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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. 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. Recently, two creative syntheses of 1 have been described by Trost and by Pattenden. 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. 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. Ozonolysis in methylene chloride at -78 °C followed by the addition of dibenzylammonium trifluoroacetate at 0 °C and warming to ambient temperature afforded acetoxy aldehyde 6 in 75% isolated yield. Hydrolysis of the acetal with aqueous base of acid at 0 °C produced complicated mixtures of products containing little of the desired hydroxy aldehyde. The acetal could be protected as acetal 7 in quantitative yield by treatment with ammonium nitrate in methanol. The acetal was then removed with lithium aluminum hydride at 0 °C in ether. The resulting alcohol 8 was subjected to the Larock-Utimoto protocol to afford the bicyclo acetal 9 as a mixture of isomers at the cyclic acetal center in 71% yield.

Initially, we had speculated that organometallic addition to allylic acetal 9 might afford enol ether 10, which in the methyl group is introduced from the convex face. Unfortunately, treatment of acetal 9 with Me2CuLi, Me2CuLi-BF3, 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 I).

The allylic acetal moiety in 8 could be cleaved with the silica gel promoted hydrolysis conditions developed by Conia. Reaction of unsaturated aldehyde 11 under conditions used for 8 afforded aldehyde 4 in 69% yield. The Corey modification of the cuprate (Me2CuLi, (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 acetal 9 with OsO4OEt, 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).

The overall yield from 11 was 55% (Scheme III).

(2) Tietze, L. F. Angew. Chem. 1983, 940.
The acetol 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 hydroxysperoside deglucoside in 35% yield from 5. Our proton NMR spectrum of hydroxysperoside 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-Ullitmo reaction can be conducted on sensitive substrates in very good yield.

**Experimental Section**

3-Acetoxy-1-cyclopentenecarboxaldehyde (6). 3-Acetoxychlorohexene (5.82 g, 41.60 mmol) was dissolved in 100 mL of CH2Cl2. This solution was cooled to −78 °C and O3 was bubbled into the solution until the solution turned blue. Nitrogen was passed through the solution to remove the excess O3, then PhP(10.89 g, 41.60 mmol) was added, and the solution was allowed to warm to 0 °C. The salt of dibenzylamine and potassium tert-butoxide followed by acidification afforded hy-

**Scheme III**

Chemical structure of the hydroxysperoside deglucoside. 

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%) as a pale yellow oil, which was a 1:1 mixture of diastereo-

3-Hydroxy-1-cyclopentenecarboxaldehyde (11). Compound 8 (2.00 g, 12.65 mmol) was dissolved in 50 mL of methylene chloride, and 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 concentrated and concentrated to afford 1.20 g (81%) of 11 as a colorless oil, which was used without purification: 300-MHz 1H NMR (CDCl3) δ 1.7-1.9 (m, 1 H), 2.15 (br s, 1 H), 2.35-2.5 (m, 1 H), 5.05-5.15 (br s, 1 H), 6.8 (m, 1 H), 9.85 (s, 1 H); IR (film) 3490, 2980, 1740, 1235 cm⁻1; HRMS for C12H14O3, calcd 182.09430, found 182.09440.

3-Ethoxy-2-oxabicyclo[3.3.0]octa-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 1.18 g (71%) of 9 as a pale yellow oil, which was a 1:1 mixture of diastereomers: 300-MHz 1H NMR (CDCl3) δ 1.8-1.95 (m, 2 H), 2.05-2.2 (m, 2 H), 2.6-2.65 (m, 1 H), 3.3-3.35 (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) 3490, 2980, 1678, 1045 cm⁻1; HRMS for C12H16O3, calcd 182.09440, found 182.09440.

3,6-Diacetoxy-2-oxabicyclo[3.3.0]octa-6-carboxaldehyde (10). 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. Methyl lithium (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 2 mL of THF and cooled to −78 °C. The trimethylsilyl chloride (0.39 g, 2.92 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 10.1 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 suspension in 6 mL of acetone. The resulting solution was 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 aceton 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, 5.00 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 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 1H NMR (CDCl3) δ 0.89-0.89 (m, 3 H), 1.2-1.4 (m, 1 H), 1.6-2.9 (m, 10 H), 3.3-3.7 (m, 2 H), 3.95-3.45 (m, 2 H), 4.6-4.7 (m, 1 H), 4.98-5.15 (m, 1 H); IR (film) 3490, 2980, 1740, 1235 cm⁻1; HRMS for C15H22O4 (M+ = 226), calcd 226.15940, found 226.15946.

6-(Acetoxyethyl)-6-hydroxy-7-methyl-2-oxabicyclo[3.3.0]octa-6-carboxaldehyde (3). Compound 14 (0.10 g, 0.30 mmol) was dissolved in 2 mL of CH2CN. Hydrochloric acid (1 mL of 0.03 N) was added in portions until the starting material no longer was detectable by thin-layer chroma-

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 'H NMR (CDCl3) 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), 13C 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) 2940, 2980, 1765, 1740, 1370, 1230 cm⁻¹; HRMS for C11H20O4, calcd 228.09978, found 228.09928.

6-(Hydroxymethyl)-6-hydroxy-2-methyl-2-oxabicyclo[3.3.0]octan-3-one (17). Compound 15 (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 6, which was a light yellow oil and used without purification: 300-MHz '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 = 1 Hz), 5.1 (m, 1 H); IR (film) 2980, 1760, 1180, 1020, cm⁻¹; HRMS for C9H14O4, calcd 166.10450, found 166.10468.

9-Hydroxy-1,3-prahalactone. 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 4 as a white solid: mp 131-132 °C; 300-MHz 'H NMR (CDCl3) δ 1.1 (d, 3 H, J = 5.5 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), 13C 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) 2940, 2980, 1765, 1740, 1370, 1230 cm⁻¹; HRMS for C11H20O4, calcd 228.09978, found 228.09928.

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, yet of the over 200 1,3-polyhydroxylated polyene macrolides known, only mycoticin and Practice; Macrolide Antibiotics: Chemistry, Biology and Practice; Houck, G.; Ed.; Academic: New York, 1984; pp 351-404.

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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Contribution from the Department of Chemistry, Columbia University, New York, New York 10027. Received April 21, 1989

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. However, the use of coupling interactions demonstrates the nonempirical basis of the "bichromophoric" exciton chirality method. Full conformational analyses for all derivatives allow 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-polylols by NMR have recently emerged,2,3 yet of the over 200 1,3-polylhydroxylated polyene macrolides known,4 only mycoticin and Practice; Macrolide Antibiotics: Chemistry, Biology and Practice; Houck, G.; Ed.; Academic: New York, 1984; pp 351-404.

Seven errors in this regions led to 12 misassigned chiral centers, as elucidated by the synthetic work of Kishi and co-workers.11


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