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Satoshi YAMAUCHI[a], Satoshi BANDO[a] & Yoshiro KINOSHITA[a]
[a] College of Agriculture, Ehime University Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan
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Synthesis of 1,2-Oxygenated 6-arylfurofuran Lignan: Stereoselective Synthesis of (1*S*,2*S*,5*R*,6*S*)-1-hydroxysamin

Satoshi YAMAUCHI,† Satoshi BANDO, and Yoshiro KINOSHITA

College of Agriculture, Ehime University, Tarumi 3-5-7, Matsuyama, Ehime 790-8566, Japan

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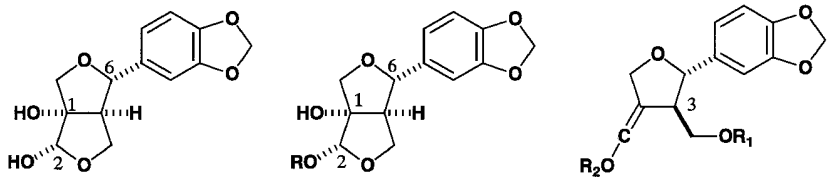
(1*S*,2*S*,5*R*,6*S*)-6-(3,4-Methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octan-1,2-diol ((+)-1-hydroxysamin 1) was synthesized, starting from olefin 8. Stereoselective α-hydroxylation was achieved after converting 8 to aldehyde 13. Resulting unstable α-hydroxy aldehyde 14 was then transformed to (+)-1-hydroxysamin (1). 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[1] 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.[2] Our synthetic study has been focused on the 1,2-oxygenated 6-arylfurofuran lignans,[3] **1** and **2**, because only a few synthetic route to this type of lignan have been reported.[4),5] 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 to a furofuran ring is also important. This present report describes the stereoselective synthesis of (1*S*,2*S*,5*R*,6*S*)-1-hydroxysamin (**1**) in fewer steps than previously described.[3] 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 **2**[4),5] (Fig.).

Although some synthetic methods for optically active samin are known,[6),7),8] only one stereoselective synthetic route to optically active 1-hydroxysamin (**1**) has been reported.[3] 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 **3** 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 **1**.

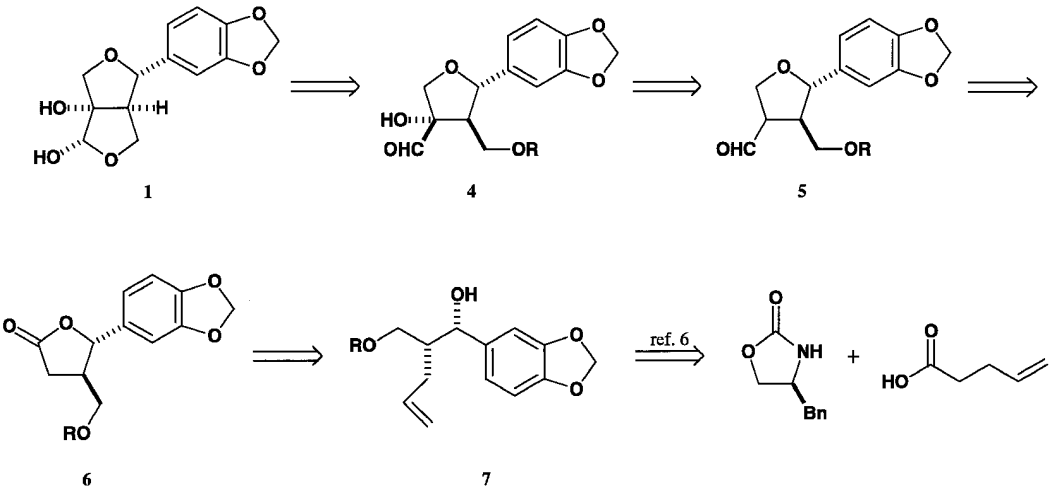
It was assumed that the substrate for this oxidation could be obtained from olefin **7**.[9] Scheme 1 shows the retrosynthetic analysis of 1-hydroxysamin (**1**). 1-Hydroxysamin (**1**) could be obtained from α-hydroxyaldehyde **4** by deprotection. Aldehyde **5** could be converted to α-hydroxyaldehyde **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



1-hydroxysamin (**1**) **2** **3**

Fig.

† To whom correspondence should be addressed. Fax: +81-89-977-4364; E-mail: syamauch@agr.ehime-u.ac.jp



Scheme 1. Retrosynthetic Analysis of (1*S*,2*S*,5*R*,6*S*)-1-Hydroxysamin (**1**).

method.[9]

Results and discussion

Olefin **8**, which was stereoselectively prepared from (*S*)-4-benzyl-2-oxazolidinone and 4-pentenoic acid in 4 steps[9] 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.

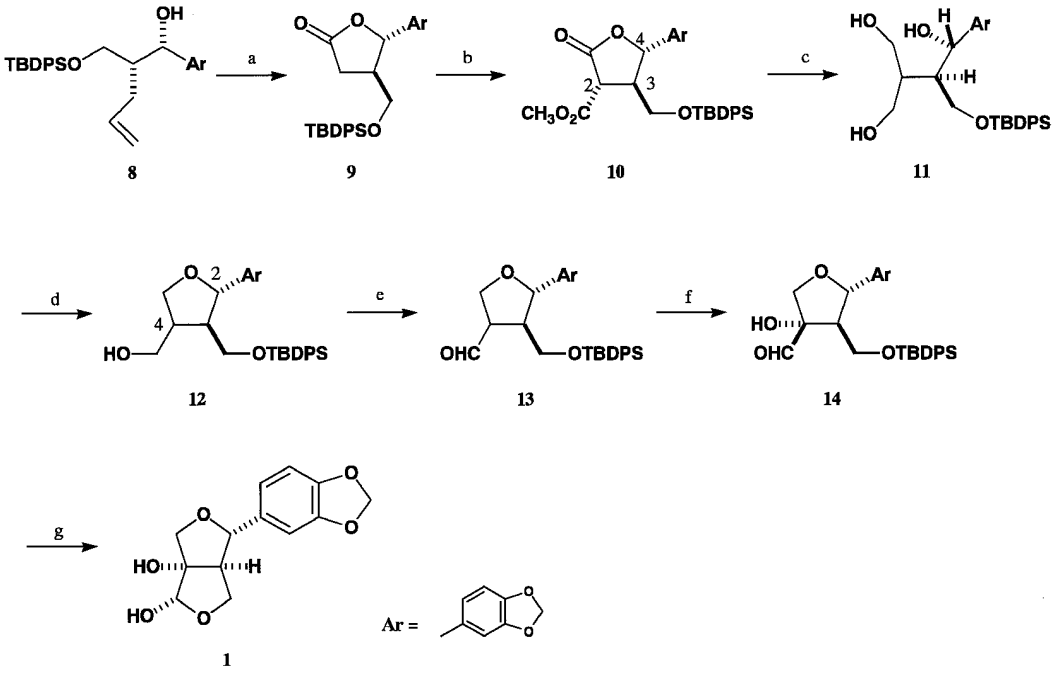
Although the aldol condensation of **9** with formaldehyde did not proceed, the reaction with methyl chloroformate gave **10** in 90% conversion yield. Stereoselectivity in this condensation reaction was not necessary, because product 2*R*-**10** was obtained as a single isomer. The observation of NOE between 4-H and the methylene protons of a silyloxymethyl group showed the 3*R*, 4*S* 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 2*S*-**12** as a diastereomeric mixture of 4*R*/*S* (1/1) in 83% yield. No undesired 2*R* 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 4*R*/*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[10] and MoOPH[11] with a base, did not give α-hydroxyaldehyde **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 triisopropylsilyl trifluoromethanesulfonate, 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*′-dimethylethylenediamine followed by silica gel column chromatography to convert the dimers of α-hydroxyaldehyde **14** to a monomer.[12] It is well known that a hydroxy aldehyde is easily dimerized. Resulting unstable α-hydroxyaldehyde **14** was therefore immediately treated with tetrabutylammonium fluoride to cleave the silyl ether, giving (1*S*,2*S*,5*R*,6*S*)-1-hydroxysamin **1** as a single isomer in 78% yield: $[\alpha]_D^{20}$ +74.5, *c* 0.51 in $CHCl_3$; lit.[3] $[\alpha]_D^{20}$ +74.8, *c* 0.21 in $CHCl_3$. The NMR data agreed with previously described data.[3]

This new stereoselective synthetic method for (1*S*,2*S*,5*R*,*S*)-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).[3] Since the transformation of the hemiacetal portion in the 1-hydroxysamin type of lignan to an acetal is possible,[5] 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 **2** type of lignan.

Experimental

All melting point (mp) data are uncorrected. NMR



Scheme 2. Synthesis of (1*S*,2*S*,5*R*,6*S*)-1-Hydroxysamin (**1**).

Reagents and conditions (yield): (a) (1) OsO_4, NMO, acetone, *tert*-BuOH, H_2O, r.t., 24 h; (2) $NaIO_4$, MeOH, r.t., 3 h; (3) Ag_2CO_3-Celite, toluene, reflux, 1 h (92%, 3 steps); (b) LHMDS, $ClCO_2CH_3$, THF, −75°C, 2 h (90% conversion yield); (c) (1) $LiAlH_4$, THF, r.t., 3 h; (2) $NaBH_4$, EtOH, 3 h (76%, 2 steps); (d) CSA, CH_2Cl_2, r.t., 24 h (83%); (e) PCC, MS 4A, CH_2Cl_2, r.t., 5 h (72%); (f) (1) TIPSOTf, DBU, DMAP, CH_2Cl_2, r.t., 2 h (100%); (2) OsO_4, NMO, acetone, *tert*-BuOH, H_2O, r.t., 24 h, and then $(CH_3NHCH_2)_2$, benzene, reflux, 0.5 h, SiO_2 (71%); (g) *n*-Bu_4NF, THF, r.t., 1 h (78%).

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. $[\alpha]_D$values are in units of 10^{-1} deg cm^2g^{-1}. The silica gel used was Wakogel C-300 (Wako, 200–300 mesh).

(3R,4S)-3-(tert-Butyldiphenylsilyloxy)methyl-4-(3,4-methylenedioxyphenyl)-4-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 OsO_4 (2% H_2O solution, 1 ml) in acetone (20 ml), *tert*-butyl alcohol (5 ml), and H_2O (5 ml) was stirred at room temperature for 24 h before addition of $NaHSO_3$. After the mixture was filtered, the filtrate was concentrated. The resulting residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation gave a crude glycol. A reaction mixture of this crude glycol and $NaIO_4$ (2.73 g, 0.013 mol) in MeOH (10 ml) was stirred at room temperature for 3 h. After the mixture was concentrated, the residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). 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 Ag_2CO_3-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, $CHCl_3$). IR ν_{max} ($CHCl_3$) cm^{-1}: 2987, 1777, 1507, 1449, 1113, 1042. NMR δ_H($CDCl_3$): 1.08 (9H, s, C(CH_3)$_3$), 2.54 (1H, m, 3-*H*), 2.64 (1H, dd, *J*=17.6, 8.3 Hz, 2-C*H*H), 2.70 (1H, dd, *J*=17.6, 9.3 Hz, 2-CH*H*), 3.68 (1H, dd, *J*=10.7, 4.4 Hz, C*H*HOTBDPS), 3.73 (1H, dd, *J*=10.7, 4.9 Hz, CH*H*OTBDPS), 5.29 (1H, d, *J*=6.8 Hz, 4-H), 5.95 (2H, s, OCH_2O), 6.62 (1H, d, *J*=7.8 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 6.73 (1H, d, *J*=7.8 Hz, Ar*H*), 7.37–7.46 (6H, m, Ar*H*), 7.61–7.62 (4H, m, Ar*H*). NMR δ_C($CDCl_3$): 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(CH_3)$_3$, 32), 387 (100), 199 (42). Anal. Found: C, 70.87; H, 6.61%. Calcd. for $C_{28}H_{30}O_5Si$: C, 70.86; H, 6.37%.

(2R,3R,4S)-3-(tert-Butyldiphenylsilyloxy)methyl-2-methoxycarbonyl-4-(3,4-methylenedioxyphenyl)-4-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. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), 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%. $[\alpha]_D^{20}$ +1.8 (*c* 1.09, $CHCl_3$). IR $\nu_{max}(CHCl_3)$ cm^{-1}: 2984, 1782, 1742, 1507, 1462, 1159, 1113, 1042. NMR $\delta_H(CDCl_3)$: 1.08 (9H, s, $C(CH_3)_3$), 2.96 (1H, m, 3-*H*), 3.65 (1H, dd, *J*=11.2, 3.7 Hz, C*H*HOTBDPS), 3.74 (1H, dd, *J*=11.2, 3.4 Hz, CH*H*OTBDPS), 3.81 (3H, s, CH_3O), 3.98 (1H, d, *J*=11.2 Hz, 2-*H*), 5.21 (1H, d, *J*=9.8 Hz, 4-*H*), 5.96 (2H, s, OCH_2O), 6.61 (1H, dd, *J*=8.1, 1.5 Hz, Ar*H*), 6.72 (1H, d, *J*=8.1 Hz, Ar*H*), 6.73 (1H, d, *J*=1.5 Hz, Ar*H*), 7.36–7.48 (6H, m, Ar*H*), 7.58–7.63 (4H, m, Ar*H*). NMR $\delta_C(CDCl_3)$: 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, 130.1, 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^+-CO_2CH_3, 82), 150 (84), 135 (91), 105 (100). Anal. Found: C, 67.87; H, 6.29%. Calcd. for $C_{30}H_{32}O_7Si$: C, 67.65; H, 6.06%.

(1S,2R)-2-(tert-Butyldiphenylsilyloxy)methyl-3-hydroxymethyl-1-(3,4-methylenedioxyphenyl)-1,4-butanediol (**11**). To an ice-cooled suspension of $LiAlH_4$ (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. $MgSO_4$ solution and K_2CO_3. 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** (0.3 g) and the corresponding hemiacetal (0.11 g). Hemiacetal: NMR $\delta_H(CDCl_3)$: 1.05 (9H, m), 1.96 (0.5H, m), 2.25 (0.5H, m), 2.37–2.44 (1H, m), 2.48–2.52 (0.5H, m), 2.98 (0.5H, m), 3.60–3.76 (4.5H, m), 3.86 (0.5H, m), 4.76 (0.5H, d, *J*=9.3 Hz), 4.89 (0.5H, d, *J*=8.8 Hz), 5.42 (0.5H, dd, *J*=5.6, 2.2 Hz, anomeric proton), 5.57 (0.5H, dd, *J*=4.6, 3.2 Hz, anomeric proton), 5.92–5.93 (2H, m), 6.60–6.69 (2H, m), 6.74 (0.5H, d, *J*=1.5 Hz), 6.88 (0.5H, d, *J*=1.5 Hz), 7.30–7.47 (6H, m), 7.55–7.65 (4H, m). A reaction mixture of this hemiacetal (0.11 g, 0.21 mmol) and $NaBH_4$ (8 mg, 0.21 mmol) in EtOH (10 ml) was stirred at room temperature for 3 h before addition of 1 M aq. HCl solution. After neutralization with sat. aq. $NaHCO_3$ solution, the mixture was concentrated. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was applied to silica gel column chromatography (EtOAc-hexane 1:1) to give triol **11** (61 mg) as a colorless oil. The total yield of **11** was 76%. $[\alpha]_D^{20}$ −20.2 (*c* 0.69, $CHCl_3$). IR $\nu_{max}(CHCl_3)$ cm^{-1}: 3386, 2947, 1505, 1445, 1429, 1113, 1042. NMR $\delta_H(CDCl_3)$: 1.05 (9H, s, $C(CH_3)_3$), 2.05–2.15 (2H, m, 2-*H*, 3-*H*), 2.77 (1H, br. s, O*H*), 3.15–3.38 (1H, br., O*H*), 3.38–3.57 (1H, br., O*H*), 3.62–3.75 (5H, m), 3.77 (1H, dd, *J*=11.2, 5.9 Hz), 4.80 (1H, d, *J*=5.9 Hz, 1-*H*), 5.92 (2H, s, OCH_2O), 6.69 (2H, s, Ar*H*), 6.76 (1H, s, Ar*H*), 7.34–7.44 (6H, m, Ar*H*), 7.55–7.60 (4H, m, Ar*H*). NMR $\delta_C(CDCl_3)$: 19.1, 26.9, 41.3, 48.5, 63.1, 63.5, 64.4, 73.4, 101.0, 106.6, 108.0, 119.6, 127.7, 127.8, 129.9, 132.7, 132.8, 135.6, 137.1, 146.8, 147.8. MS *m/z* (FAB): 531 ($M+Na^+$, 100), 173 (71), 135 (57). Found (HRMS): M^++Na, 531.2185. Calcd. for $C_{29}H_{36}O_6SiNa$: 531.2179.

(2S,3R,4R/S)-3-(tert-Butyldiphenylsilyloxy)-methyl-4-hydroxymethyl-2-(3,4-methylenedioxyphenyl)tetrahydrofuran (**12**). A reaction solution of triol **11** (0.55 g, 1.08 mmol) and CSA (10 mg, 0.043 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 24 h before addition of a few drops of Et_3N. 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 $\nu_{max}(CHCl_3)$ cm^{-1}: 3424, 2934, 1505, 1445, 1429, 1113, 1042. NMR $\delta_H(CDCl_3)$: 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). NMR $\delta_C(CDCl_3)$ 19.1, 26.7, 26.8, 43.8, 47.1, 51.7, 54.7, 61.3, 61.9, 63.9, 64.6, 70.3, 70.5, 82.2, 83.3, 100.9, 106.2, 106.5, 107.9, 108.0, 119.2, 119.8, 127.7, 127.8, 127.9, 129.8, 129.9, 130.0, 132.5, 132.6, 132.8, 135.1, 135.5, 135.9, 147.8. MS *m/z* (EI, 20 eV): 490 (M^+, 3), 234 (97), 199 (65), 161 (100). Anal. Found: C, 70.75; H, 7.08%. Calcd. for $C_{29}H_{34}O_5Si$: C, 70.99; H, 6.98%.

(2S,3R,4R/S)-4-(tert-Butyldiphenylsilyloxy)-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 CH_2Cl_2 (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 $\nu_{max}(CHCl_3)$ cm^{-1}: 2948, 1725, 1505, 1447, 1429, 1113, 1042. NMR $\delta_H(CDCl_3)$: 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 $\delta_C(CDCl_3)$ 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 m/z (EI, 20 eV): 488 (M^+, 1), 431 (43), 199 (41), 161 (50), 135 (100). Anal. Found: C, 71.37; H, 6.75%. Calcd. for $C_{29}H_{32}O_5Si$: 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) (**1**). 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_2Cl_2 (15 ml) was added TIPSOTf (0.15 ml, 0.56 mmol). The reaction solution was stirred at room temperature for 2 h before addition of sat. aq. $NaHCO_3$ solution. The organic solution was separated, washed with brine, and dried (Na_2SO_4). After evaporation, the residue was applied to silica gel column chromatography (EtOAc-hexane 1:19) to give silyl enol ether (0.33 g, 100%). A reaction solution of this silyl ether (0.33 g, 0.51 mmol), 4-methylmorpholine *N*-oxide (71 mg, 0.61 mmol), and OsO_4 (2% H_2O solution, 0.5 ml) in acetone (16 ml), *tert*-BuOH (4 ml), and H_2O (4 ml) was stirred at room temperature for 24 h before addition of $NaHSO_3$. After the mixture was filtered, the filtrate was concentrated. The residue was dissolved in H_2O and EtOAc. The organic solution was separated, washed with brine, dried (Na_2SO_4), and evaporated. A solution of the residue and *N*,*N*′-dimethylethylenediamine (0.062 ml, 0.58 mmol) in benzene (20 ml) was heated under reflux for 0.5 h before concentration. The residue was applied to silica gel column chromatography to give unstable hydroxy aldehyde **14** (0.18 g, 71%) as a colorless oil. A reaction solution of hydroxy aldehyde **14** (0.18 g, 0.36 mmol) and *n*-Bu_4NF (1 M in THF; 0.40 ml, 0.40 mmol) in THF (20 ml) was stirred at room temperature for 1 h before additions of sat. aq. NH_4Cl solution and EtOAc. The organic solution was separated, washed with brine, and dried (Na_2SO_4). Evaporation and silica gel column chromatography (EtOAc-hexane 1:1) gave 1-hydroxysamin **1** (75 mg, 78%) as a colorless oil. $[\alpha]_D^{20}$ +74.5 (*c* 0.51, $CHCl_3$), lit.[3] $[\alpha]_D^{20}$ +74.8, (*c* 0.21, $CHCl_3$).

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