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Synthesis of 1-Deoxynojirimycin-Trehalamine Fused Compound and Its Related Compounds

Masao Shiozaki,*[a] Osamu Ubukata,[b] Hideyuki Haruyama,[b] and Reiko Yoshiike[c]

[a] Exploratory Chemistry Research Laboratories, Sankyo Co. Ltd.
[b] Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd.
[c] Biomedical Research Laboratories, Sankyo Co. Ltd.
Hiromachi 1-2-58, Shinagawa-ku, Tokyo 140, Japan

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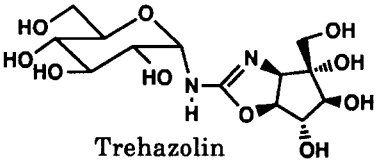
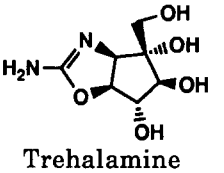
Abstract: *1-Deoxynojirimycin-trehalamine fused compound **10** as a mixture together with **11** and its related compound **19** were synthesized The enzyme inhibitory activities of the mixture (**10** and **11**), **19** and **20** exhibited IC_{50} values of 0.68, 4.2, and 1.5 μg/ml, respectively, toward rat intestinal maltase.*

α-Glucosidases catalyze the resio-specific hydrolysis of α-glucosidic linkage of oligo- and polysaccharides such as starch. Many α-D-glucosidase inhibitors for therapeutic use have been investigated to control diabetes, obesity, HIV, metastasis of cancer, and so on. 1-Deoxynojirimycin was found to be a potent inhibitor of intestinal oligo- and disaccharidases in mammals.[1] Trehazolin, which is a pseudodisaccharide consisting of an α-glucosyl group and a unique aglycon moiety (trehalamine), exhibited powerful inhibitory activity toward various trehalases.[2] We were interested in the structure and α-glucosidase inhibitory activity of 1-deoxynojirimycin-trehalamine fused compound (**10**), a pseudodisaccharide, and its related compounds. Here we describe the synthesis of compound **10** and **19**.



Trehazolin



Trehalamine

Trehazolin aminocyclitol moiety (trehazolamine) **1**, obtained by hydrolysis of natural trehazolin[3] or by synthesis,[4] was treated with benzyl chloroformate in THF-H_2O containing pyridine at 0-5 °C, and the resulting *N*-benzyloxycarbonyl compound was converted to tri-*O*-silylated **2**[5] and tetra-*O*-silylated **3** with *tert*-butyldimethylsilyl chloride and 4-dimethylaminopyridine in *N,N*-dimethylformamide. Compound **2** was also silylated at 20-25 °C for four days to give **3**, accompanied by the recovery of **2**. Hydrogenolysis of **3** using

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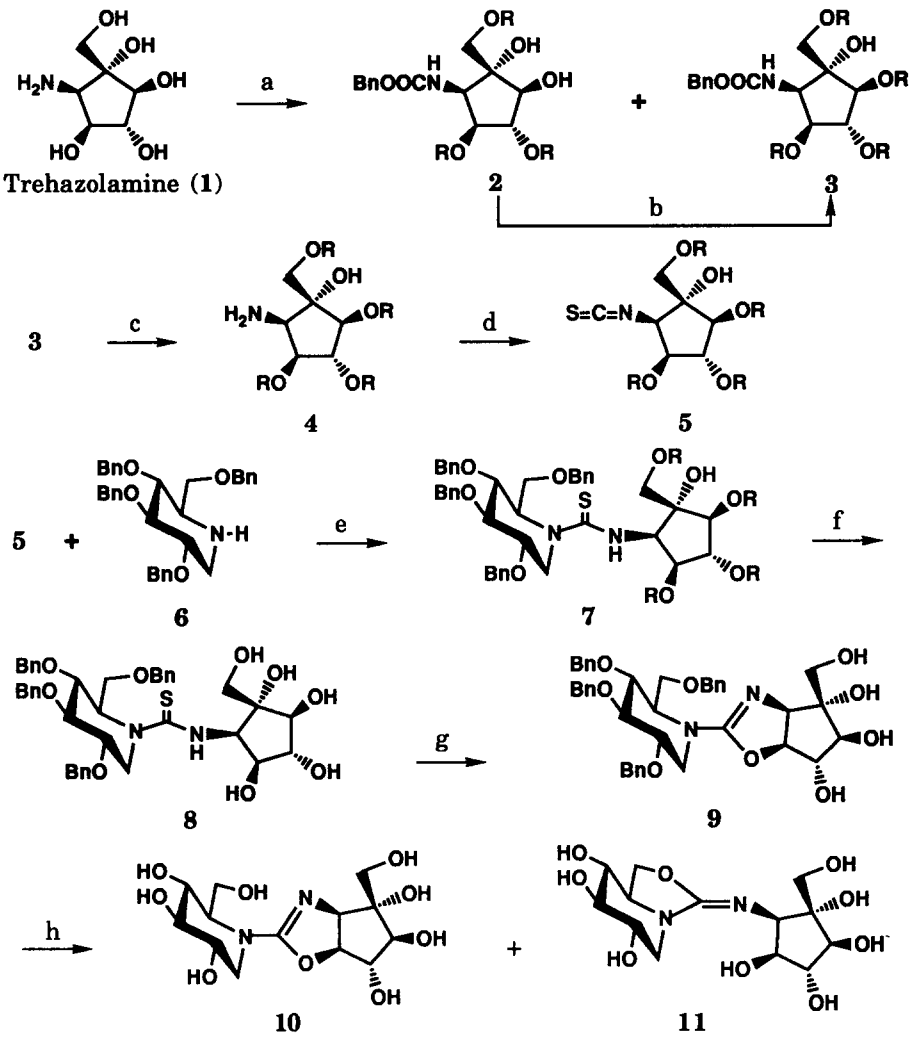
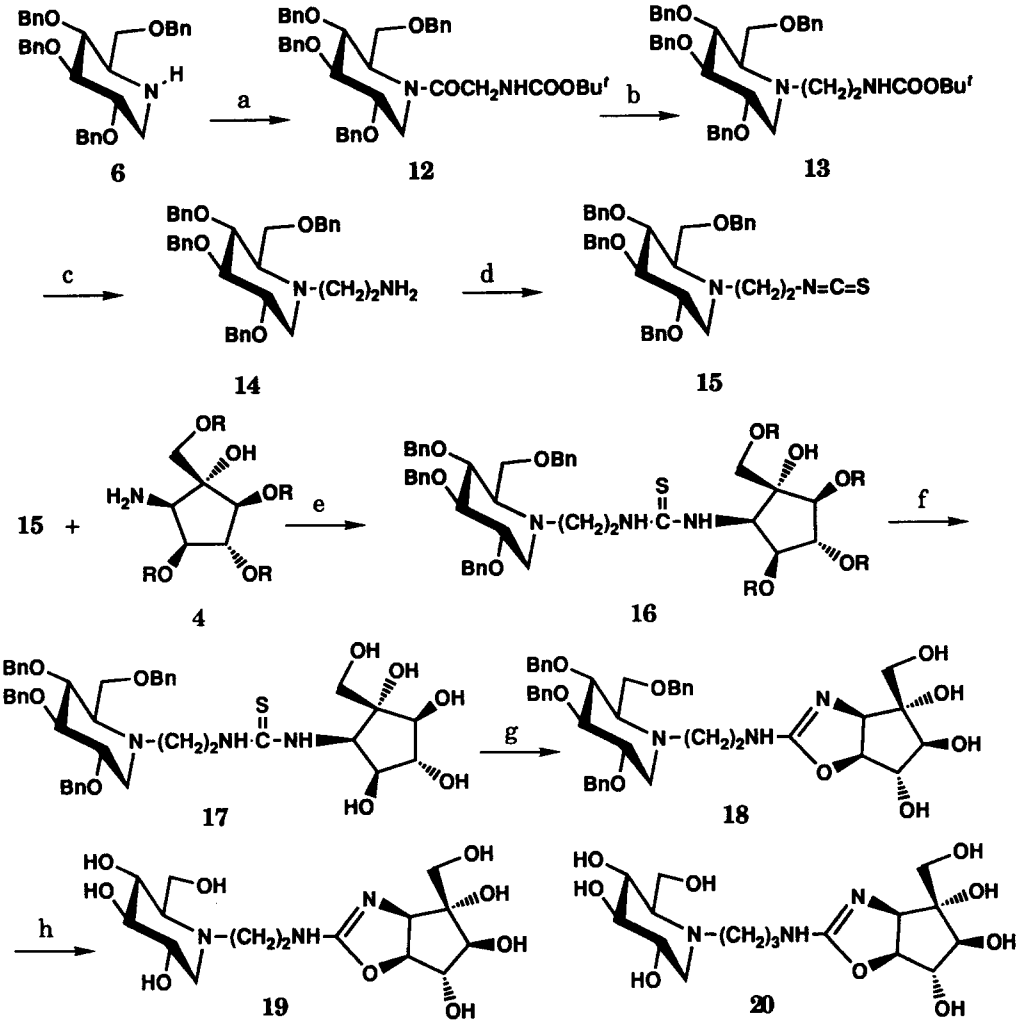
Scheme 1



Reagents and conditions: R = *t*-BuMe$_2$Si; a) ClCOOBn, pyridine, H_2O-THF (2:1), 0-5 °C, 30 min, concentrated; then *t*-BuMe$_2$SiCl, DMAP, DMF, 20-25 °C, 16 h, **2**, 34%, **3**, 11%; b) *t*-BuMe$_2$SiCl, DMAP, DMF, 20-25 °C, 4 days, ca. 62% (recovery **2**, 38%); c) H_2, Pd/C, THF, 24 °C, 8 h, 92%; d) CS_2, Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 24 °C, 2.5 h, 87%; e) Et_3N, THF, 60-65 °C, 3 h, 68% (recovery of **5**, 22% and **6**, 19%); f) *n*-Bu$_4$NF, THF, 24 °C, 3 h, 93%; g) 2-chloro-3-ethylbenzoxaolium tetrafluoroborate, Et_3N, MeCN, 0 °C, 10 min, 95%; h) H_2, $Pd(OH)_2$/C, MeOH, 60 °C, 40 min, a 4:1 equilibrium mixture of **10** and **11**, 32%.

palladium on carbon as a catalyst gave **4**. Treatment of **4** with carbon disulfide, Et3N and 2-chloro-1-methylpyridinium iodide in CH_2Cl_2 gave isothiocyanate **5** as a solid (mp 47-49 °C) after purification with silica gel chromatography. Reaction of compound **5** and tetra-*O*-benzyl-1-deoxynojirimycin (**6**), prepared by the reported method,[6] in a small volume of

Scheme 2



Reagents and conditions: R = *t*-$BuMe_2SiCl$; a) *t*-BuOOCNHCH$_2$COOH, DCC, CH_2Cl_2, 24 °C, 16 h; b) BH_3-THF complex, 24 °C, 16 h, two steps 62%; c) CF_3COOH, CH_2Cl_2, 24 °C, 30 min; d) CS_2, Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 24 °C, 2.5 h, two steps 41%; e) catalytic Et_3N, THF, 20-25 °C, 2 days, 87%; f) 10% HCl-MeOH, MeOH, 24 °C, 16 h, quantitative; g) 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, 0-5 °C, 1 h, then Et_3N, MeCN, 0 °C, 30 min, 67%; h) H_2, $Pd(OH)_2$/C, MeOH, 65 °C, 8 h, 72%.

tetrahydrofuran using triethylamine as a catalyst gave thiourea **7**. Treatment of **7** with tetrabutylammonium fluoride gave pentaol **8**. Treatment of **8** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and triethylamine in acetonitrile gave 1-deoxynojirimycin-trehalamine fused oxazoline compound **9**. Hydrogenolysis of tetra-*O*-

benzyl **9** using $Pd(OH)_2$ on carbon as a catalyst gave a 4:1 equilibrium mixture of **10** and **11** after chromatographic purification using Amberlite CG-50 (NH_4^+ type/H^+ type = 3/2) followed by lyophilization.[7]

The synthesis of **19** was conducted as follows. Condensation of **6** with *N*-(*tert*-butoxycarbonyl)glycine using DCC as a condensing reagent gave amide **12**. Reduction of **12** with BH_3-THF complex gave tertiary amine **13**. Deprotection of *t*-BOC group of **13** with CF_3COOH gave primary amine **14**. Isothiocyanate formation from **14** using CS_2, Et_3N and 2-chloro-1-methylpyridium iodide yielded **15**. Treatment of isothiocyanate **15** with amine **4** using Et_3N as a catalyst gave thiourea **16**, which was also obtainable from the condensation of isothiocyanate **5** and amine **14**. Desilylation of tetra-*O*-silylated compound **16** in MeOH containing 10% HCl yielded **17**. Treatment of **16** with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate and Et_3N gave aminooxazoline **18**. Deprotection of 2,3,4,6-tetra-*O*-benzyl groups of **18** with H_2 using $Pd(OH)_2$ on carbon as a catalyst gave **19**.[8] Compound **20** was also synthesized by the same successive treatment of isothiocyanate **5** and *N*-(3-aminopropyl)-1-deoxy-2,3,4,6-tetra-*O*-nojirimycin also obtained from **6** and *N*-(*tert*-butoxycarbonyl)-β-alanine.

The IC_{50} values for the biological activity of the mixture of (**10** and **11**), **19** and **20** toward rat intestinal maltase were 0.68, 4.2, and 1.5 μg/ml, respectively.

References and Notes

1. D. D. Schmidt, W. Frommer, L. Muller, E. Truscheit, *Naturwissenschaften*, **66**, 584 (1979).
2. O. Ando, H. Satake, K. Itoi, A. Sato, M. Nakajima, S. Takahashi, H. Haruyama, Y. Ohkuma, T. Kinoshita, and R. Enokita, *J. Antibiot.*, **44**, 1165 (1991).
3. O. Ando, M. Nakajima, K. Hamano, K. Itoi, S. Takahashi, Y. Takamatsu, A. Sato, R. Enokita, T. Okazaki, H. Haruyama, and T. Kinoshita, *J. Antibiot.*, **46**, 1116 (1993).
4. Y. Kobayashi, H. Miyazaki, and M. Shiozaki, *J. Org. Chem.*, **59**, 813 (1994).
5. The silylated position of **2** was determined from the ^{1}NMR analysis after the acetylation of the secondary alcohol of **2** by acetic anhydride-pyridine.
6. H. S. Overkleeft, J. van Wiltenburg, and U. K. Pandit, *Tetrahedron*, **50**, 4215 (1994).
7. 400 MHz ^{1}H NMR of **10**: (D_2O) δ 2.44 (H, d, J=11.4 Hz, C6*H*), 2.52 (1H, m), 3.10 (1H, dd, J=4.7, 11.4 Hz, C6*H*), 3.22 (1H, m), 3.32 (1H, t, J=9.5 Hz, C3*H*), 3.45 (1H, dd, J=4.7, 9.5 Hz, C2*H*), 3.62 (1H, m, C6*H*), 3.77 (1H, C4'C*H*), 3.80 (1H, m, C6*H*), 3.87 (1H, C4'C*H*), 3.96 (1H, m, C5'*H*), 4.25 (2H, m, C3a'*H* and C6'*H*), 5.00 (1H, m, C6a'*H*).
8. 400 MHz ^{1}H NMR of **19**: (D_2O) δ 2.13-2.22 (2H, m, C*H*$_2$NH), 2.58 (1H, quintet, J=6.4-6.8 Hz, N-C*H*), 2.75 (1H, quintet, J=6.8-7.3 Hz, N-C*H*), 2.88 (1H, dd, J=4.9, 11.7 Hz, C1*H*),), 3.08 (1H, t, J=9.3 Hz), 3.10-3.20 (2H, m), 3.18 (1H, t, J=9.3-9.8 Hz), 3.36 (1H, dt, J=4.9, 9.3 Hz), 3.55, 3.65 (2H, AB-q, J=11.7 Hz, C4'C*H*$_2$), 3.67 (1H, d, J=2.4 Hz), 3.73-3.77 (2H, m), 3.99 (1H, dd, J=2.4, 4.4 Hz), 4.16 (1H, d, J=8.3 Hz), 4.75 (1H, dd, J=1.0, 8.8 Hz).