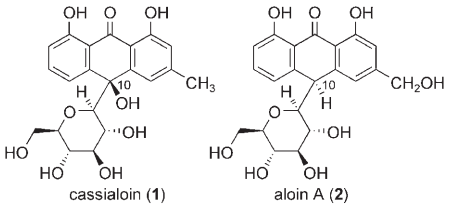
Natural Product Synthesis

DOI: 10.1002/anie.200704625

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

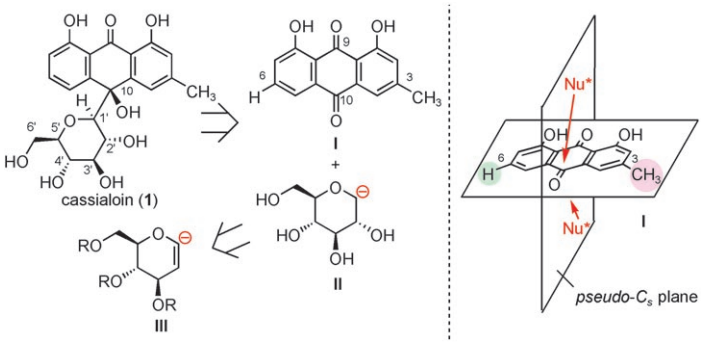
*Yasuhito Koyama, Ryo Yamaguchi, and Keisuke Suzuki**

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 ^{1}H 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

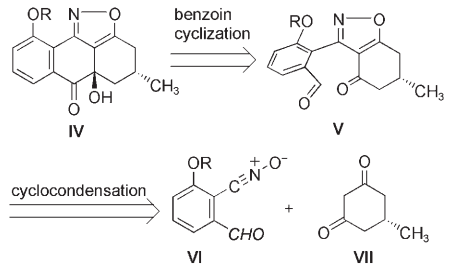


Scheme 1. Retrosynthetic analysis of **1**.

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**.

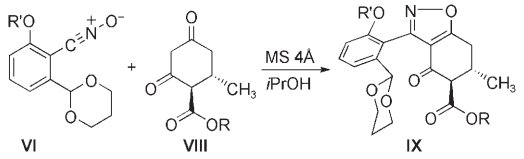
[*] Dr. Y. Koyama,[+] R. Yamaguchi, Prof. Dr. K. Suzuki
Department of Chemistry
Tokyo Institute of Technology, SORST-JST Agency
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551 (Japan)
Fax: (+81) 3-5734-2788
E-mail: ksuzuki@chem.titech.ac.jp

[+] Present address:
Department of Organic and Polymeric Materials
Tokyo Institute of Technology
2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551 (Japan)

[**] We are grateful to Dr. Hidehiro Uekusa for X-ray analyses. This work was partially supported by the Global COE program (Tokyo Institute of Technology) and a Grant-in-Aid for Scientific Research (JSPS). A Fellowship to Y.K. from the JSPS for Young Japanese Scientists is gratefully acknowledged. We thank Dr. Liselotte Krenn (Vienna University) for providing an authentic sample of cassialoin and the ^{1}H NMR spectrum.

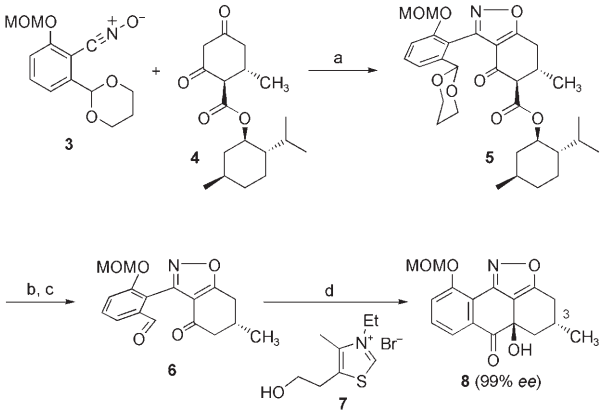
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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.

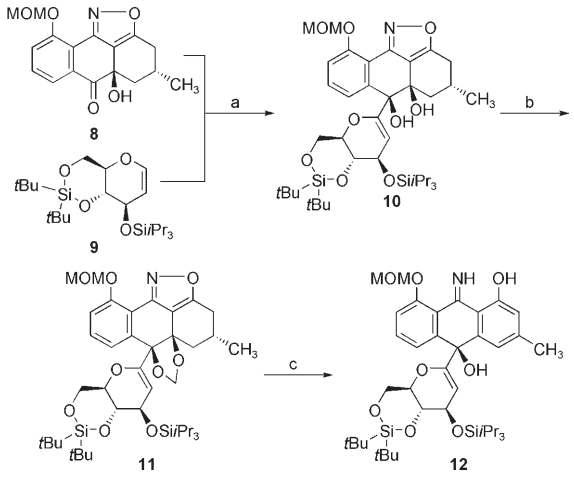
The synthesis started with the cyclocondensation of stable nitrile oxide **3**[5] and 1,3-diketone **4**, which proceeded smoothly in *i*PrOH in the presence of powdered molecular sieves (4 Å) to give isoxazole **5** as the major product in 72% yield (Scheme 4).[8]



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), H_2O, mesitylene, 150 °C, 3.5 h; c) 1 M aq. H_2SO_4, 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 = tetrahydrfuran; 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 glycal **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) $ClCH_2I$ (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.

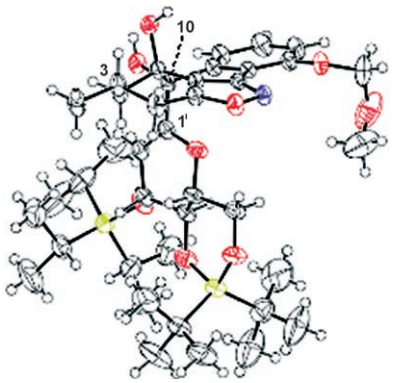
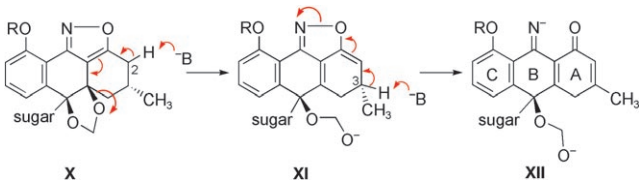


Figure 1. ORTEP diagram of **10**. Thermal ellipsoids at 50% probability. N blue, O red, Si yellow.

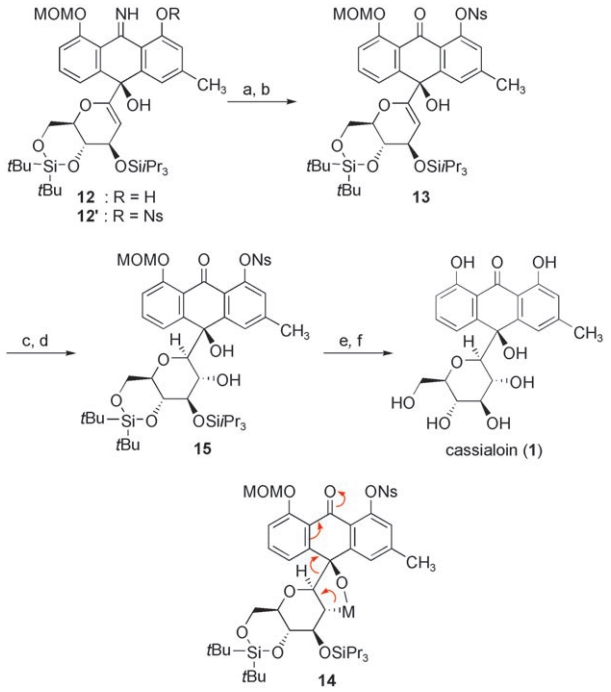
By conversion of **10** into methylene acetal **11**,[14] the stage was set for the aromatization of the A ring. Through initial unfruitful attempts based on organoselenium chemistry,[15] we were pleased to learn that the conversion could be achieved in a single step by exposure of isoxazole **11** to 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. ^{S}B = 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,



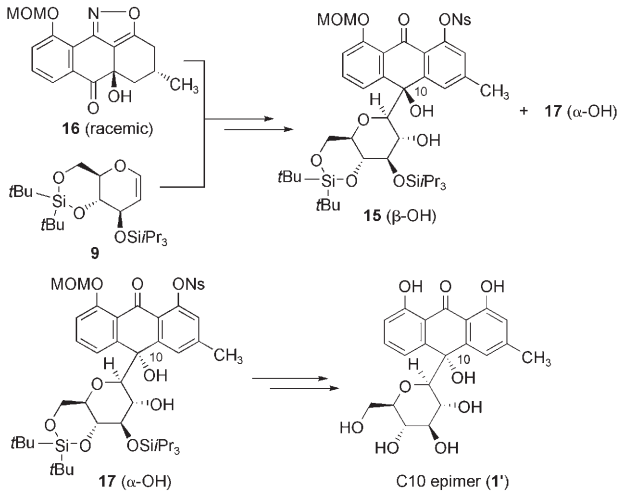
Scheme 7. Reagents and conditions: a) NsCl (5.0 equiv), K_2CO_3 (10 equiv), DMF, 0 °C, 2 h; b) SiO_2, CH_2Cl_2, room temperature, 14 h, 86% (2 steps); c) dimethyldioxirane, acetone/CH_2Cl_2 (1:2), 0 °C, 5 h; d) BH_3·THF (3.5 equiv), THF, 0 °C, 7 h, 66% (2 steps); e) PPTS (1.0 equiv), *t*BuOH, reflux, 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 glycal **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 BH_3·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/H_2O (65:35) with 0.1% trifluoroacetic acid) gave cassialoin (**1**). The spectroscopic data (^1H and ^{13}C 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.

Received: October 8, 2007
Published online: December 28, 2007

Keywords: configuration determination · glycosides · heterocycles · natural products · total synthesis

[1] K. Hata, K. Baba, M. Kozawa, *Chem. Pharm. Bull.* **1978**, *26*, 3792.

[2] L. Krenn, R. Pradhan, A. Presser, G. Reznicek, B. Kopp, *Chem. Pharm. Bull.* **2004**, *52*, 391.

[3] a) P. Manitto, D. Monti, G. Speranza, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1297; b) P. Manitto, D. Monti, G. Speranza, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1577.

[4] a) K. A. Parker, C. A. Coburn, *J. Am. Chem. Soc.* **1991**, *113*, 8516; b) for a recent review on metalated heterocycles, see: R. Chinchilla, C. Nájera, M. Yus, *Chem. Rev.* **2004**, *104*, 2667.

[5] a) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 3555; b) J. W. Bode, K. Suzuki, *Tetrahedron Lett.* **2003**, *44*, 3559; c) Y. Hachisu, J. W. Bode, K. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 8432; d) Y. Hachisu, J. W. Bode, K. Suzuki, *Adv. Synth. Catal.* **2004**, *346*, 1097; e) T. Matsuura, J. W. Bode, Y. Hachisu, K. Suzuki, *Synlett* **2003**, 1746; f) J. W. Bode, Y. Hachisu, T. Matsuura, K. Suzuki, *Org. Lett.* **2003**, *5*, 391; g) J. W. Bode, H. Uekusa, K. Suzuki, *Org. Lett.* **2003**, *5*, 395.

[6] For an enantioselective route to α-ketols, see: H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem.* **2006**, *118*, 3572; *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.

[7] A. G. Myers, N. J. Tom, M. E. Fraley, S. B. Cohen, D. J. Madar, *J. Am. Chem. Soc.* **1997**, *119*, 6072.

[8] The regioisomer was obtained in 17% yield. Structural assignments of **5** and the regioisomer were based on the HMBC correlations, after hydrolysis of the cyclic acetal.

[9] D. F. Taber, R. E. Ruckle, Jr., *Tetrahedron Lett.* **1985**, *26*, 3059.

[10] The stereostructure of **8** was assigned by the NOE observed between the tertiary alcohol and the C3 methine proton.

[11] S. W. Roberts, J. D. Rainier, *Org. Lett.* **2005**, *7*, 1141.

[12] The ^{1}H NMR spectra of **10** is highly dependent on the concentration and temperature, due most likely to the change in the aggregation state.

[13] See the Supporting Information.

[14] J. S. Brimacombe, A. B. Foster, B. D. Jones, J. J. Willard, *Chem. Commun.* **1967**, 2404.

[15] For reviews on organoselenium chemistry, see: *Organoselenium Chemistry: Modern Development in Organic Synthesis* (*Topics in Current Chemistry, Vol. 208)* (Ed.: T. Wirth), Springer, Heidelberg, **2000**.

[16] Formation of the methylene acetal was essential, as the *cis*-diol **10** remained unchanged under such reaction conditions.

[17] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373.

[18] Conversely, if electron-donating groups (*para*-methoxyphenylmethyl, MOM, or methylthiomethyl) were used for the phenol protection, the product was unstable on silica gel and gave a complex mixture of unidentified byproducts.

[19] The anthraquinone lacking the sugar moiety was identified as a side product in the complex mixture.

[20] a) R. L. Halcomb, S. J. Danishefsky, *J. Am. Chem. Soc.* **1989**, *111*, 6661; b) J. D. Rainier, S. P. Allwein, *J. Org. Chem.* **1998**, *63*, 5310; c) M. Inoue, S. Yamashita, A. Tatami, K. Miyazaki, M. Hirama, *J. Org. Chem.* **2004**, *69*, 2797.

[21] The hydride attack proceeded only from the α face, to give **15**. For a related report, see; H. C. Brown, N. M. Yoon, *J. Am. Chem. Soc.* **1968**, *90*, 2686.

[22] H. Monti, G. Léandri, M. Klos-Ringquet, C. Corriol, *Synth. Commun.* **1983**, *13*, 1021.

[23] The TBAF-derived materials were removed by treatment with Dowex 50WX8-400 and $CaCO_3$ in MeOH (room temperature, 1 d); see: Y. Kaburagi, Y. Kishi, *Org. Lett.* **2007**, *9*, 723.

[24] With normal silica gel chromatography, the behaviors of the epimers **1** and **1′** were very similar; the separation was only realized by HPLC with a chiral stationary phase, which revealed that the natural sample was composed of a 4:1 mixture of **1** and **1′**.

