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Synthesis of salacinol

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Abstract

Salacinol, a new type of α-glucosidase inhibitor discovered from the antidiabetic herb, was synthesized for the first time. Under the strategy that salacinol would be synthesized by the coupling reaction between 1,4-epithio-D-arabinitol and the cyclic sulfate of an erythritol derivative, the model coupling reactions between tetrahydrothiophene and versatile cyclic sulfate derivatives were undertaken. These experiments indicated that the 1,3-diol of the cyclic sulfate should be protected with the isopropylidene group, otherwise, even the benzylidene-protected cyclic sulfate decomposed during the reaction. Thus, the salacinol was synthesized using the cyclic sulfate of 1,3-*O*-isopypropylidene-D-erythritol. The resulting coupling product was deisopropylidenated to afford salacinol. A diastereomer of salacinol was also synthesized.

Keywords: salacinol; glycosidase inhibitors; sulfonium compounds; cyclic sulfates.

Thiacyclopentane derivative with the sulfur atom being in trivalent state is a new class of glucosidase inhibitor. This class of compound was first created as the sulfimide derivative **1**, which has shown a weak inhibitory effect toward β-glucosidase.[1] The molecular model of the compound **1** superimposed on an assumed transition state (**TS**) of the glucoside hydrolysis showed that a cationic character of the trivalent sulfur atom resembles that of the anomeric carbon of the structure **TS**. More recently, the sulfonium ion derivative (salacinol; **2**) was discovered from *Salacia reticulata*, the herb used in Indian traditional medicine for diabetes, and was shown to be a strong inhibitor of α-glucosidases.[2] The structure of salacinol is unique in that the ring sulfonium ion is stabilized by a sulfate counter anion tethered with an erythritol chain, constructing spirobicyclic-like structure. This characteristic structure may account for the strong inhibitory effect of salacinol. In continuous studies on inhibitory activities of the ring sulfur analogs of aldose toward glycosidases,[3] we were interested in the effect of the tethered sulfonium salt. We thus started studies on the construction of the tethered sulfonium salt on thiacyclopetane.

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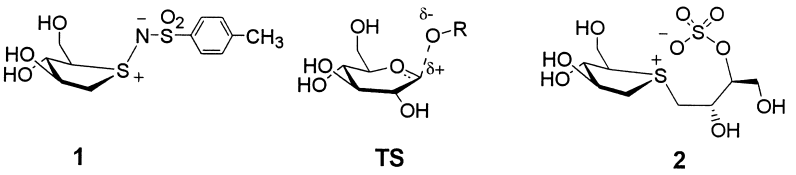


We planned the synthesis as shown in Fig. 1. A key step of the synthetic strategy is the ring opening of the cyclic sulfate **5** by the nucleophilic attack of 1,4-epithio-D-arabinitol (**4**). While the reaction of cyclic sulfates is well studied,[4] we could not find any examples in which a tethered sulfonium salt is produced. Moreover, we were so uninformed about chemical properties of salacinol that we were not confident in the conditions for the deprotection of compound **3**.

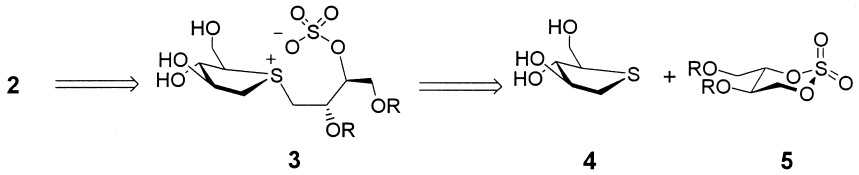
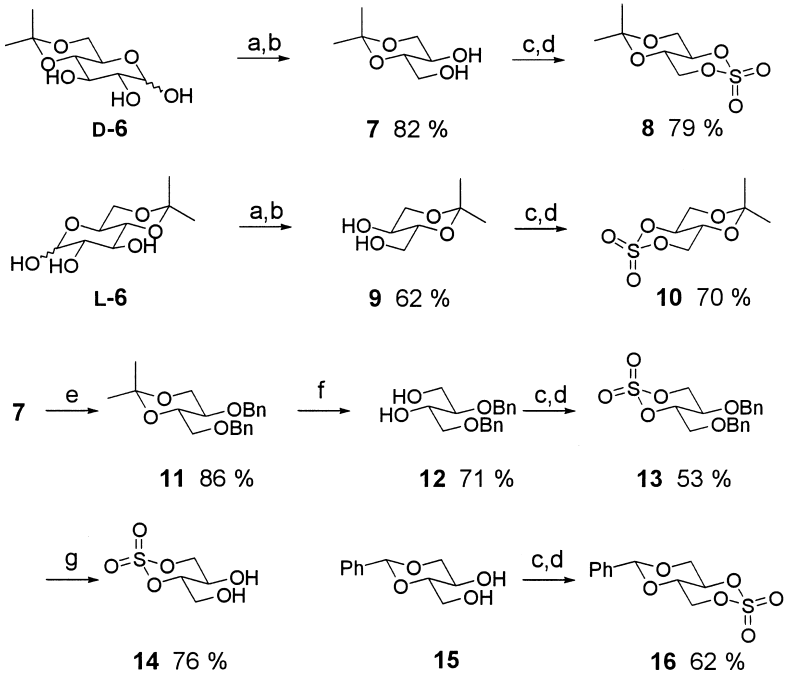


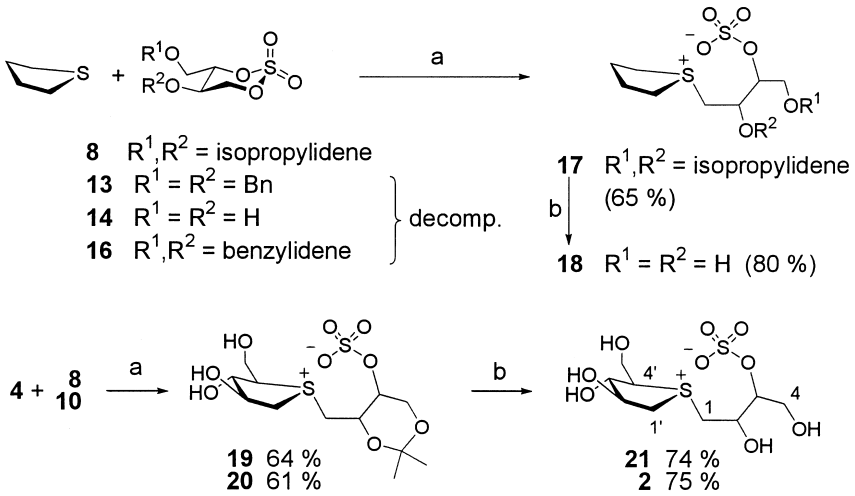
Figure 1. A strategy for the synthesis of salacinol **2**



Scheme 1. (a) $NaIO_4$ (2 equiv.), $NaHCO_3$, H_2O, bromocresol green, 5 h; (b) $NaBH_4$, CH_3OH, 10 min; (c) $SOCl_2$ (1.2 equiv.), Et_3N (2.5 equiv.), CH_2Cl_2, 0°C 10 min; (d) $RuCl_3$ (cat.), $NaIO_4$ (2 equiv.), CH_3CN, CCl_4, H_2O, 30 min; (e) BnBr (4 equiv.), NaH (4.5 equiv.), DMF, 1 h; (f) 80% AcOH, 60°C, 3 h; (g) $NaBrO_3$ (6 equiv.), $Na_2S_2O_4$ (6 equiv.), EtOAc, H_2O, 12 h

The compound **4** was prepared by the method of Yuasa and co-workers.[1] The tethering arm of salacinol is a derivative of erythritol and the cyclic sulfate precursor could be derived either from D- or L-glucose, depending on the protecting group for the hydroxyl groups as shown in Scheme 1. Periodate oxidation of 4,6-*O*-isopropylidene-D- or L-glucose (**6**)[5] followed by reduction of the resulting aldehyde gave the 2,4- or 1,3-*O*-isopropylidene-D-erythritol (**7** or **9**). Formation of the cyclic sulfate at the remaining diol function was carried out by the reported method to give the compound **8** or **10**. Benzylation of hydroxyl groups of the compound **7** followed by deisopropylidenation gave the precursor (**12**) of the cyclic sulfate (**13**). Oxidative debenzylation[6] of the compound **13** afforded the cyclic sulfate (**14**) with free hydroxyl groups. Benzylidenated cyclic sulfate (**16**) was deduced from 2,4-*O*-benzylidene-D-erythritol (**15**).[7]

Model experiments simulating the coupling reactions between the compound **4** and the cyclic sulfates were undertaken by using tetrahydrothiophene (THT) as a nucleophile. While the cyclic sulfate (**8**) protected with the isopropylidene group reacted with THT at 45°C in dimethylformamide (DMF) giving the coupled product (**17**),[8] that protected with benzyl group (**13**) or with the benzylidene group (**16**) or unprotected cyclic sulfate (**14**) did not react under the same conditions used for the formation of **17** (Scheme 2). These cyclic sulfates only decomposed when the bath temperature was increased to 60–70°C. Use of methanol, water, or acetonitrile as solvent gave no products, while dimethyl sulfoxide can substitute for DMF. Deisopropylidenation of the compound **17** was carried out by 0.01% HCl to give the compound **18**, which is the assumed product of the coupling reaction between THT and the unprotected cyclic sulfate (**14**). The compound **18** was stable under the conditions for the coupling reaction (45°C in DMF for 9 h), indicating that the reason for the unsuccessful coupling reaction with the unprotected cyclic sulfate **14** was not due to instability of the product that might exist temporarily. Protons of the hydroxyl groups might interfere with the nucleophilic attack of THT. In the same manner, the nucleophilic attack can be blocked by a benzyl or benzylidene group.



Scheme 2. (a) DMF, 45 °C, 13 h; (b) 0.01% HCl, 40°C, 4 h

The coupling reaction between the compound **4** and 1,3- or 2,4-*O*-isopropylidene-D-erythritol (**8** or **10**) was successful and afforded the coupling product (**19** or **20**). The coupling products were then deisopropylidenated to give salacinol **2**[9] and its diastereomer (**21**),[10] respectively. The NMR

spectra and optical rotation of salacinol **2** were in good accordance with those reported.[2] Yoshikawa and co-workers reported the absolute configuration of salacinol differently in the first[2a] and the latter[2b,c] papers. Our result supported the structure depicted in the latter papers. Stereochemistry at the sulfonium center of the diastereomer **21** was determined to be *S*, the same configuration as that of salacinol, from the existence of strong NOEs between one of two H-1s and H-4′. Syntheses of the derivatives of salacinol, the new candidates as glycosidase inhibitors, using the strategy developed in this study are underway.

Acknowledgements

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8. Compound **17**: $[\alpha]_D^{23}$ –15.4 (*c* 1.05, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (ddd, J = 5.7, 9.6, 9.8 Hz, 1H, H-3), 4.30 (ddd, J = 3.0, 3.8, 9.8 Hz, 1H, H-2), 4.13 (dd, J = 5.7, 11.5 Hz, 1H, H-4), 3.94 (dd, J = 3.0, 13.7 Hz, 1H, H-1a), 3.85 (m, 1H, -*CH*H-S), 3.80 (dd, J = 9.6, 11.5 Hz, 1H, H-4), 3.68 (m, 1H, -*CH*H-S), 3.56 (dd, J = 3.8, 13.7 Hz, 1H, H-1b), 3.56 (m, 1H, -*CH*H-S), 3.45 (m, 1H, -*CH*H-S), 2.36 (m, 4H, -CH_2-C-S), 1.49, 1.41 (each s, each 3H, CH_3); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 99.9, 77.2, 69.6, 67.6, 62.3, 46.7, 45.2, 44.8, 28.6, 28.4, 19.1; HRMS (ESI) calcd for $[C_{11}H_{20}O_6S_2+H]^+$: 313.0780; found: 313.0784.
9. Compound **2**: $[\alpha]_D^{23}$ +5.1 (*c* 1.02, methanol), lit.[2] $[\alpha]_D^{28}$ +4.9 (*c* 0.35, methanol); HRMS (ESI) calcd for $[C_9H_{18}O_9S_2+H]^+$: 335.0470; found: 335.0466.
10. Compound **21**: $[\alpha]_D^{23}$ –25.2 (*c* 1.17, methanol); ^{1}H NMR (400 MHz, pyridine-d_5 with a drop of D_2O) δ 5.19 (ddd, J = 3.4, 3.7, 8.2 Hz, 1H, H-3′), 5.15 (m, 1H, H-2), 5.14 (m, 1H, H-3), 4.97 (ddd, J = 5.1, 4.0, 8.2 Hz, 1H, H-2′), 4.81 (dd, J = 4.0, 13.0 Hz, 1H, H-1′), 4.76 (m, 1H, H-4), 4.67 (dd, J = 3.4, 11.9 Hz, 1H, H-4′), 4.59 (dd, J = 6.7, 6.1 Hz, 2H, H-5), 4.51 (dd, J = 5.1, 13.0 Hz, 1H, H-1′), 4.41 (dd, J = 3.7, 11.9 Hz, 1H, H-4′), 4.28 (dd, J = 3.7, 12.7 Hz, 1H, H-1), 4.16 (dd, J = 2.7, 12.7 Hz, 1H, H-1); ^{13}C NMR (67.8 MHz, pyridine-d_5) δ 79.3, 79.2, 79.0, 71.8, 67.5, 62.1, 60.2, 52.8, 51.0; HRMS (ESI) calcd for $[C_9H_{18}O_9S_2+H]^+$: 335.0470; found: 335.0477.