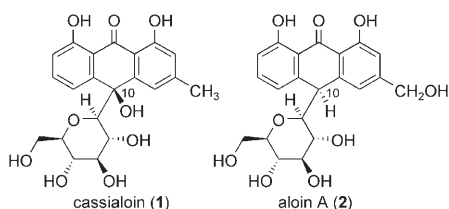


Total Synthesis and Structure Assignment of the Anthrone C-Glycoside Cassialoin**

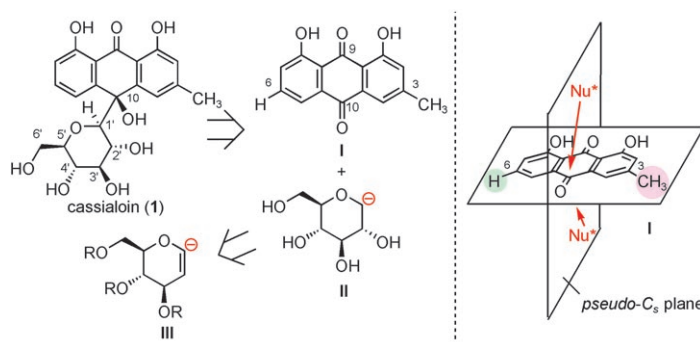
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Anthrone C-glycosides constitute an intriguing class of natural products, in which sugars are connected to an anthrone skeleton at its C10 position through a C–C bond. Cassialoin (**1**), a representative member of this class, was isolated from plant extracts traditionally used in Ayurvedic and Asian folk medicine, namely a heartwood of *Cassia garrettiana* CRAIB^[1] or the roots of *Rheum emodi* WALL.^[2] Such unique sugar–anthrone hybridized structures present challenges for stereocontrolled synthesis, as well as for structure elucidation. Although the sugar stereochemistry of **1** was assigned as the β -C-glucoside based on ¹H NMR spectroscopy, the C10 configuration is not easy to assign.^[2,3] While the structure of the related aloin A (**2**) was established by single-crystal X-ray analysis, the structure of **1** remained speculative.



Herein we describe the stereocontrolled first total synthesis of **1**, thereby establishing the stereostructure of cassialoin as that of **1**. The analysis further revealed that the natural product contains the C10 epimer **1'** as a minor constituent.

Scheme 1 shows the retrosynthetic analysis based on the dissection of **1** into anthraquinone **I** and carbohydrate **II**. We

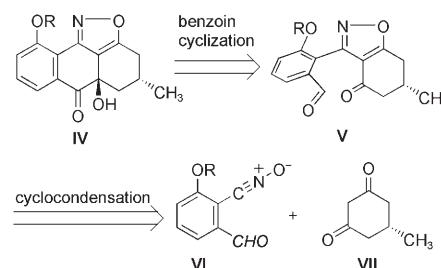


Scheme 1. Retrosynthetic analysis of **1**.

planned to introduce the sugar as a nucleophile via glycal anion **III**,^[4] which posed two potential difficulties: 1) the discrimination of two carbonyl groups at the C9 and C10 positions and 2) the facial selectivity at the C10 position. The latter issue seemed nontrivial because acceptor **I** has a pseudomirror symmetry, only differing in the C3 and C6 positions. Even if a chiral nucleophile were employed, rigorous control of the facial selectivity seemed unlikely.

To address this stereochemical challenge, we sought to exploit our recent approach to densely functionalized polycyclic structures.^[5,6] More precisely, we planned to use chiral, nonracemic ketol **IV** as a selectively protected, stereogenic surrogate of anthraquinone **I** (Scheme 2), with the hope that a nucleophile would attack ketol **IV** from the α face.

This key intermediate **IV** would be prepared by the stereoselective benzoin cyclization of ketoaldehyde **V**. Although compound **V** could be obtained by cyclocondensation of nitrile oxide **VI** and diketone **VII**, the dilemma was that the diketone **VII** has C_s symmetry, so the cyclocondensation with nitrile oxide **VI** would inevitably produce a racemate.



Scheme 2. Retrosynthetic analysis of **IV**.

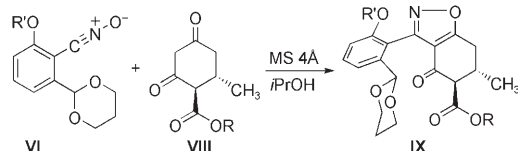
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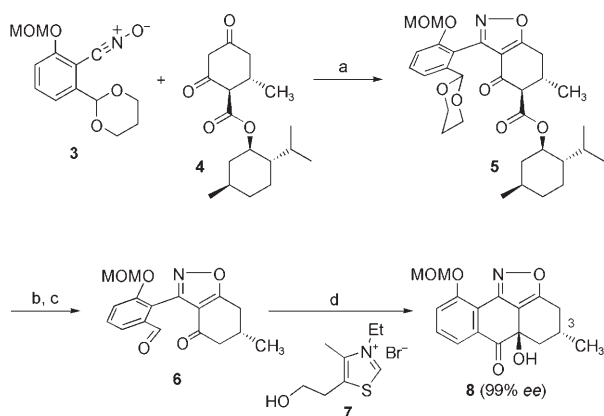
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As a potential solution to this issue, we postulated that the chiral, nonracemic diketoester **VIII** would serve as a useful precursor to **V**, because we knew that the corresponding racemic compound **VIII** ($R = Et$) can undergo regioselective cyclocondensation with benzonitrile oxides to give isoxazole-annulated product **IX** (Scheme 3).^[5e] The remaining issue was the availability of diketoester **VIII** in an enantiomerically enriched form, for which we decided to rely on the readily prepared, enantiomerically pure surrogate **4** reported by Myers et al.^[7]



Scheme 3. Regioselective formation of **IX** from diketone **VIII**. MS = Molecular sieves.

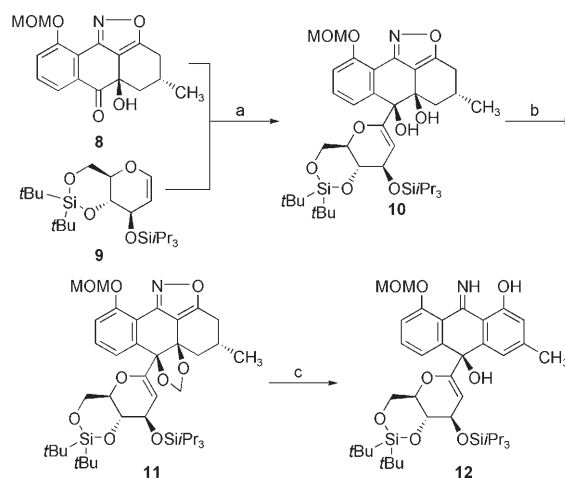
The synthesis started with the cyclocondensation of stable nitrile oxide **3**^[5] and 1,3-diketone **4**, which proceeded smoothly in *i*PrOH in the presence of powdered molecular sieves (4 Å) to give isoxazole **5** as the major product in 72% yield (Scheme 4).^[8]



Scheme 4. Reagents and conditions: a) **4** (1.2 equiv), MS (4 Å; 1 g mmol⁻¹), *i*PrOH, 50 °C, 1 d, 72%; b) 4-DMAP (1.0 equiv), H₂O, mesitylene, 150 °C, 3.5 h; c) 1 M aq. H₂SO₄, THF, room temperature, 3.5 h, 66% (2 steps); d) **7** (0.1 equiv), DBU (0.1 equiv), *t*BuOH, 40 °C, 2 h, 99%. MOM = methoxymethyl; 4-DMAP = 4-dimethylaminopyridine; THF = tetrahydrofuran; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

To remove the menthyl ester moiety in **5**, several classical decarboxylation protocols were examined without success, with each giving a complex mixture of unidentified products. After considerable experimentation, the goal was achieved by thermolysis of **5** in the presence of 4-DMAP.^[9] Subsequent hydrolysis of the 1,3-dioxane acetal afforded ketoaldehyde **6**, ready for the benzoin-forming reaction. Treatment of **6** with thiazolium salt **7** (10 mol%) and DBU allowed a smooth benzoin cyclization to give ketol **8** as a single diastereomer in 99% yield.^[10]

Scheme 5 highlights the stereoselective union of the lithiated species of glycol **9**^[11] and α -ketol **8** to give *cis*-diol **10** as a single diastereomer in 75% yield.^[12] The X-ray analysis verified the C10 configuration of **10** to be *S* (Figure 1).^[13]



Scheme 5. Reagents and conditions: a) **9** (3.6 equiv), *t*BuLi (3.0 equiv), THF, 0 °C, 2 h; then **8**, -78 °C, 30 min, 75%; b) ClCH₂I (2.5 equiv), NaH (2.5 equiv), DMF, room temperature, 4 h, 84%; c) KO*t*Bu (10 equiv), THF, -78 °C → room temperature, 35 min, 76%. DMF = *N,N*-dimethylformamide.

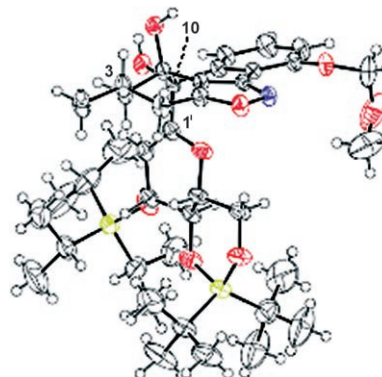
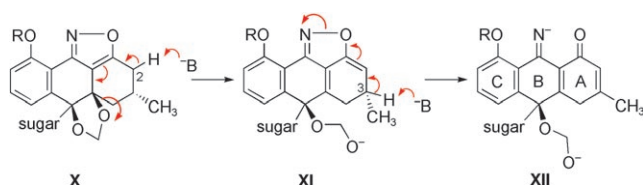


Figure 1. ORTEP diagram of **10**. Thermal ellipsoids at 50% probability. N blue, O red, Si yellow.

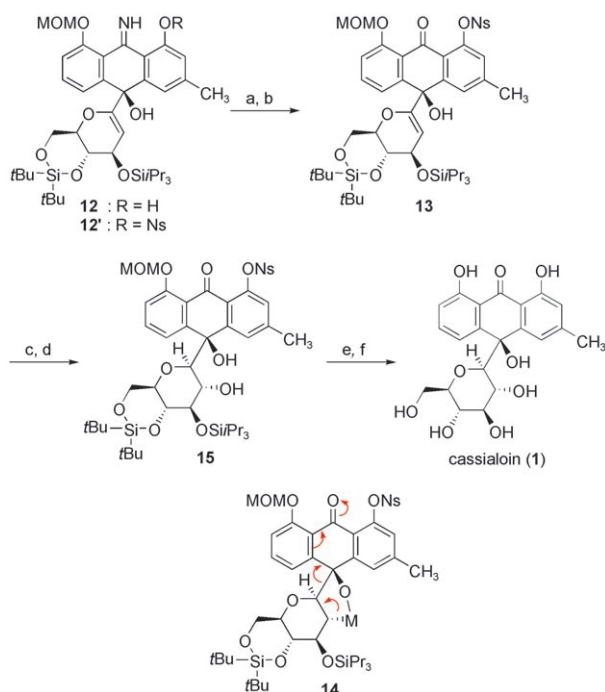
By conversion of **10** into methylene acetal **11**,^[14] the stage was set for the aromatization of the A ring. Through initial unfruitful attempts based on organoselenium chemistry,^[15] we were pleased to learn that the conversion could be achieved in a single step by exposure of isoxazole **11** to a strong base (KO*t*Bu), thereby giving anthrone **12** in 76% yield. The process formally involves the cleavage of the isoxazole ring and the aromatization of the A ring.

Scheme 6 shows the rationale for this intramolecular redox process. Deprotonation at the C2 position expels the angular oxygen atom in **X** to give intermediate **XI**, which then undergoes another deprotonation at the C3 position to cleave the N–O bond and to afford dianion **XII**. Upon quenching, tautomerization gives imine **12** with the A ring aromatized.^[16]



Scheme 6. Intramolecular redox reaction. ^sB = strong base.

The next stage was the hydrolysis of imine **12** to the corresponding ketone (Scheme 7), which was not achievable under conventional acidic conditions. After unfruitful trials,



Scheme 7. Reagents and conditions: a) NaCl (5.0 equiv), K₂CO₃ (10 equiv), DMF, 0°C, 2 h; b) SiO₂, CH₂Cl₂, room temperature, 14 h, 86% (2 steps); c) dimethyldioxirane, acetone/CH₂Cl₂ (1:2), 0°C, 5 h; d) BH₃·THF (3.5 equiv), THF, 0°C, 7 h, 66% (2 steps); e) PPTS (1.0 equiv), *t*BuOH, reflux, 1 h, 81%; f) TBAF (5.0 equiv), THF, room temperature, 10 h, 53%. Ns = 2-nitrobenzenesulfonyl; PPTS = pyridinium *p*-toluenesulfonate; TBAF = tetrabutylammonium fluoride.

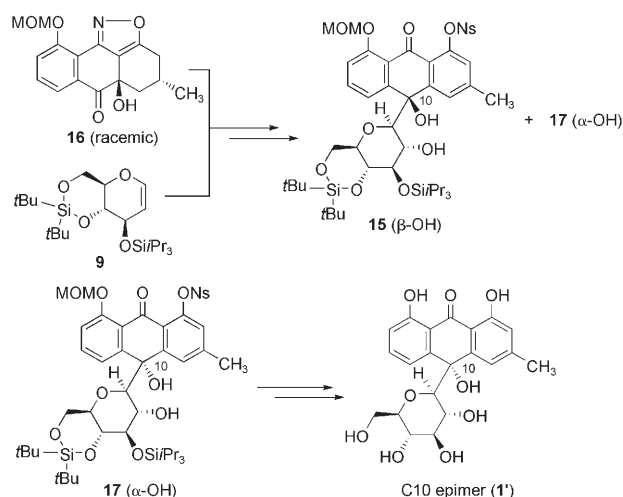
the issue was solved by protecting the phenol with an electron-withdrawing 2-nitrobenzenesulfonyl (nosyl) group,^[17] which rendered the imine easily hydrolyzable. Upon treatment of nosylate **12'** with silica gel, the corresponding ketone **13** was obtained in high yield. The strong electron-withdrawal by the nosylate group served also to increase the stability of the tertiary alcohol under acidic conditions.^[18]

The remaining task was the hydration of glycol **13** to complete the β-glucoside structure. While attempts by hydroboration or hydrosilylation uniformly failed, due presumably to the decomposition path from metallacycle **14**,^[19] the projected hydration was realized by epoxidation followed by reductive opening of the oxirane ring. The epoxidation with dimethyldioxirane^[11,20] proceeded smoothly to give an

unstable oxirane, which was reduced with BH₃·THF^[21] to give alcohol **15** (*J*_{1',2'} = 10.6 Hz, *J*_{2',3'} = 8.5 Hz) as a single product in 66% yield.

The MOM group in **15** was selectively removed with PPTS in the presence of molecular sieves (4 Å)^[22] and the product was treated with TBAF to remove the silyl protecting groups. In a pleasant surprise, the remaining nosyl group was also detached during concentration of the resulting mixture in vacuo. The TBAF-derived byproducts were removed by the procedure described by Kaburagi and Kishi,^[23] reversed-phase column chromatography (MeOH/H₂O (65:35) with 0.1% trifluoroacetic acid) gave cassialoin (**1**). The spectroscopic data (¹H and ¹³C NMR spectra, mass spectra, IR data, TLC mobilities in several different solvent systems) of this product were consistent with those reported for the natural product.

Having the homogeneous synthetic material with a stereochemical identity, we noticed that ¹H NMR spectrum of the naturally obtained sample contained additional minor peaks, which suggested the presence of an impurity or minor component. Assuming that it could well be the C10 epimer, we prepared a comparison sample by starting with **16**, the racemate of **8** (Scheme 8). The same series of transformations



Scheme 8. Synthesis of C10 epimer **1'**.

as those described above gave an easily separable mixture of epimers **15** (β-OH) and **17** (α-OH); and deprotection of the latter gave the C10 epimer **1'**.^[24] The ¹H NMR spectrum of **1'** coincided with the minor peaks present in the ¹H NMR spectrum of the natural sample.

In summary, this synthesis established the stereochemistry of **1** and also revealed that the epimer **1'** is present as a minor component in the natural material. The synthesis features the first application of isoxazole-containing stereogenic α-ketol **8** as an anthraquinone equivalent and may be extended to the syntheses and structure assignments of other anthrone C-glycosides.

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