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Facile Preparation of a Highly Functionalized Tetrahydropyran by Catalytic Hydrogenation of an Oxazoline

Dusan Hesek, Mijoon Lee, Takao Yamaguchi, Bruce C. Noll, and Shahriar Mobashery*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

mobashery@nd.edu

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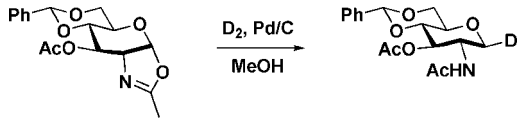
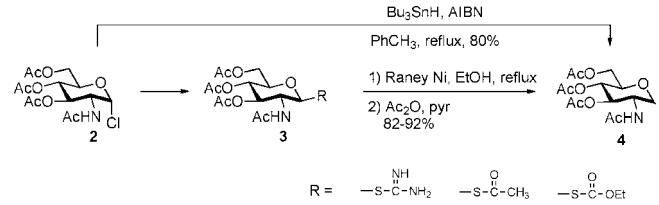
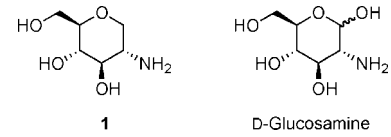


2-Amino-1,5-anhydro-2-deoxy-D-glucitol, a highly functionalized tetrahydropyran, is a versatile building unit in many natural products. A facile route to this type of synthetic building unit from the corresponding 2-aminopyranoses, as exemplified by an application to D-glucosamine, is outlined. A simple catalytic hydrogenation at C-1 of an oxazoline constructed from the corresponding 2-aminopyranose results in the desired product.

2-Amino-1,5-anhydro-2-deoxy-D-glucitol (**1**) and its derivatives serve as a mimic of glucosamine-containing natural products[1−5] or as intermediates in syntheses of D-galactitol derivatives.[6] There are literature precedents on the synthesis of **1**, which exploit the two main approaches shown in Scheme 1.[7−10] One is the use of Raney nickel desulfurization of 1-thioglucopyranose derivatives (**3**), which in turn have been prepared from glucopyranosyl chloride (**2**).[7,8] Yields are generally good by this method, but it requires the use of excess Raney nickel (5−10 g of metal per 1 g of substrate). The use of the excess metal catalyst has problems of its own, such as partial removal of the acetyl groups necessitating reacetylation of the samples. Removal of the 1-phenyl sulfide moiety was observed also during deprotection of the benzyl ether and phenylsulfonamide, using sodium in liquid ammonia, as an undesired side reaction.[9] The second approach is a more recent application, starting from the chloride **2** and its reduction in the presence of AIBN and tributyltin hydride under reflux.[10]

SCHEME 1. Known Synthetic Entries to 2-Acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-glucitol





Tetrahydropyrans such as **1** are valuable synthetically tools. They can be accessed from the corresponding aminopyranoses, yet the structural class is highly functionalized with defined stereochemistry at various positions, all of which can in turn be manipulated further by selective reactivity of each stereogenic center. These tetrahydropyrans are found as structural modules of many D-glucosamine-related natural products mimics.[1−5]

We report herein a new method for the generation of 2-acetamido-1,5-anhydro-2-deoxy-D-glucitol derivative (as an example, see **8f**) using a simple catalytic hydrogenation reaction to access the structural class. The method might arguably be the most facile entry into these molecules from the readily available precursors. Its facility should make the approach amenable to a host of synthetic applications.

The oxazoline intermediates of the type **7** have widely been used as glycosyl donors in sugar chemistry.[11] They are easily accessed from *N*-acetyl-D-glucosamine (**5**) in two to three steps (Scheme 2). They direct the formation of the β-(1,4) glycosidic linkage, and they do not require additional steps to protect and to deprotect the amino functionality. We prepared the oxazoline **7** in two steps starting from *N*-acetyl glucosamine (**5**) according to literature precedents.[12,13] Catalytic hydrogenation of compound **7** could potentially result in several products, as depicted in Scheme 2. These potential reactions include reduction of the benzylidene by itself (**8a**), reduction of the benzylidene in conjunction with reduction at C-1 (**8b**), or reduction of the benzylidene concurrent with methanolysis at C-1 in the presence of a metal catalyst (**8c**). Alternatively, one could envision methanolysis taking place at C-1 (**8d**), reduction of the imine

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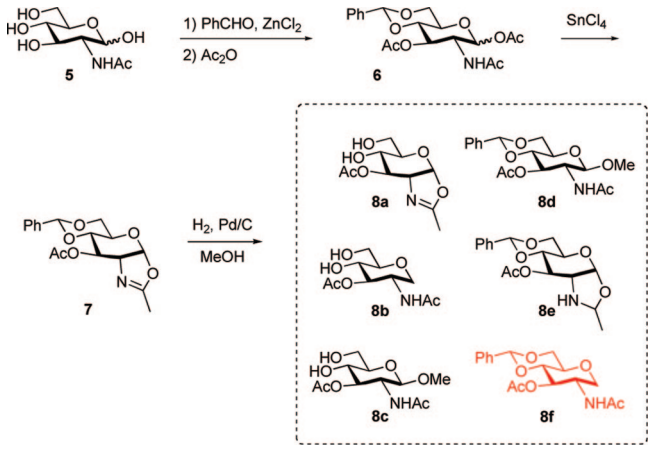
SCHEME 2



moiety in the oxazoline ring (**8e**), or merely reduction at C-1 (**8f**). As is disclosed in this paper, we can set up the system to give exclusively the reduction at C-1, leading to the formation of the desired tetrahydropyran.

The main product of catalytic hydrogenation of oxazoline **7** in the presence of palladium (10% Pd/C, 20 wt % at room temperature) in a 1:1 mixture of methanol and THF was compound **8f**, which was formed by the reduction of **7** at C-1 in the 1,2-oxazoline ring. The 4,6-*O*-benzylidene remained intact. Analyses by NMR and mass spectrometry were entirely consistent with this assignment of structure, but the structure was confirmed by X-ray crystallography (Figure 1B).

Compound **8f** shows a slightly distorted chair ($^4C_1$) pyranose conformation with O1 out of plane by 0.20 Å. The X-ray structure of the precursor oxazoline **7** exhibits a distorted half-chair ($^4H_5$) pyranose conformation with O1 out of plane by 0.29 Å.

A pertinent question is whether this reaction proceeds in a regiospecific manner. If the reaction were run under a deuterium (D_2) atmosphere, the possible outcomes could be compound **9a**, **9b**, or a mixture of the two.

We set up the deuteration reaction of compound **7** under identical catalytic hydrogenation conditions, except using D_2 and CD_3OD (Scheme 3). The product, which was isolated in

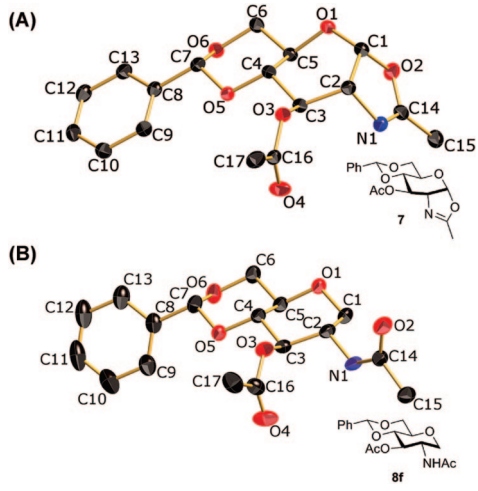
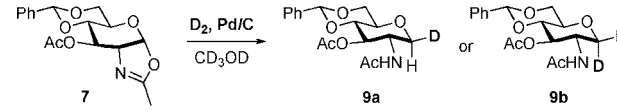


FIGURE 1. ORTEP diagrams of compounds **7** (A) and **8f** (B) are shown at 50% probability level. Hydrogen atoms are omitted for clarity.

SCHEME 3



the pure form after a single recrystallization, was compound **9a**. The deuterium in **9a** was at the equatorial position according to the NMR results. As shown by the ^1H NMR spectra of Figure 2, the doublet of doublet of equatorial H-1 in compound **8f** disappeared and a triplet signal of axial H-1 in compound **8f** became a doublet on formation of compound **9a**. The multiplet resonance of H-2 in **8f** simplified to a triplet in compound **9a**. No trace of compound **9b** was observed. We hasten to add that some **8f** was also present (see Figure 2 and the larger spectrum in the Supporting Information). We attributed this to the existence of some H_2 in the commercial sample of D_2 and also to the possibility that some H_2 having been absorbed on the commercial sample of the palladium, as it was supplied to us.

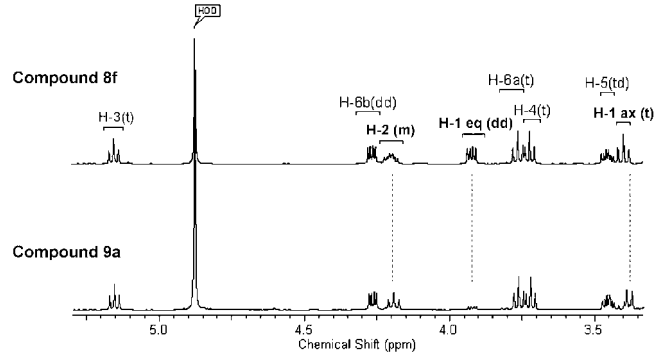


FIGURE 2. ^1H NMR spectra of compounds **8f** and **9a** in CD_3OD.

We have found one literature precedent for synthesis of a deuterated derivative at C-1 by transmetalation of 1-pyranosyl-stannane, obtained from the corresponding 1-chloride analogue and the subsequent quenching with CD_3OD.[14] The deuterated analogues are useful for elucidation of biosynthetic pathways of molecules of this kind and indeed are difficult to access in regiospecific manner.

We also have noticed that triacetyl oxazoline (**10**) was resistant to the kind of catalytic hydrogenation discussed above. This might be due to different conformations of the oxazolines in compounds **7** and **10**. Compound **7** in the solid state shows a distorted half-chair conformation ($^4H_5$), the same as in solution per analysis by the Karplus equation of the NMR data.[15] Structural information of triacetyl derivative **10** in the solid state is not available, since this compound is an oil. Studies have been done on conformations of compound **10** in solution based on vicinal coupling constants by NMR and the calculated dihedral angles by the Karplus equation.[15−17] These analyses suggest that this compound exists is a distorted skew ($^OS_2$) conformation.[16,17] X-ray crystal structures of similar or related compounds are known in the literature.[16,18] For example, phenyloxazoline triacetate (**11**) is known to exist between a skew

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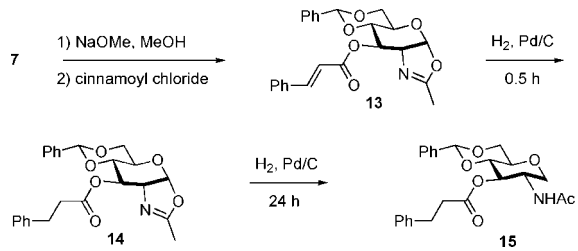
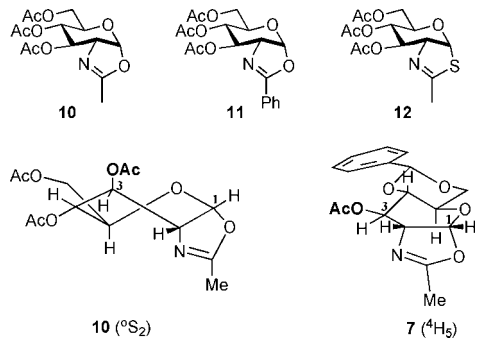
SCHEME 4



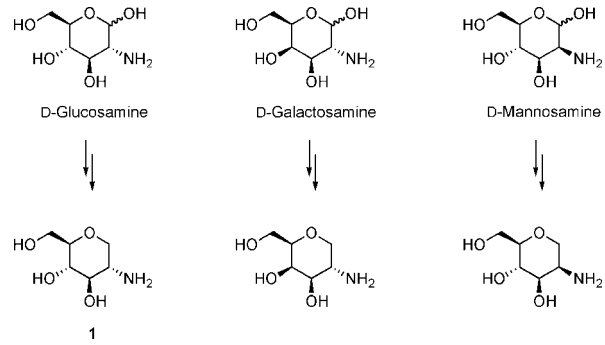
($^{O}S_2$) and diplanar ($D^{O,4}$)[16] conformations and thiazoline triacetate (**12**) exits in a skew ($^{O}S_2$) conformation.[18]



Assuming that compound **10** exists in the skew conformation, significant differences would then be present between conformations of **10** and **7**. The acetyl group at C-3 is equatorial in compound **7**, which does not block the trajectory of the interaction of the compound at the C-1 with the catalyst surface. On the other hand, the acetyl group at C-3 in compound **10** is more axially disposed, which would block interactions with the surface of the palladium catalyst. This might be the reason why triacetylated oxazoline **10** cannot be hydrogenated to form the corresponding glucitol.

A pertinent question becomes if there exists any generality to the observations above regarding the application of hydrogenation to oxazoline ring opening. Compound **13** was prepared from **7** in two steps. When compound **13** was subjected to catalytic hydrogenation in THF, the double bond in the cinnamoyl group was reduced first within 30 min to yield compound **14**. The desired glucitol **15** was obtained cleanly by prolonging the hydrogenation reaction to 24 h (Scheme 4).

As a final note, the strategy reported above should be generally applicable to any oxazoline compounds derived from 2-aminopyranoses, such as galactosamine and mannosamine, as depicted below.



Experimental Section

The synthesis of acetyl 2-acetamido-3-*O*-acetyl-4,6-*O*-benzylidene-α,*β*-D-glucopyranoside (**6**) and its conversion to compound **7** (2-methyl-4,5-(3-*O*-acetyl-4,6-*O*-benzylidene-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-oxazoline) were performed according to literature procedures.[12,13] NMR signal assignments for compounds **8f**, **14**, and **15** were performed on the basis of H−H COSY, H−C HETCOR, and DEPT experiments.

2-Acetamido-3-*O*-acetyl-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-glucitol (8f). Compound **7** (0.15 g, 0.45 mmol) was dissolved in a 1:1 mixture of methanol and THF (15 mL), and 10% Pd/C (30 mg) was added to the mixture cautiously to avoid ignition. The mixture was stirred under an atmosphere of hydrogen at room temperature overnight. The mixture was diluted with an additional portion of methanol (10 mL) and filtered through a layer of Celite, and the Celite pad was washed well with additional methanol. The solvent was removed in vacuo. The resulting crude product was crystallized from MeOH−CH_2Cl_2 (0.13 g, 86%): ^{1}H NMR (600 MHz, methanol-d_4) δ 1.91 (s, 3H), 2.02 (s, 3H), 3.39 (t, J = 11.3 Hz, H-1ax, 1H), 3.45 (td, J = 9.8, 5.0 Hz, H-5, 1H), 3.71 (t, J = 9.5 Hz, H-4, 1H), 3.75 (t, J = 10.3 Hz, H-6a, 1H), 3.91 (dd, J = 11.4, 5.6 Hz, H-1eq, 1H), 4.19 (m, J = 10.7, 5.6 Hz, H-2, 1H), 4.26 (dd, J = 10.3, 5.0 Hz, H-6b, 1H), 5.15 (t, J = 9.8 Hz, H-3, 1H), 5.57 (s, C*H*Ph, 1H), 7.33 (m, 3H), 7.41 (m, 2H); ^{13}C NMR (151 MHz, methanol-d_4) δ 20.9, 22.8, 51.3 (C-2), 69.6 (C-1), 69.8 (C-6), 73.0 (C-5), 74.5 (C-3), 80.8 (C-4), 102.9 (*C*HPh), 127.5, 129.2, 130.1, 139.0, 172.5, 173.6; HRMS (FAB) calcd for $C_{17}H_{22}NO_6$ (M + H^+) 336.1447, found 336.1444.

2-Acetamido-3-*O*-acetyl-1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-1-*β*-^{2}H-D-glucitol (9a). Compound **9a** was prepared according to the procedure described above for compound **8f**, except D_2 and CD_3OD were used. The resulting crude product was crystallized from acetonitrile to give the titled compound as a needle: ^{1}H NMR (600 MHz, methanol-d_4) δ 1.91 (s, 3H), 2.03 (s, 3H), 3.38 (d, J = 11.2 Hz, H-1ax, 1H), 3.45 (td, J = 9.8, 5.1 Hz, H-5, 1H), 3.72 (t, J = 9.4 Hz, H-4, 1H), 3.76 (t, J = 10.3 Hz, H-6a, 1H), 4.19 (t, J = 10.7 Hz, H-2, 1H), 4.26 (dd, J = 10.6, 5.0 Hz, H-6b, 1H), 5.15 (t, J = 9.8 Hz, H-3, 1H), 5.58 (s, C*H*Ph, 1H), 7.29−7.48 (m, 5H); ^{13}C NMR (151 MHz, methanol-d_4) δ 20.9, 22.8, 51.3 (C-2), 69.3 (m, C-1), 69.8 (C-6), 73.0 (C-5), 74.5 (C-3), 80.8 (C-4), 102.9 (*C*HPh), 127.5, 129.2, 130.1, 139.0, 172.5, 173.6; HRMS (FAB) calcd for $C_{17}H_{21}DNO_6$ (M + H^+) 337.1510, found 337.1493.

2-Methyl-4,5-(3-*O*-(*trans*-3-phenylacryloyl)-4,6-*O*-benzylidene-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-oxazoline (13). A solution of compound **7** (0.63 g, 1.9 mmol) and NaOMe (0.05 g) in anhydrous MeOH (15 mL) was stirred at room temperature until the starting material was consumed (1 h). The reaction was quenched by the addition of an excess amount of Amberlite IR-120 (H^+). After the mixture was stirred for an additional 20 min, the resin was filtered and the resulting solution was concentrated to dryness. The residue was dissolved in CH_2Cl_2 and was treated with cinnamoyl chloride (0.33 g, 2.0 mmol) in the presence of pyridine (0.24 mL, 3.0 mmol) at room temperature overnight. Water was added to the reaction mixture, and the layers were separated. The organic layer was washed with water and concentrated to dryness. The residue was chromatographed on silica gel to give the title compound as a white solid (0.6 g, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.10 (d, J = 1.8 Hz, 3H), 3.68−3.78 (m, 2H), 3.94 (t, J = 8.7 Hz, 1H), 4.16−4.20 (m, 1H), 4.42 (dd, J = 9.7, 4.1 Hz, 1H), 5.32 (dd, J = 7.8, 3.4 Hz, 1H), 5.57 (s, 1H), 6.03 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 15.8 Hz, 1H), 7.33−7.54 (m, 10H), 7.76 (d, J = 16.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 62.7, 67.8, 68.6, 76.6, 77.9, 101.3, 101.5, 117.4, 126.0, 128.0, 128.1, 128.8, 129.0, 130.3, 134.1, 136.7, 145.7, 165.5, 165.7; HRMS (FAB), calcd for $C_{24}H_{24}NO_6$ (M + H^+), 422.1604, found 422.1601.

2-Acetamido-1,5-anhydro-4,6-*O*-benzylidene-3-*O*-(3-phenylpropionyl)-2-deoxy-D-glucitol (15). Compound **15** was prepared

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according to the procedure described above for compound **8f**, except THF was used as solvent. The resulting crude product was purified by short column chromatography on silica gel to give the titled compound (74%). Compound **14** was obtained quantitatively after 30 min of the reaction. Compound **14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (d, J = 1.0 Hz, 3H), 2.71 (t, J = 7.7 Hz, 2H), 2.99 (t, J = 7.7 Hz, 2H), 3.62−3.72 (m, 2H, H-5 and H-6a), 3.76 (t, J = 8.7 Hz, 1H, H-4), 3.96 (dt, J = 6.0, 1.6 Hz, 1H, H-2), 4.38 (dd, J = 9.1, 3.7 Hz, 1H, H-6b), 5.20 (dd, J = 7.8, 3.4 Hz, 1H, H-3), 5.51 (s, 1H, C*H*Ph), 5.92 (d, J = 7.6 Hz, 1H, H-1), 7.15−7.50 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.4, 31.0 (t), 35.9 (t), 62.9 (C-5), 67.7 (C-2), 68.9 (C-6), 74.2 (C-3), 78.1 (C-4), 101.6 (C-1), 101.7 (*C*HPh), 126.3, 126.4, 128.4, 128.4, 128.6, 128.7, 129.3, 137.0, 140.4, 165.8, 171.9; HRMS (FAB) calcd for $C_{24}H_{26}NO_6$ ($M + H^+$) 424.1760, found 424.1750. Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83 (s, 3H), 2.66−2.76 (m, 2H), 2.93 (t, J = 7.5 Hz, 2H), 3.17 (t, J = 10.7 Hz, 1H, H-1eq), 3.40−3.47 (m, 1H, H-5), 3.71 (t, J = 9.6 Hz, 1H, H-4), 3.73 (t, J = 10.4 Hz, 1H, H-6a), 4.11−4.24 (m, 2H, H-1ax and H-2), 4.32 (dd, J = 10.5, 4.9 Hz, 1H, H-6b), 5.10 (t, J = 9.8 Hz, 1H, H-3), 5.53 (s, 1H, C*H*Ph), 5.91 (d, J = 7.2 Hz, 1H, NH), 7.14−7.23 (m, 5H), 7.33−7.39 (m, 2H), 7.41−7.46 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.3, 30.9 (t), 35.7 (t), 51.3 (C-2), 68.9 (C-6), 69.0 (C-1), 71.9 (C-5), 73.3 (C-3), 79.0 (C-4), 101.7 (*C*HPh), 126.3, 126.5, 128.3, 128.5, 128.7, 129.3, 137.2, 140.1, 170.6, 174.5; HRMS (FAB) calcd for $C_{24}H_{28}NO_6$ ($M + H^+$) 426.1917, found 426.1891.

Crystals Growth and Analysis. Compound **8f** (50 mg) in MeOH and CH_2Cl_2 (1 mL) was heated to produce a clear, colorless solution. Crystals of suitable size for single-crystal X-ray diffraction analysis were obtained by recrystallization from MeOH at room temperature overnight. Compound **7** was subjected to same conditions of recrystallization described above, and the resultant colorless crystal was used for single-crystal X-ray diffraction analysis.

Crystals were examined under Infineum V8512 oil, placed on a MiTeGen mount, and then transferred to the 100 K N_2 stream of a Bruker SMART Apex CCD diffractometer. Unit cell parameters were determined from reflections with $I > 10\sigma(I)$ harvested from three orthogonal sets of 30 0.5° ω scans. Data collection strategy was calculated using COSMO, included in the Apex2 suite of programs[19] to maximize coverage of reciprocal space in a minimum amount of time. Average 4-fold redundancy of measurements was sought. Data were corrected for Lorentz and polarization effects, as well as for absorption.

Structure solution and refinement utilized the programs of the SHELXTL software package.[20] Full details of the X-ray structure determinations are in the CIF files included as Supporting Information.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: Compound characterization data, including copies of 1D NMR spectra (^{1}H, ^{13}C NMR, and DEPT) and 2D NMR spectra (H−H COSY and H−C HETCOR) of compounds **8f**, **9a**, **13**, **14**, and **15**, and X-ray data of compounds **7** and **8f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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