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Oxidative Decarboxylation as a Route to Ketene Acetals: Assignment of Relative and Absolute Stereochemistry to the Fungal Metabolite Benesudon by Total Synthesis

Derrick L. J. Clive* and Minaruzzaman

Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

derrick.clive@ualberta.ca

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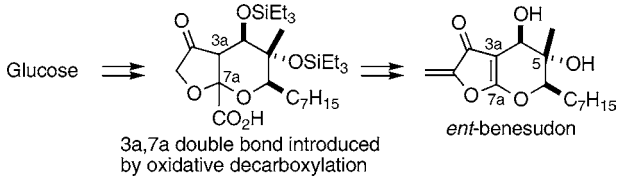
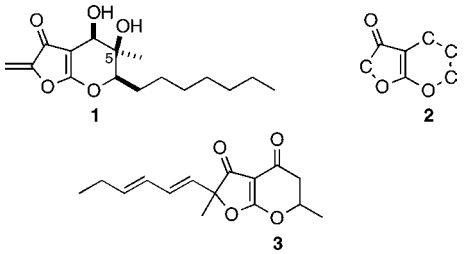
ABSTRACT



The unusual ketene acetal benesudon, which is a bioactive fungal metabolite, was synthesized from D-glucose by a route involving radical cyclization to form the five-membered ring and oxidative decarboxylation to generate the key central double bond. The originally suggested stereochemistry for the quaternary center C(5) must be revised, as both possibilities were prepared and a comparison with an authentic sample was made. The absolute configuration of benesudon is 4*S*,5*R*,6*S*.

Benesudon, a metabolite of the fungus *Mollisia benesuada*, is a biologically active substance originally assigned structure **1** (absolute stereochemistry not implied), largely on the basis of NMR measurements, with the relative stereochemistry suggested by the observed nuclear Overhauser enhancements.[1] The structure is unusual, not only among natural products but also in its own right, and a search of the literature for related compounds having the substructure **2** retrieved only cyclogregatin (**3**), which is also a fungal metabolite.[2] Benesudon shows activity against the growth of bacteria and fungi and is also cytotoxic.[1] Because these potentially significant properties are associated with a new structural type, the compound merits attention as a synthetic target. Although the molecule is small, it possesses a high degree of complexity because it contains interrelated ketene acetal, vinylogous ester, α-methylene carbonyl, and enol ether subunits—by any measure, a striking level of closely associated functional groups which would likely complicate its synthesis.



There was no prior synthetic work in this area, and therefore we first undertook a model study[3] to explore a route to the ketene acetal subunit. In that investigation, the core structure **5** was eventually found to be accessible by way of

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(2) Anke, H.; Casser, I.; Schrage, M.; Steglich, W. *J. Antibiot*. **1988**, *41*, 1681−1684.

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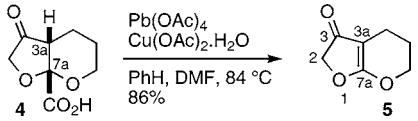
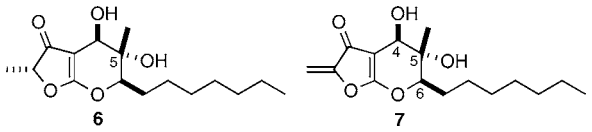
a modified version of the classical Kochi oxidative decarboxylation[4] (Scheme 1). With this method available for

Scheme 1. Generation of Ketene Acetal System



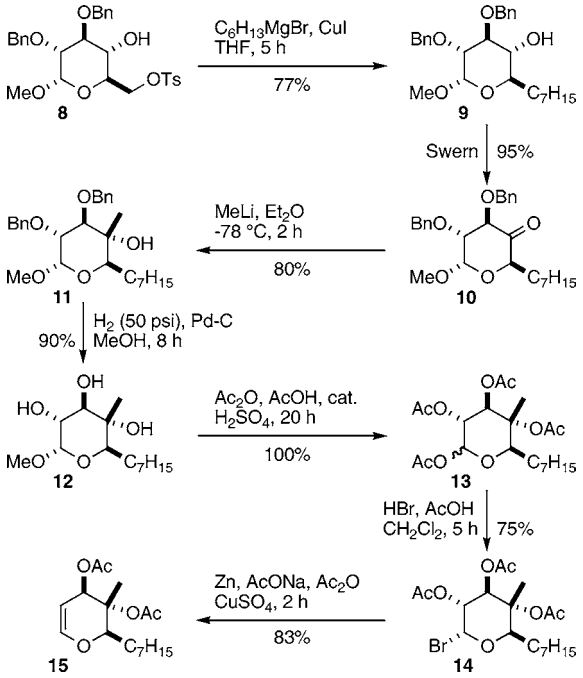
introducing the characteristic C(3a)−C(7a) double bond—at least into a simple model—we began a synthesis of benesudon itself. During that work, isolation of the marine fungal metabolite aigialone (**6**) was reported.[5] The similarity of its structure, which was deduced by spectroscopic means and X-ray analysis, to that proposed for benesudon prompted a reconsideration[5] of the original[1] NOE data. This led to the suggestion[5] that the observed NOEs for benesudon might also be compatible with the relative stereochemistry shown in **7** (absolute stereochemistry not implied). The evidence in favor of revising the original assignment was certainly suggestive but not compelling and, as we were already far advanced in our route to **1**, we decided to complete that synthesis. However, examination of the NMR spectra of synthetic **1** showed that structural revision was indeed required, and so we turned our attention to the proposed alternative **7**, expecting (in the event, wrongly) that the reactions used to make **1** would be equally applicable to **7**.

Tosylate **8**, made from D-glucose,[6] was homologated[6a] with



the organocuprate derived from *n*-$C_6H_{13}MgBr$ (Scheme 2). Swern oxidation then afforded ketone **10**, and reaction with MeLi gave mainly (24:1) the equatorial alcohol **11** (80%),[7,8] The stereochemistry[9] of this step (**10**→**11**) depends on the reagent and temperature; with MeMgI in Et_2O at −78 °C, the corresponding axial alcohol is the major product, and this pathway was used in our synthesis of **1**.[7,8] Hydrogenolysis of the benzyl groups and acetylation afforded the tetraacetates **13**, and the anomeric acetoxy group was replaced by bromine (**13**→**14**). Treatment with Zn then generated glucal **15**, which is a key intermediate, as it

Scheme 2. Preparation of Key Glucal



represents the six-membered ring segment and is properly functionalized for attachment of the five-membered ring.

Hydrolysis of the acetates liberated the *trans*-diol **16** (Scheme 3). On the basis of experience in the synthesis of **1**, we masked the secondary alcohol as a *tert*-butyldimethylsilyl ether and the tertiary hydroxyl as a triethylsilyl ether. However, the *tert*-butyldimethylsilyl group proved too robust, and its removal in the last step of the route to **7** could not be achieved. Consequently, both hydroxyls were protected with $Et_3SiOSO_2CF_3$. The triethylsilyl group withstood all subsequent reactions, and its use allowed both hydroxyls to be protected in a single step. Attempts to introduce a cyano group at C(2) in **17**, by reaction with NBS and MeOH, followed by replacement of the resulting anomeric methoxy group—a method we had used in making **1**[10] —were not successful, despite extensive efforts. It appears that the orientation of the C(5) oxygen in **17** greatly decreases the lability of leaving groups later installed at C(2).[11] Consequently, we treated glucal **17** with PCC[12] to obtain the *β*-siloxy lactone **18** (66%). Little, if any, elimination occurred during this step, and the lactone was a stable, easily handled compound. Conversion to the enol triflate **19** was readily achieved with $(Me_3Si)_2NK$ and 2-[*N*,*N*-bis(trifluoromethylsulfonylamino]pyridine,[13] and carbonylation in the presence of MeOH then afforded the ester **20**. The fact that **18** can be deprotonated en route to the enol triflate **19** without

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(5) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457−460.
(6) (a) Toshima, H.; Sato, H.; Ichihara, A. *Tetrahedron* **1999**, *55*, 2581−2590. (b) Davis, N. J.; Flitsch, S. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 359−368.
(7) Sato, K.; Kubo, K.; Hong, N.; Kodama, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 938−942.
(8) Miljkovic, M.; Gligorijevic, M.; Satoh, T.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 1379−1384.
(9) The correctness of the present stereochemical assignment is based on the X-ray structure of an intermediate in the synthesis of **1**, where MeMgI had been used to generate the tertiary alcohol. The material was isomeric with that obtained from the use of MeLi.
(10) In the sequence leading to **1**, the reaction with NBS in MeOH places a methoxy group at C(2) and a bromine at C(3); the anomeric methoxy group was then replaced by CN, using Me_3SiCN in the presence of BF_3·OEt_2. Base treatment (DBU) served to generate the C(2)−C(3) double bond and the C(2) CN was then hydrolyzed to CO_2H, which was esterified.
(11) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265.
(12) Rollin, P.; Sinaÿ, P. *Carbohydr. Res.* **1981**, *98*, 139−142.
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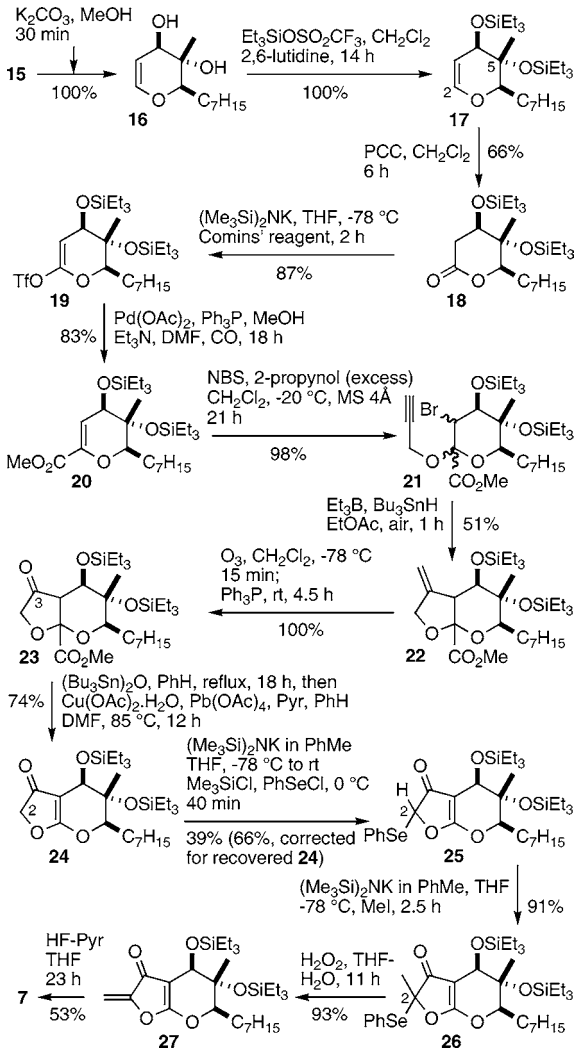
Scheme 3. Formation of *ent*-Benesudon



β-elimination is noteworthy, as preservation of such a β-oxygen substituent on a δ-lactone is unusual in the presence of a strong base.[14] Bromoetherification of **20**, using a large excess (180-fold) of propargyl alcohol and NBS, took the route as far as **21**. From this point, radical cyclization by the triethylborane method[15] at room temperature generated the desired bicyclic framework. The standard method of slow addition of a stannane to a hot solution of the bromides did not work well, but the borane−air method was sufficiently effective (51% yield) for our purpose. The C(3) carbonyl was then introduced by ozonolysis, so as to set the stage for introduction of the critical C(3a)−C(7a) double bond. In our model study,[3] ester hydrolysis could be achieved only with $(Bu_3Sn)_2O$. Accordingly, this reagent[16] was used in the present case, and the resulting unstable carboxylic acid was subjected to the oxidative decarboxylation procedure (**23**→**24**) developed in the model study. Methylation of the ketene acetal **24** at C(2) always led to extensive bismethylation. Phenylselenation (**24**→**25**) was likewise troublesome at first, but we eventually found a reliable procedure that gave the required selenide in 39% yield, as well as substantial starting material (66% corrected yield of **25**) and the corresponding bisphenylselenide (19%), which was reconverted into **24** (82%) by reaction with Ph_3P in water−CH_2Cl_2. Once the PhSe group was in place, methylation became straightforward (**25**→**26**, 91%), and there remained only selenoxide fragmentation and deprotection of the silylated hydroxyls. Formation of the exocyclic double bond[17] (**26**→**27**) went in high yield (93%), but many procedures had to be tried for deprotection to **7**, with the best (53%) being the use of a controlled amount of HF−pyridine.

Although the reported NOEs were observed with **7**, the ^1H and ^{13}C NMR spectra showed small but disconcerting differences from the published[1] values. Fortunately, the original material[1] had been preserved at a low temperature, and we were able to rerun the spectra. These new measurements show that synthetic **7** and natural benesudon have identical NMR spectra. The natural compound has $[\alpha]_D = -120.5$ ($c = 0.1$, $CHCl_3$), while **7** has $[\alpha]_D = +124.2$ ($c = 0.11$, $CHCl_3$); accordingly, the absolute configuration of benesudon is 4*S*,5*R*,6*S*, and **7** (as depicted) is actually *ent*-benesudon.

The dramatic influence on chemical behavior exerted by the stereochemistry at C(5) was a challenging surprise, and attachment of the ester group (cf. **17**→**20**) required a different approach in the series leading to **7** from that used in the route to **1**.[10] Also, **7** showed a greater sensitivity to fluoride ion than **1**. The present synthesis tests in a natural product context our oxidative decarboxylation route to the ketene acetal substructure, and the method now provides opportunities to explore structure−activity relationships for this unusual compound class.

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Supporting Information Available: Full experimental details and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *J. Org. Chem*. **1994**, *59*, 7259−7266.

(17) We did not examine alternatives to the selenium-based route for attachment of the exocyclic methylene.