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SYNTHESIS AND ABSOLUTE CONFIGURATION OF TREHAZOLIN AMINOCYCLITOL MOIETY

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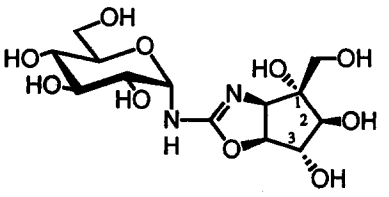
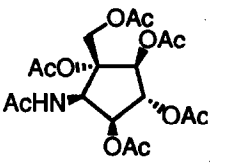
Abstract: Optically active [1*R*-(1α,2β,3α,4β,5β)]-5-acetamide-1-acetoxymethyl-1,2,3,4-tetraacetoxycyclopentane **2** was synthesized from D-glucose. Compound **2** was identical in all respects with the hexaacetate derived from the natural trehazolin aminocyclitol moiety.

In 1991, Ando *et al*[1]. reported the isolation of trehazolin (**1**) from a culture broth of *Micromonospora* strain SANK 62390. Its structure was elucidated as a pseudodisaccharide from degradation and ^{1}H-NMR analysis. Trehazolin has powerful inhibitory activities toward various trehalases, and we expect it to become an important lead compound for medicines. A Suntory group reported the isolation of trehalostatin. The stereochemistry of the C-2 position of trehalostatin is different from that of trehazolin.[2] Therefore, we felt it nessesary to confirm the structure, including the absolute configuration, of trehazolin.

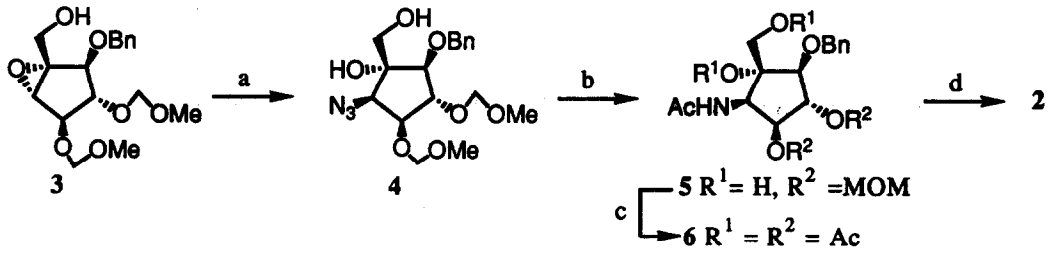


Trehazolin (**1**)



2

The Ogawa group has synthesized racemic pentaacetates of trehazolin and trehalostatin aminocyclitol moieties. Recently we completed the syntheses of chiral trehazolin and its aglycon,[4] which has the same specific rotation as natural trehazolin aglycon. Herein we disclose a synthesis of trehazolin aminocyclitol moiety hexaacetate (**2**) from the important intermediate (**3**).



a) 14 eq. NaN_3, 14 eq. NH_4Cl, DMF, 120°C, 72 h, 79%. b) H_2, 10% Pd-C, MeOH, room temperature, 2 h; then 5.0 eq. Ac_2O, MeOH, room temperature, 5 h, 76%. c) 5%-HCl-MeOH, 30 min; then excess Ac_2O, cat. 4-DMAP, pyridine, room temperature, 24 h, 74%. d) H_2, $Pd(OH)_2$-C, EtOH, room temperature,1 h; then excess Ac_2O, cat. 4-DMAP, pyridine, room temperature, 5 h, 61%.

Azidation [5] of compound **3**, which was derived from 4,6-*O*-benzylidene methyl-α-D-glucopyranoside in 11 steps containing [2+3] cycloaddition and Sharpless' epoxidation as key steps, gave an azidodiol **4**, regiospecifically. Subsequent hydrogenation of the azide group and acetylation of the corresponding amino group afforded acetamide **5** . After cleavage of two methoxymethyl groups by treatment with 5% HCl in methanol at 50°C, the complete acetylation of the corresponding tetraol afforded compound **6** (m.p. 129°-130°) . Finally **6** was hydrogenolyzed to cleave the benzyl group, and subsequent acetylation afforded **2** ($[\alpha]_D^{25}$ +6.0° (C;1.23, $CHCl_3$)).[6] Compound **2** was identical in all respects with hexaacetate ($[\alpha]_D^{25}$ +5.9° (C; 1.08, $CHCl_3$)) of the aminocyclitol (degradation product of natural trehazolin). We could thus determine that the absolute configuration of natural trehazolin aminocyclitol moiety is [1*R*-(1α,2β,3α,4β,5β)].

References:

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6. 270 MHz, ^{1}H-NMR ($CDCl_3$) δ: 2.02 (3H, s), 2.07 (3H, s), 2.08 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 4.56, 4.63 (2H, AB-q, *J*=12.2 Hz, C-1 -CH_2O-), 5.24 (1H, t, *J*=4.9 Hz, H-3) 5.33 (1H, dd, *J*=7.8, 9.3 Hz, H-5), 5.38 (1H, dd, *J*=4.9, 7.8 Hz, H-4), 5.81 (1H, d, *J*=4.9 Hz, H-2), 5.86 (1H, d, *J*=9.3 Hz, NH).

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