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Enantioselective Total Synthesis of Semperoside A

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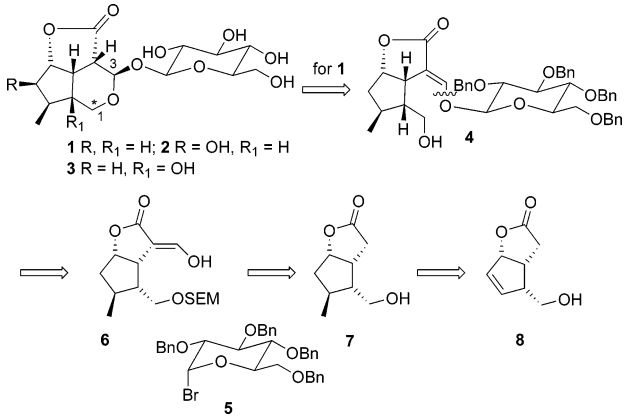
Semperoside A **1** (Scheme 1) is an iridoid glucoside isolated in 1987 from the chemotype of *Gelsemium sempervirens* collected in the wild North Carolina, U.S.A.[1a] It belongs to a large group of monoterpenes structurally characterized by a hydrogenated *cis* fused cyclopenta[*c*]pyran ring system linked to D-glucose with a β-glycosidic hemiacetal bond. Noteworthy, in semperoside A **1**, D-glucose is linked to the 3-OH instead of the 1-OH group (iridoid numbering, starred carbon in structure **1**) as in most iridoid glycosides.[1b] Although the complete structure of **1** was unequivocally established by Jensen et al., the absolute configuration has not yet been determined.

The unusual oxygenation pattern of **1** is also shown by vebraside **2** and hydroxysemperoside **3**.[1b] Over the years, several imaginative routes have been delineated for the stereoselective synthesis of iridoids,[1c−d] many of which are enlightened by a challenging structural complexity and a wide spectrum of biological properties.[2] No synthesis of compounds **1**−**3** has been published so far. Herein we describe a concise and highly convergent enantioselective approach to semperoside A **1** which, in principle, can be modulated to accomplish also the synthesis of iridoids **2** and **3**. This expeditious route is unprecedented among synthetic approaches to iridoid glycosides[1c] and smoothly overcomes the hemiacetals glucosidation issue.

At the onset of our work, we realized that the two crucial issues of the synthesis, namely the unusual oxygenation pattern and the hemiacetal β-glycosidic bond of iridoid **1** had to be addressed by a novel methodology. Thus, we envisaged a retrosynthetic analysis (Scheme 1) where the pyran ring might arise through a stereoselective intramolecular addition of the primary hydroxyl group of glucoside **4** across the *E* enol-double bond. Compound **4** could be disconnected along the glycosidic bond to lead retrosynthetically to α-glucopyranosyl bromide **5** and protected hydroxymethyl-lactone **6**. Further retrosynthesis of intermediate **6** through a regio- and stereoselective retro Curran's reaction,[3,4] indicated hydroxymethyl γ-lactone **8** as a suitable starting material**.** According to the common absolute configuration of iridoids,[1b] the enantioselective synthesis of **4** thus began from the known (3a*R*,4*R*,6a*S*)-lactone **8**[3] (Scheme 2). After some experimentation, we discovered that, to be highly diastereoselective, the Curran reaction required preliminary acetylation of **8** to **9**. Then, regiocontrolled S_N2' ring opening of vinyl lactone **9** (MeMgBr, $CuBrMe_2S$, THF/DMS −45 °C, 85%) afforded a mixture of *exo*- and *endo*-methyl derivatives **10** in a diastereomeric ratio higher than 49:1. Upon exposure to an EtOH:H_2O (1:1) solution of NaOH at 80 °C, lactones **10** delivered the corresponding sodium salts which, immediately after neutralization with CO_2, were subjected to a KI_3-promoted iodolactonization reaction.[5] Iodolactone **11** was thus obtained as a single isomer in 95% isolated yield. Subsequent Raney nickel-mediated hydrodeiodination of **11** afforded γ-lactone **7** in 71% isolated yield,[6] which was readily converted to β-glucoside **4** via a four-step sequence.

Scheme 1. Structures of Compounds **1**−**3** and Retrosynthetic Analysis of Semperoside A **1**



Thus, protection of the hydroxyl group as a SEM ether, followed by formylation of the resulting lactone **12** (NaH, HCO_2Et), smoothly afforded hydroxymethylene-lactone **6**[7] in 93% isolated yield. Subsequent *O*-alkylation of enol **6** with stereohomogeneous α-glucopyranosyl bromide **5** required strictly S_N2 condition to yield β-glucoside **13** selectively. Moreover, the *E* configuration of the enol moiety had to be installed in product **13**,[8] in order to deliver the correct stereochemistry at the hemiacetal C-3 stereocenter in the subsequent cyclization step (vide infra). In the event, compound **6**, on exposure to tetra-*O*-benzyl-α-glucopyranosyl bromide **5**[9] and K_2CO_3 in 1-methyl-2-pyrrolidone, readily afforded the required stereodefined *E*,β-glucoside **13** in a gratifying 95% yield. ^{1}H- and ^{13}C NMR spectra of **13** confirmed the stereochemistry of the *E* double bond and the β-glucosidic bond. Actually, the exocyclic vinyl proton appeared as a doublet (J = 2.15 Hz) at 7.57 ppm, in good agreement with the published data of *E* enolether double bonds,[10] while the observed ^1J(C,H) coupling constant of 162 Hz was in good agreement with the value expected for the C-1 carbon of β-glucosides.[11] Lactone **13** was then set up for the pivotal cyclization by removing the SEM protection under extremely mild conditions on exposure to $MgBr_2$/*n*-BuSH (**4**, 75% yield).[12] Surprisingly, alcohol **4** gave no product of proton acid-catalyzed cyclization upon exposure either to HCl in $CHCl_3$ or to PPTS in DCM or THF.[13] Alternatively, we realized that an intramolecular oxymercuriation reaction could provide the desired ring system. Indeed, we expected that the peculiar mechanism of the oxymercuriation of α,β-insaturated acids and ketones (Scheme 2)[14] would favor the required regiochemistry in the cyclization step. According to this scenario, initial coordination of the mercury(II) ion to the carbonyl oxygen of lactone **4** in a Lewis acid fashion would result in an enhanced electrophilicity of the olefinic β-carbon, thus forcing the cyclization to occur with a 6-*endo*-trig regiochemistry.

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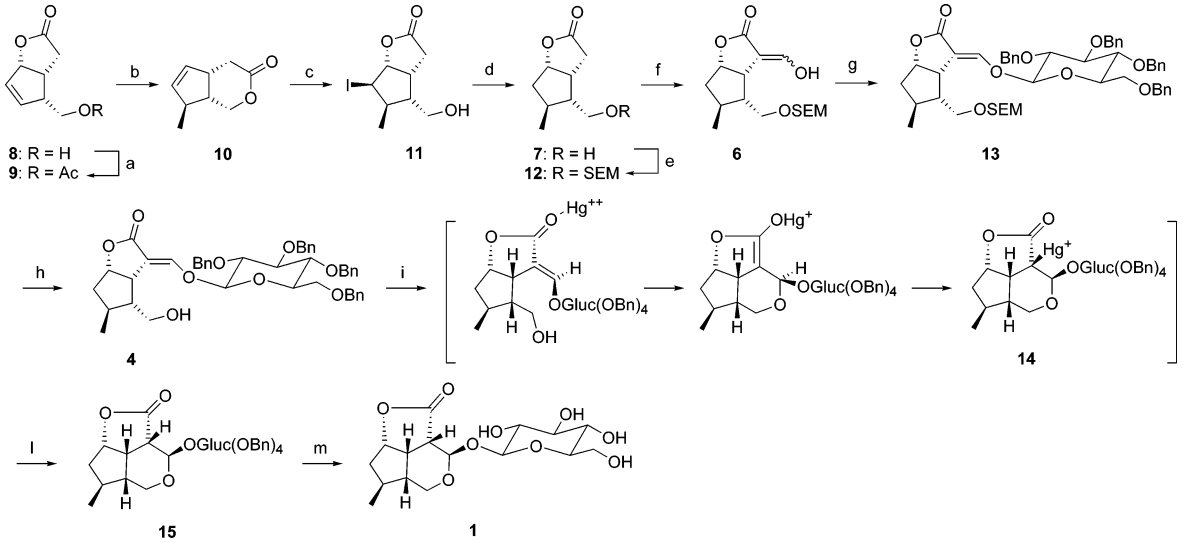
Scheme 2 [a]



[a] Reagents and conditions: (a) Ac_2O, cat. DMAP, Py, 95%; (b) 1. MeMgBr, CuBr·DMS, THF/DMS (2:1) at −20 °C, then **9** in THF at −45 °C; 2. Cat. PTSA, DCM, 85%; (c) 1. NaOH, EtOH/H_2O (1:1), 80 °C; 2. CO_2, then KI_3, H_2O, 95%; (d) Raney Ni, DCM/EtOH, 71%; (e) SEM-Cl, *i*-Pr_2NEt, TBAF, DCM, 97%; (f) NaH, HCO_2Et, Et_2O, 96%; (g) **5**, NMP, K_2CO_3, 95%; (h) $MgBr_2$, *n*-BuSH, Et_2O, 75%; (i) $Hg(OCOCF_3)_2$, THF; (l) $NaBH_4$, THF, aq NaOH 5%, 50% over two steps; (m) AcOEt/MeOH, (2:1), cat. Pd(C), H_2 1 atm, 95%.

The absolute configuration at the C-3 and C-4 stereocenters of the so formed iridoid **15** would then ensue from addition of the primary hydroxyl groups across the *si*-face of the (*E*) double bond, followed by 1,3 migration of the mercury atom from oxygen to carbon on the less encumbered side of the tricyclic system and free radical displacement of the mercury atom (Scheme 2).[15] In the event, treatment of glucoside **4** with $Hg(OCOCF_3)_2$ in THF, followed by reduction of the intermediate organomercurial with basic $NaBH_4$, smoothly provided protected semperoside A **15** as a single stereoisomer in 50% yield. Subsequent Pd(0)-mediated hydrogenolysis (H_2, 5% Pd/C in AcOEt/MeOH) of the four benzyl groups delivered compound **1** in 95% isolated yield. ^1H and ^{13}C spectra, and IR spectroscopic data of **1** were identical to those described for semperoside A.[1a] The melting point and optical rotation of **1** finely matched those of a repurified sample of natural semperoside [natural semperoside A: mp = 181−183 °C, $[\alpha]^{20}_D$ +65.7 (*c* 0.2, MeOH);[16] synthetic **1**: mp = 182−184 °C; $[\alpha]^{20}_D$ +67.2 (*c* 0.3, MeOH)]. In addition, CD spectra of the natural and the synthetic samples showed an identical Cotton effect at 215 nm ($\Delta\epsilon = -1.3$). Thus, the sterecontrolled synthesis of glucoside **1** from (3a*R*,4*R*,-6a*S*)-lactone **8** proved the absolute configuration of semperoside A unequivocally. This stereostructure corresponds to the stereochemistry originally suggested by Jensen and co-workers.[1a] In summary, a versatile and concise strategy for the total synthesis of semperoside A **1**, an iridoid endowed with an unusual glycosidation pattern, has been developed. This inaugural total synthesis of semperoside A was achieved in 10 steps and 17% overall yield from the enantiomerically pure lactone **8**, which is now available in multigram amount.[17]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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