A Direct Synthesis of Hydroxysemperoside Deglucoside

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Abstract: A 10-step synthesis of hydroxysemperoside deglucoside has been achieved. The key step is an organopalladium-mediated cyclization that produces a highly functionalized oxabicyclooctane. The remaining functional groups are introduced by addition to the exo face of the fused bicyclic system.

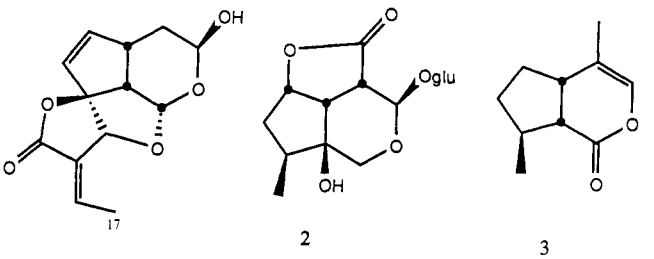
The iridoids comprise a class of terpenes with diverse biological activity.[1] Although they possess a basic monoterpene skeleton, a high degree of oxygenation permits a wide array of subclasses. Of the many iridoids that contain a lactone subunit, allamcin (**1**) contains a spiro lactone, hydroxysemperoside (**2**) possesses a fused γ-lactone, and nepetalactone (**3**) has a fused bicyclic δ-lactone system. Several efficient syntheses of nepetalactone have been reported.[2] Recently, two creative syntheses of **1** have been described by Trost and by Pattenden.[3] Interestingly, no syntheses of compounds such as **2** have been achieved (Chart I). We report herein the first synthesis of hydroxysemperoside deglucoside.

Our strategy for the synthesis of this compound focused on the direct production of the AC subunit **4** via organopalladium chemistry. Appendage of the B ring to **5** by formylation and in situ cyclization completed an expedient synthesis. This strategy appears to be a unique one for the synthesis of iridoids. Most syntheses generate the iridoid skeleton by oxidative cleavage of a functionalized cyclopentene or by fragmentation of a cyclobutanol derived from photoaddition of an acrylate.[4] Our strategy should also enable us to readily synthesize other subclasses of iridoids (Scheme I).

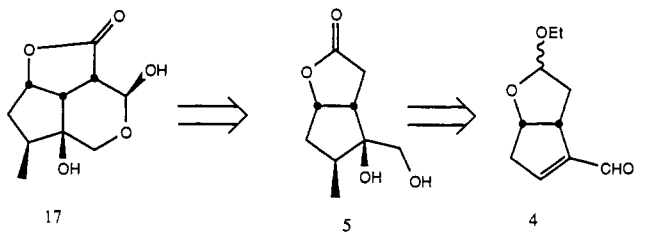
The synthetic route began with the readily available 3-acetoxycyclohexene.[5] Ozonolysis in methylene chloride at −78 °C followed by the addition of dibenzylammonium trifluoroacetate[6] at 0 °C and warming to ambient temperature afforded acetoxy aldehyde **6** in 75% isolated yield. Hydrolysis of the acetate with aqueous base or acid at 0 °C produced complicated mixtures of products containing little of the desired hydroxy aldehyde. The aldehyde could be protected as acetal **7** in quantitative yield by treatment with ammonium nitrate in methanol.[7] The acetate was then removed with lithium aluminum hydride at 0 °C in ether. The resulting alcohol **8** was subjected to the Larock–Utimoto protocol[8] to afford the bicyclic acetal **9** as a mixture of isomers at the cyclic acetal center in 71% yield.

Initially, we had speculated that organometallic addition[9] to allylic acetal **9** might afford enol ether **10**, wherein the methyl group is introduced from the convex face. Unfortunately, treatment of acetal **9** with Me_2CuLi, $Me_2CuLi{\cdot}BF_3$, or higher order cuprate reagents failed to effect the desired conjugate addition. The spectra of the crude products indicated that the nonallylic acetal had been destroyed (Scheme II).

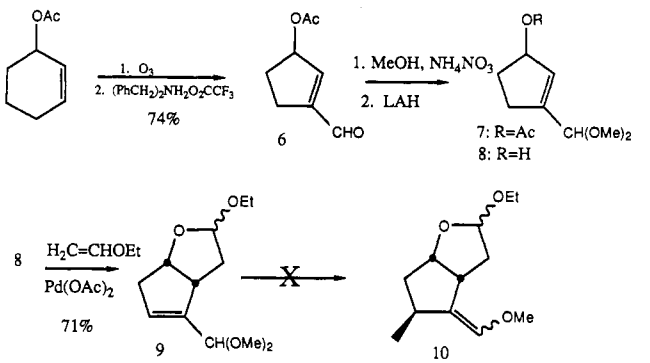
Chart I



Scheme I



Scheme II



The allylic acetal moiety in **8** could be cleaved with the silica gel promoted hydrolysis conditions developed by Conia.[10] Reaction of unsaturated aldehyde **11** under conditions used for **8** afforded aldehyde **4** in 69% yield. The Corey modification[11] of the cuprate (Me_2CuLi, (TMS)Cl) was used to generate the unstable enol silyl ether **12**. The hydroxyl group needed at C-9 was then introduced from the convex face by treating the crude enol silyl ether with osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO). The resulting crude hydroxy aldehyde **13** was reduced with lithium aluminum hydride to provide a diol, which was acetylated to furnish **14**. Acetylation was necessary to reduce the water solubility of the hemiacetal and to prevent the formation of tricyclic acetal **15**. The overall yield from **11** was 55% (Scheme III).

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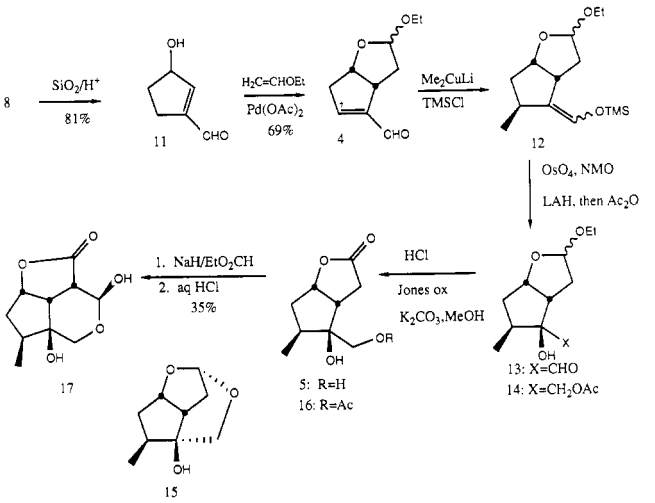
Scheme III



The acetal moiety was hydrolyzed to a hemiacetal with 0.03 N HCl in THF. Jones oxidation of the hemiacetal **16** cleanly afforded lactone **5**. Formylation of **5** using ethyl formate and potassium *tert*-butoxide followed by acidification afforded hydroxysemperoside deglucoside in 35% yield from **5**. Our proton NMR spectrum of hydroxysemperoside deglucoside was identical with the one reported in the literature.[12]

This synthesis provides a direct entry to one important subclass of iridoids. This route generates a compound containing six stereogenic centers in only 10 steps. It also illustrates that the Larock–Utimoto reaction can be conducted on sensitive substrates in very good yield.

Experimental Section

3-Acetoxy-1-cyclopentenecarboxaldehyde (6). 3-Acetoxycyclohexene (5.82 g, 41.60 mmol) was dissolved in 100 mL of CH_2Cl_2. This solution was cooled to −78 °C, and O_3 was bubbled into the solution until the solution turned blue. Nitrogen was passed through the solution to remove the excess O_3, then Ph_3P (10.89 g, 41.60 mmol) was added, and the solution was allowed to warm to 0 °C. The salt of dibenzylamine and trifluoracetic acid (1.94 g, 6.24 mmol) was added, and the solution was stirred for 24 h. The reaction was then poured into 200 mL of hexane. The hexane was washed twice with 50 mL of water and then dried. The crude product was purified by chromatography using 3:1 hexane/ethyl acetate to afford 74% of **6** as a pale yellow oil that was unstable: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.9–2.0 (m, 1 H), 2.1 (s, 3 H), 2.4–2.5 (m, 2 H), 2.6–2.8 (m, 1 H), 5.8 (m, 1 H), 6.78 (m, 1 H), 9.85 (s, 1 H); IR (film) 2990, 2970, 1735, 1680, 1370, 1230 cm^{-1}.

1-(Dimethoxymethyl)-3-acetoxy-1-cyclopentene (7). Compound **6** (2.00 g, 12.98 mmol) was dissolved in 6 mL of methanol. Trimethyl orthoformate (2.06 g, 19.48 mmol) and ammonium nitrate (0.05 g, 0.65 mmol) were added, and the solution was stirred overnight. To this solution was added 30 mL of hexane followed by 10 mL of saturated sodium bicarbonate. The water layer was back-extracted three times with 10-mL portions of hexane. The hexane extracts were combined and dried to afford **7** in quantitative yield as a colorless oil: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.8–1.95 (m, 1 H), 2.02 (s, 3 H), 2.25–2.4 (m, 2 H), 2.45–2.6 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 4.88 (br s, 1 H), 5.68 (m, 1 H), 5.88 (m, 1 H); ^{13}C NMR, 21.08, 29.72, 29.91, 79.79, 100.88, 127.44, 147.50, 170.63 ppm; IR (film) 2970, 2910, 1730, 1450, 1370, 1240, 1050 cm^{-1}; MS, *m/z* 43, 75, 95, 101, 109, 127, 141, 169, 199.

3-(Dimethoxymethyl)-2-cyclopentenol (8). Lithium aluminum hydride (0.20 g, 5.0 mmol) was suspended in 20 mL of ether. Compound **7** (1.00 g, 5.00 mmol) was added dropwise to the stirred solution. After 3 h saturated sodium sulfate was added dropwise to the solution until the color turned from gray to white. The solution was filtered and the solvent removed to afford a quantitative yield of **8** as a colorless oil: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.7–1.8 (m, 1 H), 1.85–1.95 (br s, 1 H, 2.2–2.4 (m, 2 H), 2.45–2.55 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 4.85–4.95 (br s, 2 H), 5.9 (br s, 1 H); IR (film) 3400, 2965, 2910, 1450, 1150, 1050 cm^{-1}; HRMS for $C_8H_{14}O_3$, calcd 158.094 30, found 158.094 06.

6-(Dimethoxymethyl)-3-ethoxy-2-oxabicyclo[3.3.0]oct-6-ene (9). Compound **8** (0.50 g, 3.17 mmol) was dissolved in 7 mL of CH_3CN. Ethyl vinyl ether (3 mL, 31 mmol), palladium(II) acetate (0.29 g, 1.27 mmol), and copper(II) acetate (1.44 g, 7.93 mmol) were added, and the solution was stirred at room temperature for 24 h. The solution was diluted with 60 mL of hexane, and 0.6 mL of pyridine was added. The solution was stirred for an additional 30 min and then filtered to remove the copper and palladium salts. The filtrate was concentrated and purified by chromatography using 3:1 hexane/ethyl acetate to afford 0.51 g (71%) of **9** as a pale yellow oil, which was a 1:1 mixture of diastereomers: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.05–1.25 (m, 3 H), 1.85–2.7 (m, 5 H), 3.2–3.4 (m, 8 H), 4.7–4.9 (m, 2 H), 5.1–5.2 (m, 1 H), 5.6–5.7 (m, 1 H); IR (film) 2960, 2910, 1440, 1095, 1045, 730 cm^{-1}; HRMS for $C_{10}H_{14}O_3$ (M^+ − 46), calcd 182.094 30, found 182.094 24.

3-Hydroxy-1-cyclopentenecarboxaldehyde (11). Compound **8** (2.00 g, 12.65 mmol) was dissolved in 50 mL of methylene chloride. Silica gel (6 g, silica gel 60, Merck, for column chromatography, 70–230 mesh) and a 10% aqueous solution of oxalic acid (0.60 g) were added, and the resulting solution was stirred for 12 h. The solution was filtered and concentrated to afford 1.20 g (81%) of **11** as a colorless oil, which was used without purification: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.7–1.9 (m, 1 H), 2.15 (br s, 1 H), 2.35–2.5 (m, 2 H), 2.6–2.75 (m, 1 H), 5.05–5.15 (br s, 1 H), 6.8 (m, 1 H), 9.85 (s, 1 H); ^{13}C NMR, δ 26.78, 33.05, 95.92, 147.52, 151.21, 190.34; IR (film) 3460, 2980, 2940, 1690, 1250, 1165, 1050, 800 cm^{-1}; HRMS for $C_6H_8O_2$, calcd 112.052 43, found 112.052 29.

3-Ethoxy-2-oxabicyclo[3.3.0]oct-6-ene-6-carboxaldehyde (4). The procedure for the preparation of **9** was used. The crude product was purified by chromatography using 3:1 hexane/ethyl acetate to afford 68% of **4** as a pale yellow oil, which was a 1:1 mixture of diastereomers: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.05–1.22 (m, 3 H), 1.8–1.95 (m, 1 H), 2.05–2.2 (m, 2 H), 2.6–3.0 (m, 2 H), 3.3–3.7 (m, 2 H), 4.7–4.9 (m, 1 H), 5.1 (m, 1 H), 6.7 (m, 1 H), 9.78 (2 s, 1 H); IR (film) 2960, 1678, 1045, cm^{-1}; HRMS for $C_{10}H_{14}O_3$, calcd 182.094 30, found 182.094 40.

6-(Acetoxymethyl)-3-ethoxy-7-methyl-2-oxabicyclo[3.3.0]octan-6-ol (14). Copper(I) bromide dimethyl sulfide (0.34 g, 1.65 mmol) was placed in 3 mL of THF and the solution cooled to −10 °C. Methyllithium (3.26 mmol) was added dropwise to the stirring solution (note that the solution turns bright yellow then returns to colorless). The resulting solution was cooled to −78 °C.

Aldehyde **4** (0.20 g, 1.10 mmol) was dissolved in 3 mL of THF and cooled to −78 °C. The trimethylsilyl chloride (0.39 g, 4.29 mmol) was added. This solution was transferred to the previous solution via cannula. The resulting solution was warmed to −40 °C and stirred for 8 h. It was then poured into 30 mL of hexane, and the hexane was washed twice with 10 mL of saturated ammonium chloride. The hexane layer was dried to afford the crude product **12** in quantitative yield, which was used without purification.

Osmium tetroxide (0.017 g, 0.067 mmol) and *N*-methylmorpholine *N*-oxide (0.51 g, 3.76 mmol) were dissolved in 18 mL of acetone that contained 8 mL of water. Compound **12** (0.93 g, 3.42 mmol) was added as a solution in 6 mL of acetone and the resulting solution stirred for 12 h. Sodium hydrosulfite (0.70 g) and Florisil (2.70 g) were added, and the solution was stirred for an additional 30 min. The solution was filtered, and the acetone was removed. The remaining solvent was saturated with sodium sulfate and extracted four times with 20-mL portions of ether. The ether was dried and concentrated to afford **13** in quantitative yield.

Lithium aluminum hydride (0.12 g, 5.0 mmol) was suspended in 10 mL of ether. Compound **13** (0.66 g, 3.05 mmol) was added dropwise to the stirring solution. After 3 h saturated sodium sulfate was added dropwise to the solution until the color turned from gray to white. The solution was filtered to afford a quantitative yield of the diol. This diol (0.45 g, 2.06 mmol) was dissolved in 25 mL of methylene chloride, and acetyl chloride (0.36 g, 4.54 mmol) and pyridine (0.43 g, 5.44 mmol) were added. The resulting solution was stirred for 4 h. The solution was washed twice with 10 mL of 10% aqueous sodium bicarbonate, followed by 10 mL of saturated $CuSO_4$, and then dried. The product was purified by chromatography using 1:1 hexane/ethyl acetate to afford 0.53 g (55%) of **14** as a colorless oil (note this is a 55% overall yield from **4**): 300-MHz ^{1}H NMR ($CDCl_3$) δ 0.89–0.98 (m, 3 H), 1.2–1.4 (m, 3 H), 1.6–2.9 (m, 10 H), 3.3–3.7 (m, 2 H), 3.95–4.35 (m, 2 H), 4.6–4.7 (m, 1 H), 4.98–5.13 (m, 1 H); IR (film) 3490, 2980, 1740, 1235 cm^{-1}; HRMS for $C_{13}H_{21}O_5$ (M^+ −1), calcd 257.138 90, found 257.138 79.

6-(Acetoxymethyl)-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octan-3-one (16). Compound **14** (0.10 g, 0.30 mmol) was dissolved in 2 mL of CH_3CN. Hydrochloric acid (1 mL of 0.03 N) was added in portions until the starting material no longer was detectable by thin-layer chromatography. Ether (15 mL) was added and the solution dried with sodium sulfate, which contained a trace of sodium bicarbonate to neutralize the acid. The crude product (0.09 g, 0.30 mmol) was dissolved in 3 mL of acetone and the solution cooled to 0 °C. Jones reagent (0.52 mmol, 0.20 mL) was added, and the solution was stirred for 15 min.

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2-Propanol was added to quench the excess Jones reagent followed by 10 mL of ether. The solution was filtered and the filtrate washed twice with saturated sodium sulfate. The crude product was purified by chromatography using 8:1 ether/acetone to afford 0.043 g (64%) of **16** as a white solid: mp 131-132 °C; 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 5.4 Hz), 1.9-2.1 (m, 4 H), 2.1 (s, 3 H), 2.3-2.45 (m, 1 H), 2.6-2.8 (m, 1 H), 2.9-3.05 (m, 1 H), 3.99-4.29 (AB q, 2 H, J = 6.9 Hz), 5.05 (m, 1 H); ^{13}C NMR, δ 11.85, 20.71, 30.85, 36.78, 38.58, 48.17, 67.16, 81.85, 83.64, 170.93, 176.67; IR (film) 3490, 2980, 1765, 1740, 1370, 1230 cm^{-1}; HRMS for $C_{11}H_{16}O_5$, calcd 228.099 78, found 228.099 28.

6-(Hydroxymethyl)-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octan-3-one (5). Compound **16** (0.09 g, 0.39 mmol) was dissolved in 1 mL of methanol. Potassium carbonate (0.01 g, 0.08 mmol) was added and the solution stirred for 3 h. Ethyl acetate (5 mL) was added and the resulting solution filtered. The solvent was removed to afford 0.05 g (66%) of **5**, which was a light yellow oil and used without purification: 300-MHz ^{1}H NMR, δ 0.98 (d, 3 H, J = 5.5 Hz), 1.8-2.5 (m, 6 H), 2.7-2.9 (m, 1 H), 2.9-3.0 (m, 1 H), 3.5-3.8 (AB q, 2 H, J = 11 Hz), 5.1 (m, 1 H); IR (film) 3470, 2980, 1760, 1180, 1020, cm^{-1}; HRMS for $C_9H_{14}O_4$, calcd 186.089 21, found 186.089 51.

9-Hydroxysemperoside (17). Compound **5** (0.035 g, 0.113 mmol) was dissolved in 1 mL of ether. Sodium hydride (0.015 g, 0.37 mmol) and ethyl formate (0.027 g, 0.37 mmol) were added, and the solution was refluxed for 3 h. The solution was acidified with 0.5 N hydrochloric acid and stirred for 1 h. The reaction was poured into 10 mL of ether, and the water layer was removed. The product was purified by chromatography using 1:2 hexane/ethyl acetate to afford 0.008 g (35%) of **17** as a white solid: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.1 (d, 3 H, J = 6.3 Hz), 1.75-2.20 (m, 4 H), 2.65 (br s, 1 H), 2.99 (s, 2 H), 3.51 and 3.97 (AB q, 2 H, J = 11.7 Hz), 5.03 (m, 1 H), 5.58 (s, 1 H); MS, m/e 97, 108, 149, 166, 183, 196, 213, 214; HRMS, m/e for $C_{10}H_{14}O_5$ (M^+) calcd 214.084 13, found 214.083 80; HRMS, m/e for $C_{10}H_{12}O_4$ ($M^+ - H_2O$), calcd 196.0735, found 196.0742. No authentic sample was available. However, our NMR matched up peak for peak with the NMR spectrum listed in ref 12.

Registry No. 2, 110309-28-9; (±)-α-**4**, 123594-34-3; (±)-β-**4**, 123671-85-2; (±)-**5**, 123594-35-4; (±)-**6**, 120584-50-1; (±)-**7**, 123594-36-5; (±)-**8**, 123594-37-6; (±)-α-**9**, 123594-38-7; (±)-β-**9**, 123671-82-9; (±)-α-**10**, 123594-39-8; (±)-β-**10**, 123671-88-5; (±)-**11**, 123594-40-1; (±)-α-**12**, 123594-41-2; (±)-β-**12**, 123671-83-0; (±)-α-**13**, 123594-42-3; (±)-β-**13**, 123671-84-1; (±)-α-**14**, 123594-43-4; (±)-β-**14**, 123671-81-8; (±)-α-**14** (X = CH_2OH), 123594-45-6; (±)-β-**14** (X = CH_2OH), 123671-86-3; (±)-**16**, 123594-44-5; (±)-**16** α-lactol, 123594-46-7; (±)-**1b** β-lactol, 123671-87-4; (±)-**17**, 123671-80-7; (±)-3-acetoxycyclohexene, 76704-31-9.

Relative and Absolute Configurational Assignments of Acyclic Polyols by Circular Dichroism. 1. Rationale for a Simple Procedure Based on the Exciton Chirality Method

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Abstract: A general procedure for assigning multiple stereocenters in acyclic polyols is presented. Relative and absolute stereochemistry of 1,2,3-triols, 1,2,3,4-tetrols, and 1,2,3,4,5-pentols can be assigned by circular dichroism (CD) after a simple, two-step derivatization with exciton-coupling chromophores. Selective 9-anthroylation of primary hydroxyls followed by per-*p*-methoxycinnamoylation of secondary hydroxyls affords "bichromophoric" derivatives, the CD spectra of which are *characteristic and predictable for each stereochemical pattern.* A complete set of reference curves for empirical assignment of configuration in these polyols is presented. Accurate simulations of the CD spectra by summation of pairwise interchromophoric interactions demonstrate the nonempirical basis of the "bichromophoric" exciton chirality method. Full conformational analyses for all derivatives allows for rational interpretation of the manner in which the various stereoisomers give rise to the characteristic CD spectra. Applications to other hydroxylation patterns are discussed.

The assignment of stereochemistry in acyclic polyols remains a difficult task. The emergence of many highly stereoselective synthetic techniques, such as Sharpless epoxidation,[1] has facilitated assignment by trial-and-error syntheses of possible stereoisomers. However, the number of structures elucidated by time-consuming syntheses indicates the distinct lack of spectroscopic methodology in this area. Methods for assigning relative configuration in 1,3-polyols by NMR have recently emerged,[2-5] yet of the over 200 1,3-polyhydroxylated polyene macrolides known,[6] only mycoticin A and B[7] have been fully assigned since the X-ray crystallographic elucidation of amphotericin B.[8]

In polyols with contiguous hydroxylation, relative configuration can be deduced by using a combination of ^{1}H NMR J values and NOE's for one or more cyclic derivatives, preferably with comparisons to model compounds.[9] However, the use of coupling constant data alone has often proven unreliable, as illustrated by stereochemical studies of palytoxin by Moore et al.[10] Deduction of relative stereochemistry by ^{1}H NMR analysis was straightforward for chiral centers included in rings but not for those in acyclic regions of the molecule due to conformational uncertainties. Seven errors in these regions led to 12 misassigned chiral centers, as elucidated by the synthetic work of Kishi and co-workers.[11]

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