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SYNTHESIS OF 6-*EPI*-TREHAZOLIN FROM D-RIBONOLACTONE: EVIDENCE FOR THE NON-EXISTENCE OF A 5,6-RINGFUSED STRUCTURAL ISOMER OF 6-*EPI*-TREHAZOLIN

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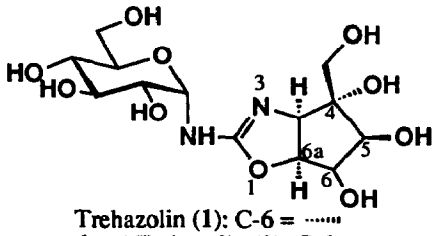
Abstract: 6-*Epi*-trehazolin was synthesized in a stereocontrolled manner, and this synthesis provided proof for the non-existence of oxazine structural isomer of 6-*epi*-trehazolin.

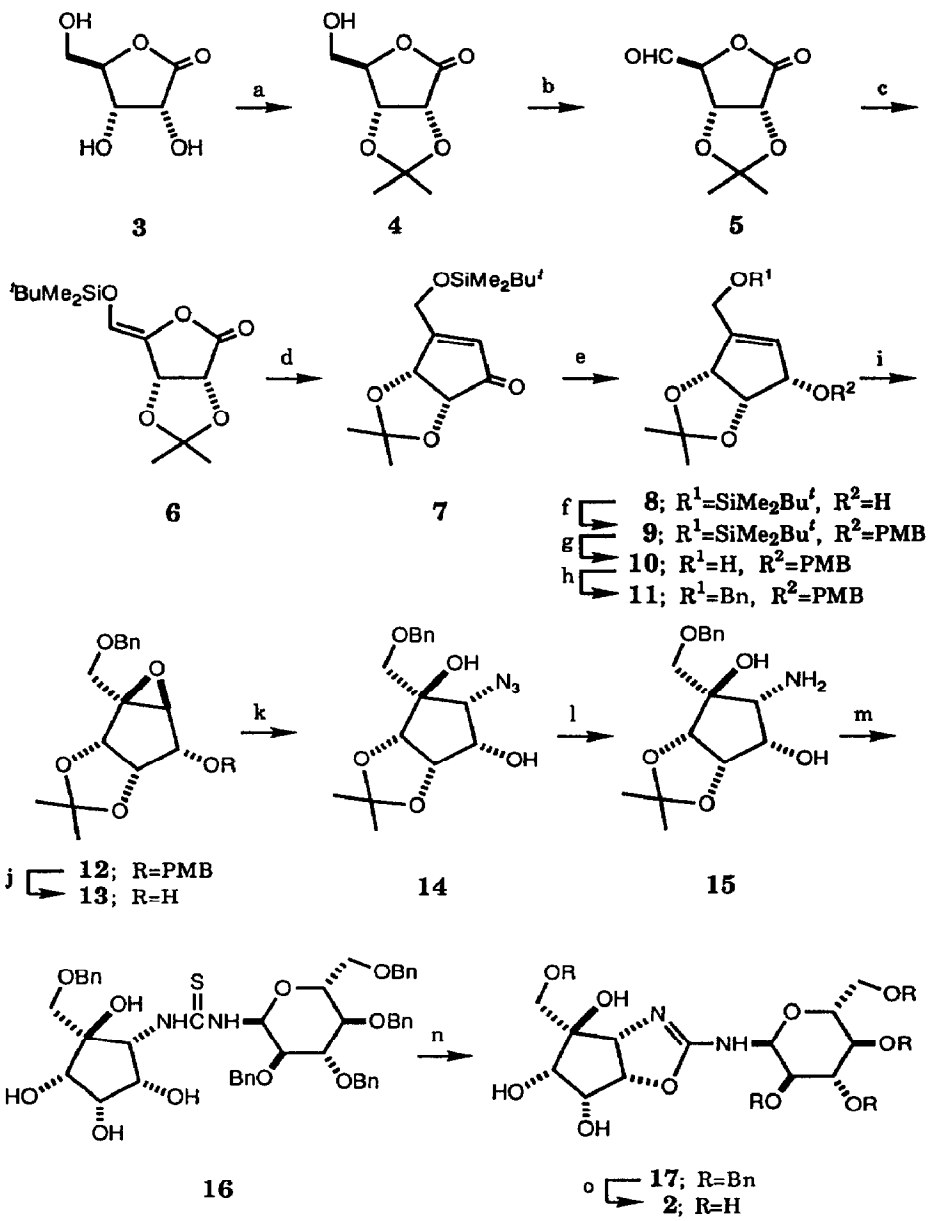
Recently, it has been recognized that trehalase is an enzyme of paramount ecological importance in control of insects and certain fungi. Trehazolin, a potent inhibitor of trehalase produced by *Micromonospora* sp. SANK 62390, was isolated from the culture broth by a Sankyo group.[1] Based on spectral data analyses, the pseudosaccharide structure consisting of an α-glucosyl group and a unique aglycon moiety was elucidated for **1**. The absolute configuration of **1** has been confirmed by a synthetic study.[2]

We were interested in the biological activity of trehalase, particulary in the inhibitory activity of trehazolin and trehazolin analogues, namely, trehalostatin (5-*epi*-trehazolin), other epimers and 5,6-ringfused structural isomers on the trehalase enzyme itself. In this paper, we describe the synthesis of 6-*epi*-trehazolin (**2**) and its 5,6-ringfused structural isomer from D-ribonolactone.



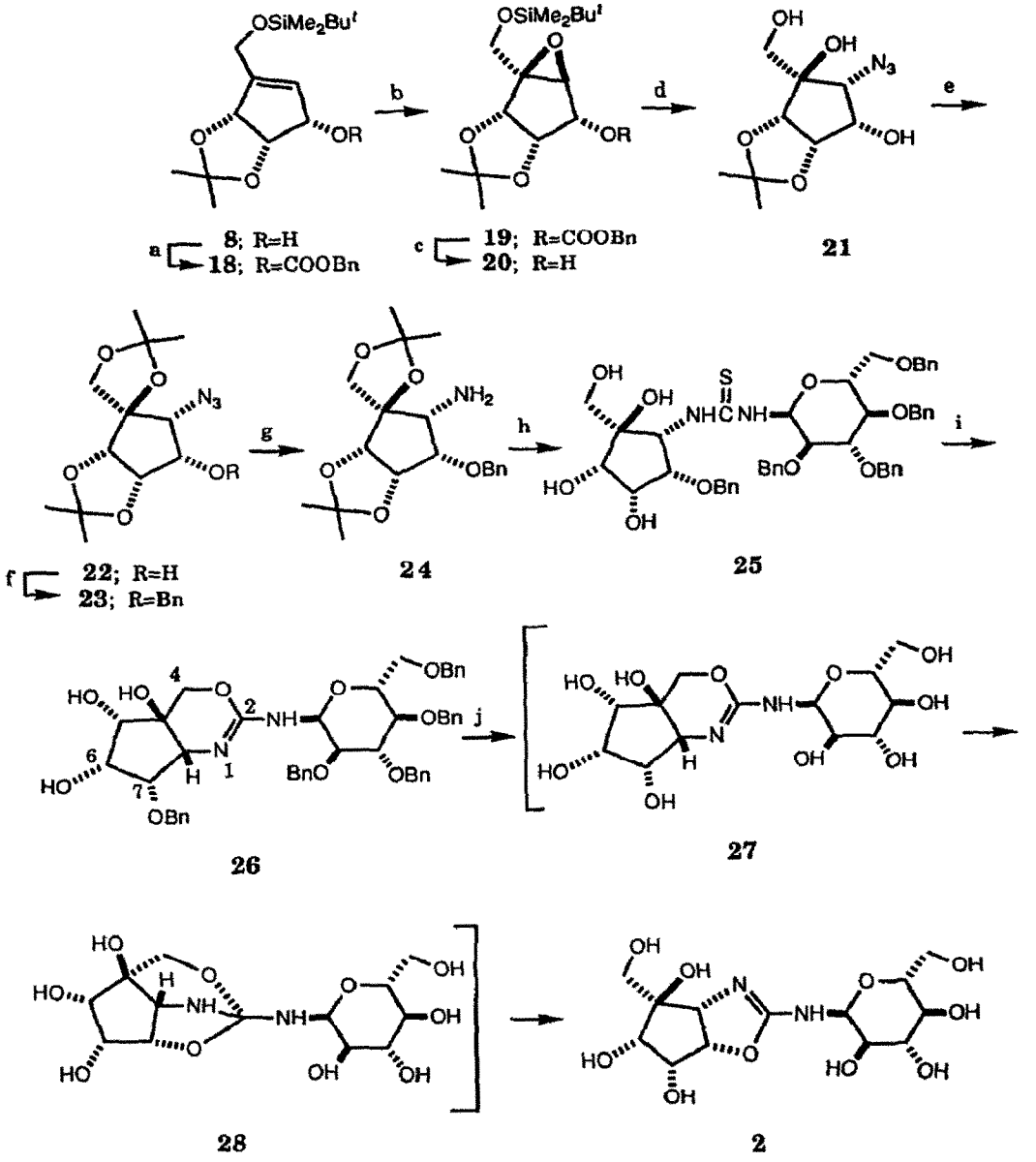
Trehazolin (**1**): C-6 = ·····
6-*epi*-Trehazolin (**2**): C-6 = ——

Treatment of D-(+)-ribonolactone **3** in the suspension of 2,2-dimethoxypropane using pyridinium *p*-toluenesulfonate (PPTS) as a catalyst , and then 1M-HCl aqueous in tetrahydrofuran (THF) gave 2,3-*O*-isopropylidene-D-ribonolactone **4**.[3] Pfitzner-Moffatt oxidation[4] of **4** gave an aldehyde **5**. Treatment of **5** with *tert*-butyldimethylsilyl chloride and 1,4-diazabicyclo[2.2.2]octane (DABCO) in *N,N*-dimethylformamide (DMF) gave *Z*-silyl enolether **6** (mp 94-96°C). A tandem Aldol-Wittig type reaction of **6** with α-lithiomethylenetriphenylphosphorane ($LiCH{=}PPh_3$)[5] in THF gave the cyclopentenone **7** in one pot. This reaction should be synthetic utility as a one step synthesis of cyclic α,β-unsaturated ketones from cyclic enolester type derivatives.



Bn = benzyl; PMB = *p*-methoxybenzyl

(a) 2,2-dimethoxypropane, PPTS, DMF, 50°C, 1 h, then 1M-HCl, THF, 1 h, 82%; (b) DCC, DMSO, cat H_3PO_4, 80%; (c) DABCO, $^tBuMe_2SiCl$, DMF, 0-5°C, 1 h, 43%; (d) $LiCH{=}PPh_3$, THF, -78°C, 15 min, then 24°C, 17 h, 46%; (e) $NaBH_4$-$CeCl_3{\cdot}7H_2O$, EtOH, 24°C, 30 min, 89%; (f) *p*-methoxybenzyl chloride, NaH, DMF, 24°C, 3 h, 69%; (g) Bu_4NF, THF, 24°C, 3 h, 93%; (h) BnBr, NaII, DMF, 24°C, 2 h, 100%; (i) MCPBA, $CHCl_3$, 24°C, 24 h, 55%; (j) DDQ, CH_2Cl_2-H_2O, 99%; (k) NaN_3, NH_4Cl, DMF, 100°C, 16 h, 99%; (l) PPh_3, THF, 20-25°C, 7 days, then addition of H_2O, 24°C, 16 h, 97%; (m) 2% HCl-MeOH, 50°C, 3 h, then 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate, Et_3N, THF-H_2O (5:1), 24°C, 2 h, 71%; (n) 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, MeCN, N_2, 0-5°C, 2 h, then addition of Et_3N, 0°C, 30 min and 24°C, 30 min, 85%; (o) $Pd(OH)_2$/C, MeOH, 60°C, 30 min, 37%.



Bn = benzyl

(a) BnOOCCl, DMAP, CH_2Cl_2, 5°C, 1 h and 24°C, 30 min, 84%; (b) MCPBA, $CHCl_3$, 24°C, 4 days, 89%; (c) H_2, 10% Pd/C, EtOAc, 24°C, 30 min, 100%; (d) NaN_3, NH_4Cl, DMF, 100°C, 16 h, 92%; (e) 2,2-dimethoxypropane, TsOH, DMF, 24°C, 16 h, 80%; (f) BnBr, NaH, DMF, 24°C, 1 h, 100%; (g) PPh_3, THF, 24°C, 7 days, then addition of H_2O, 24°C, 10 h; (h) 2% HCl-MeOH, 50°C, 4 h; and 2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucopyranosyl isothiocyanate, Et_3N, THF-H_2O (5:1), 24°C, 2 h, 72% from **23**; (i) 2-chloro-3-ethylbenzoxazolium tetrafluoroborate, MeCN, N_2, 0-5°C, 71%; (j) H_2, $Pd(OH)_2/C$, MeOH, 60°C, 1 h, 42%.

Selective reduction of the ketone **7** using sodium borohydride and cerium trichloride[6] whilst leaving the double bond intact gave an alcohol **8**, exclusively. Protection of the alcohol of **8** with *p*-methoxybenzyl chloride and sodium hydride in DMF gave **9**. The silyl protective group of **7** with tetrabutylammonium fluoride was removed to give **10**, which was re-protected with benzyl bromide and sodium hydride to yield **11**. Epoxidation of **11** with *m*-chloroperoxybenzoic acid (MCPBA) afforded an epoxide **12**. The methoxybenzyl group was removed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[7] to give **13**. Treatment of **13** with sodium azide and ammonium chloride gave an azide **14**. The azide group was reduced with triphenylphosphine[8] in THF, and then water gave **15** (mp 86-87°C). Deprotection of isopropylidene group of **15** with 2% hydrochloric acid in methanol gave an amine hydrochloride and then key coupling step of this amine salt with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl isothiocyanate[9] afforded an α-D-glucopyranosyl thiourea **16** by treatment with triethyl amine in THF-H_2O. Compound **16** was further converted to **2**, $[\alpha]_D^{25}$ +123° (c 0.71, H_2O), via **17** according to the reported method.[2]

Further, we attempted to synthesize 5,6-ringfused structural isomer **27**. Treatment of **8** with benzyl chloroformate and 4-dimethylaminopyridine (DMAP) gave **18**. Epoxidation of **18** with MCPBA afforded an epoxide **19** exclusively. With 10% Pd on carbon as a catalyst, hydrogenolysis of **19** gave an alcohol **20**. Treatment of **20** with NaN_3 and NH_4Cl in DMF gave a desilylated azidotriol **21**. The vicinal diol of **21** was protected as an isopropylidene to give a crystalline **22** (mp 75.5-76.5°C).[10] Protection of alcohol **22** with benzyl chloride and sodium hydride yielded **23**. Treatment of **23** by the same procedure described above: (i) reduction of azide to amine (**24**); (ii) deprotection of diisopropylidene groups; then thiourea formation (**25**); and (iii) aminooxazine formation gave **26**.

To our surprise, when the benzyl groups of **26** were removed by hydrogenolysis, **26** gave **2**. It seems that the unstable **27** possibly underwent transformation to intermediate **28**, and finally **28** was converted to the most stable **2**.

References

(1) (a) Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H. *J. Antibiotics* **1991**, *44*, 1165-1168. (b) Ando, O.; Nakajima, M.; Hamano, K.; Itoi, K.; Takahashi, S.; Haruyama, H.; Kinoshita, T. *J. Antibiotics* accepted for publication.
(2) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 10065-10066.
(3) Barton, D. H. R.; Camara, J.; Cheng, X.; Gero, S. D.; Jaszberenyi, J. Cs.; Quiclet-Sire, B. *Tetrahedron* **1992**, *48*, 9261-9276.
(4) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc* **1963**, *85*, 3027-3028. (b) Jones, G. H.; Moffatt, J. G. *Methods in Carbohydrate Chem*istry **1972**, *6*, 315-322.
(5) Corey, E. J.; Kang, J.; Kyler, K. *Tetrahedron Lett.* **1985**, *26*, 555-558.
(6) Gemal, A. L.; Luche, J. L. *J. Am. Chem Soc.* **1981**, *103*, 5454-5459.
(7) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021-3028.
(8) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763-764.
(9) Camarasa, M. J.; F-Resa, P.; D-L-Heras, F. G.; M-Castrillin, P. P.; Felix, A. S. *Synthesis* **1984**, 509-510.
(10) The structure was further confirmed by X-ray crystallographyic analysis.

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