomeric mixture as a colorless oil. IR νmax(CHCl₃) cm⁻¹: 3424, 2934, 1505, 1445, 1429, 1113, 1042. NMR δ(CDC1₃): 1.04 (4.5H, s), 1.06 (4.5H, s), 1.97 (0.5H, m), 2.34 (0.5H, m), 2.51 (0.5H, m), 2.64 (0.5H, dd, J = 7.8, 3.4 Hz), 2.74 (0.5H, m), 3.13 (0.5H, dd, J = 7.8, 3.9 Hz), 3.59–3.75 (3.5H, m), 3.83–3.96 (1.5H, m), 4.03 (0.5H, dd, J = 8.8, 8.3 Hz), 4.21 (0.5H, dd, J = 8.8, 7.8 Hz), 4.43 (1H, d, J = 8.3 Hz), 5.92–5.94 (2H, m), 6.49 (0.5H, dd, J = 8.3, 1.5 Hz), 6.59 (0.5H, dd, J = 8.3, 1.5 Hz), 6.62–6.68 (1.5H, m), 6.74 (0.5H, d, J = 1.5 Hz), 7.30–7.47 (6H, m), 7.55–7.65 (4H, m). MS m/z (EI, 70 eV): 490 (M⁺, 3), 234 (97), 199 (65), 161 (100). Anal. Found: C, 70.75; H, 7.08%. Calcd. for C₂₉H₂₃O₆SiNa: C, 70.99; H, 6.98%.

(2S,3R,4R)[S]-4-(tert-Butyldiphenylsiloxy)methyl-5-(3,4-methylenedioxyphenyl)-3-tetrahydrofurancarbaldehyde (13). A reaction mixture of alcohol 12 (0.40 g, 0.82 mmol), PCC (0.20 g, 0.93 mmol) and MS 4A (1 g) in CH₂Cl₂ (20 ml) was stirred at room temperature for 5 h. After the mixture was filtered, the filtrate was concentrated. The residue was applied to silica gel column chromatography (EtOAc-hexane 1:5) to give aldehyde 13 (0.29 g, 72%) in a 2/3 diastereomeric mixture as a colorless
oil. IR ν<sub>max</sub>(CHCl<sub>3</sub>) cm<sup>-1</sup>: 2948, 1725, 1505, 1447, 1429, 1113, 1042. NMR δ<sub>C</sub>(CDCl<sub>3</sub>): 1.06 (9H, s), 2.49 (0.6H, m), 2.55 (0.4H, m), 3.20 (0.6H, m), 3.26 (0.4H, m), 3.68–3.73 (1H, m), 3.80 (0.6H, dd, J = 10.7, 4.4 Hz), 3.86 (0.4H, dd, J = 10.7, 4.1 Hz), 4.02 (0.6H, dd, J = 9.3, 8.3 Hz), 4.24 (0.4H, dd, J = 9.3, 7.3 Hz), 4.29 (0.4H, dd, J = 9.3, 6.8 Hz), 4.39 (0.6H, dd, J = 9.3, 4.4 Hz), 4.60 (0.6H, d, J = 8.3 Hz), 4.68 (0.4H, d, J = 7.3 Hz), 5.91 (0.8 H, s), 5.92 (1.2H, s), 6.45 (0.4H, d, J = 8.3 Hz), 6.58–6.64 (1.4H, m), 6.67–6.72 (1.2 H, m), 7.35–7.47 (6H, m), 7.58–7.65 (4H, m), 9.70 (0.6H, d, J = 2.0 Hz, CHO), 10.0 (0.4H, d, J = 2.5 Hz, CHO). NMR δ<sub>C</sub>(CDCl<sub>3</sub>) 19.1, 19.2, 26.8, 26.9, 51.2, 53.5, 55.1, 60.4, 62.4, 67.2, 67.4, 81.9, 83.1, 101.0, 106.2, 106.7, 108.0, 119.4, 119.9, 127.8, 127.9, 129.9, 130.0, 132.6, 132.9, 133.0, 134.0, 134.7, 135.6, 135.7, 147.1, 147.3, 147.8, 147.9, 200.5, 201.1. MS with sin m/z (EI, 20 eV): 488 (M<sup>+</sup>*, 1), 431 (43), 199 (41), 161 (50), 135 (100). Anal. Found: C, 71.37; H, 6.75. Caled. for C<sub>29</sub>H<sub>32</sub>O<sub>5</sub>Si: C, 71.28; H, 6.60.

(1S,2S,5R,6S)-6-(3,4-Methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-1,2-diol (1-hydroxysamin) (I). To an ice-cooled solution of aldehyde 13 (0.25 g, 0.51 mmol), DBU (0.17 ml, 1.14 mmol), and DMAP (20 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml) was added TIPS0T (0.15 ml, 0.56 mmol). The reaction solution was stirred at room temperature for 2 h before addition of sat. aq. NaHCO<sub>3</sub> solution. The organic solution was separated, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated. A solution of the residue and OsO<sub>4</sub> (0.5 ml) in acetone (16 ml), tert-BuOH (4 ml), and H<sub>2</sub>O (4 ml) was stirred at room temperature for 24 h before addition of NaHSO<sub>3</sub> solution. After the mixture was filtered, the filtrate was concentrated. The residue was dissolved in H<sub>2</sub>O and EtOAc. The organic solution was separated, washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). After evaporation, the residue was applied to silica gel column chromatography (EtOAc-hexane 1:1) gave 1-hydroxysamin I (75 mg, 78%) as a colorless oil. [α]<sub>D</sub> <sub>20</sub> +74.5 (c 0.51, CHCl<sub>3</sub>), lit. [α]<sub>D</sub> <sub>20</sub> +74.8 (c 0.21, CHCl<sub>3</sub>).

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