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Generation of Molecular Complexity from Aromatics: A Formal Total Synthesis of Coriolin from 6-Methylsaligenin

Vishwakarma Singh* and Biswajit Samanta

Department of Chemistry, Indian Institute of Technology, Bombay, 400076, India

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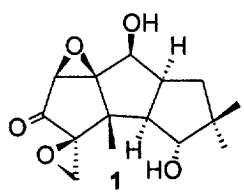
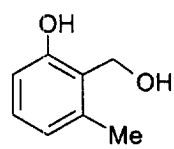
Abstract: A formal synthesis of coriolin from 6-methylsaligenin is described.

Key words: cycloaddition; photochemistry; oxidation; polyquinanes

Efficient creation of molecular complexity from simple precursors is one of the most desirable aspects of synthesis design.[1,2] Occasionally reactions in tandem,[2b,c] or a cascade of reactions,[2d,e] are employed to achieve this objective. Recently, the holosynthon concept has been proposed[3] to describe such reactions. In view of the recent interest in the chemistry of polyquinanes which is continuing unabated,[4,5] we developed a method for rapid generation of molecular complexity from simple precursors.[6] Among various polyquinanes, coriolin **1**, a triquinane metabolite of *coriolus consors*,[7] has been a popular target[4a,8] for synthesis due to its unique highly functionalised carbocyclic structure, presence of angular, and geminal methyl groups and promising biological activities.[7] Though several ingenious syntheses of coriolin have been reported,[4a] most create the triquinane framework iteratively in a multistep sequence often in a non-stereoselective fashion. In continuation of our interest in this area,[6] we wish to report a formal total synthesis of coriolin **1** from a simple aromatic precursor **2** which features efficient generation of molecular complexity *via* cycloaddition of a highly labile spiroepoxycyclohexa-2,4-dienone and a photochemical 1,2-acyl shift in an *endo* tricyclo[5.2.2.$0^{2,6}$]undecane system as delineated below.



1



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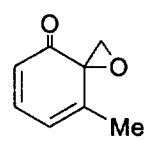

3

We contemplated that generation of the spiroepoxycyclohexa-2,4-dienone **3** from 6-methylsaligenin **2** and interception with cyclopentadiene would provide efficiently the tricyclic adduct **4** which may be easily elaborated to the tricyclic system **5** *via* manipulation of the oxirane ring and the double-bond in the five-membered ring. It was further envisaged that a 1,2-acyl shift [9] (or oxa di-π-methane rearrangement) in **5** on triplet sensitization would furnish the tetracyclic precursor **6** in a single stereoselective step and that, regioselective cleavage of the peripheral cyclopropane bond in **6** would readily give the intermediate **7** (Scheme 1) which has already been elaborated[10] to coriolin.

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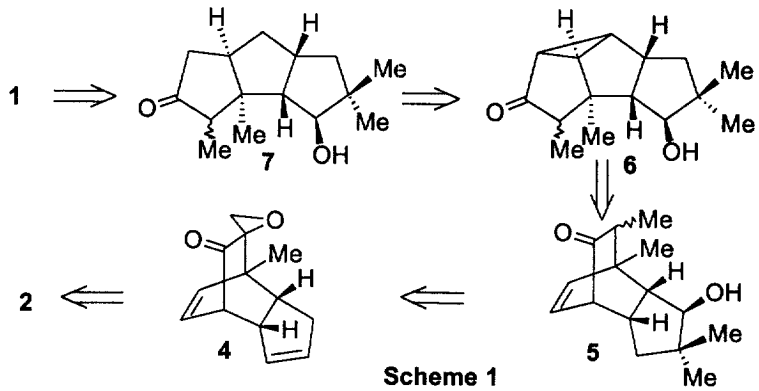


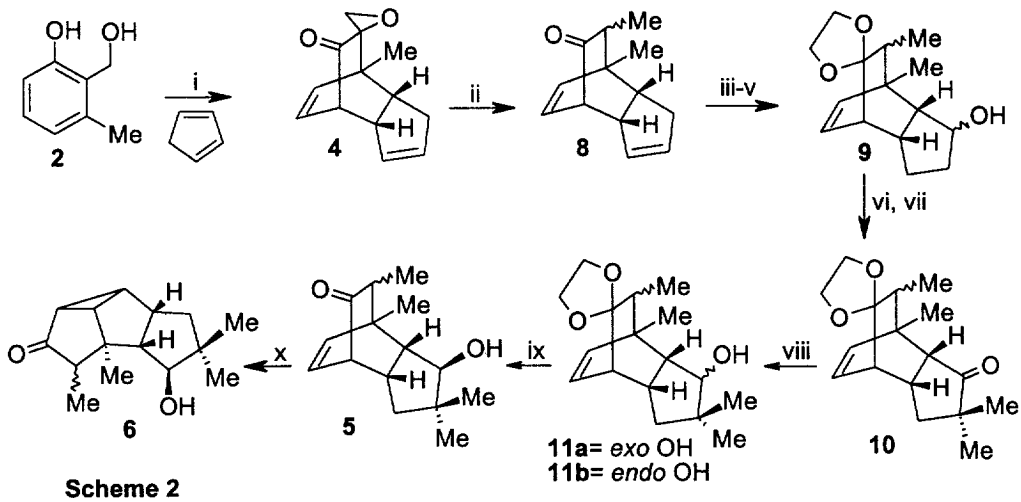
Scheme 1

There are several noteworthy features of the present strategy. For example, the *cis:anti:cis* triquinane framework of coriolin, having appropriately disposed angular and geminal methyl and hydroxyl groups, is generated in a single stereoselective step. Moreover, the tricyclic system **5** containing all three rings of coriolin including two five-membered rings in latent form, is readily derived from the tricyclic ketoepoxide **4**. Remarkably, the epoxide **4** having a β,γ-enone chromophore is assembled from 6-methylsaligenin **2** and cyclopentadiene in a single step thus *generating maximum complexity in the beginning of the synthetic route itself*, one of the most desirable features in synthesis design.[1]

Thus, the oxidation of 6-methylsaligenin **2**, readily prepared from 2,3-dimethylanisole *via* its oxidation to 3-methyl anisaldehyde[11] followed by demethylation and reduction, with sodium *meta*periodate in aqueous acetonitrile and subsequent interception of the resulting spiroepoxycyclohexa-2,4-dienone **3** with cyclopentadiene furnished the tricyclic ketoepoxide **4**. The structure and stereochemistry of the adduct **4** was established through spectral data and comparison with spectral features of similar adducts prepared in our laboratory.[6] Though the cycloaddition gave a single adduct in a highly regio- and stereoselective manner, it could have given other products as a result of other pericyclic modes of reaction between the cyclohexa-2,4-dienone **3** and cyclopentadiene. It may be mentioned that there exists a mechanistic dichotomy regarding the mode of addition and formation of cycloadducts during cycloaddition of cyclohexa-2,4-dienones and dienes.[12]

The adduct **4** was easily transformed into the desired chromophoric system **5** as shown in scheme 2. Thus, reduction of **4** with Zn in dry dioxane containing ammonium chloride selectively furnished the deoxygenated ketone **8** in excellent yield (85%) as a mixture of *syn:anti* isomers (*anti* as major). Allylic oxidation of **8** with SeO_2 and further oxidation of the resulting alcohol with Jones reagent gave a mixture of regio-isomeric enones which upon protection of the carbonyl at the bridge and subsequent reduction of the enone group furnished a mixture of hydroxyl-ketals from which the ketal **9** was obtained as a major product. The ^{1}H NMR spectrum (300 MHz) of the hydroxy-ketal **9** indicated it to be a single diastereomer at the alcohol centre. Howeve, no attempts were made to ascertain the orientaion of the hydroxyl group since it had to be oxidized to a ketone. Thus, the oxidation of **9** with PCC and alkylation of the resulting keto-ketal gave the dimethylated compound **10** in good yield (62%) (Scheme 2). Reduction of the carbonyl group in **10** gave a mixture of hydroxy ketals **11a,b** (70:30) in quantitative yield, which were separated by column chromatography. The ^{1}H NMR spectrum (300 MHz) of **11a** showed a signal at δ 3.18 (dd, J_1= 8Hz, J_2= 6Hz) corresponding to H-C-OH proton due to coupling with the proton at the adjacent ring junction and the proton of the OH group (coupling with OH proton was clearly revealed through D_2O exchange), respectively. The H-C-OH proton in the *endo* stereoisomer **11b** displayed a down field signal at δ 3.50 as a

dd (J_1= 12Hz, J_2= 6Hz) having a large coupling with the ring junction proton. These chemical shifts and the coupling constants clearly revealed the stereochemical orientation of the hydroxyl groups in **11a** (and hence in **5**) and **11b**. The major product **11a** was hydrolyzed to give the highly embellished tricyclic system **5** having all the structural, functional and stereochemical elements of the coriolin precursor **7**.

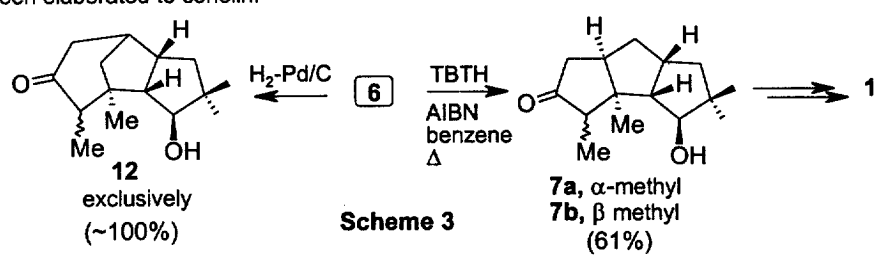


Scheme 2

Reagents/ conditions: i, $NaIO_4$, aq CH_3CN,r.t. (45%); ii, Zn, NH_4Cl, dry dioxane, Δ (85%); iii,(a) SeO_2, KH_2PO_4 dioxane-H_2O, Δ (55%),(b), Jones (95%); iv, *p*-TsOH, ethyleneglycol, benzene, Δ (80%); v, $NaBH_4$, MeOH(60%); vi,PCC, CH_2Cl_2 (quantitative); vii KO^{t}Bu, MeI, Δ (62%); viii, $NaBH_4$,THF-H_2O, r.t. (70%); ix, HCl-acetone (90%); x, hν, acetone (65%)

Towards the synthesis of coriolin, a solution of the keto-alcohol **5** in acetone (sensitizer and solvent) was irradiated with a mercury vapour lamp (125 W, Applied Photophysics) for about 1.5h. Removal of solvent followed by chromatography of the photolysate furnished the tetracyclic precursor **6** in good yield (65%). At this juncture, elaboration of **6** to the desired tricyclopentanoid **7** required the selective cleavage of the peripheral cyclopropane bond. Unfortunately the reductive cleavage of **6** with H_2 on Pd-C furnished the tricyclic compound **12** as a result of an alternative cleavage of the cyclopropane ring, with no trace of the desired product **7**.

This problem, however, was soon alleviated *via* reduction of **6** with tributyltin hydride (TBTH). Thus, treatment of the tetracyclic compound **6** with tributyltin hydride-AIBN in benzene under reflux followed by work up and chromatography furnished the diastereomeric tricyclopentanoids **7a** and **7b** (Scheme 3) in reasonably good yield which were thoroughly characterized,[13] completing the formal synthesis since **7a** has already been elaborated to coriolin.[10]



Scheme 3

In summary, we have developed a novel formal synthesis of coriolin from 6-methylsaligenin and cyclopentadiene. It constitutes a unique example in which an aromatic ring is combined with cyclopentadiene to give a precursor endowed with thirteen carbons of coriolin with appropriate connectivity and stereochemical orientation. Introduction of two more carbons and hydroxyl group at the appropriate juncture followed by photochemical reorganization and cleavage readily furnished the desired intermediate.

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13. Selected data for **7a:** mp 161-162^{0}C. IRν_{max} :3502, 3467, and 1724 cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$) δ : 3.51 (dd, J_1=8Hz, J_2=~6Hz, 1H, C<u>H</u>OH), 2.7 (Complex m, 1H), 2.4-2.16 (Complex m, 3H), 2.0 (q, J=6Hz, 1H), 1.83 (dd, J_1=12Hz, J_2=9Hz, 1H),1.76-1.55 (multiplets, 2H, partly hidden under signal due to H_2O in $CDCl_3$), 1.30(d, J= 6Hz, 1H, O<u>H</u>, becomes singlet after D_2O exchange), 1.1 (m, 2H, partly hidden under signals due to methyls), 1.03 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.97 (d, J=6Hz, 3H, CH_3), 0.9 (s, 3H, CH_3). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 220.88 (CO), 81.93, 57.39, 51.92, 51.80, 45.99, 43.43, 42.68, 41.26, 39.25, 37.40, 26.47, 19.48, 16.43, 7.94. Mass (m/z) : 236 (M^+), 218 (M^+-H_2O), 203 (M^+-H_2O-CH_3). These spectral features are in good agreement with the literature.[10]