

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

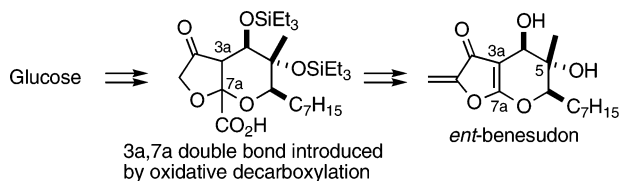
Derrick L. J. Clive* and Minaruzzaman

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

derrick.clive@ualberta.ca

Received October 13, 2007

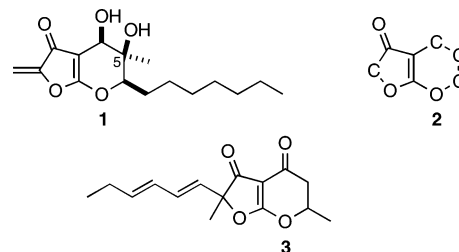
ABSTRACT



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 4S,5R,6S.

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 study³ 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

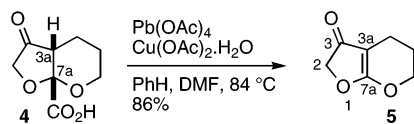
(1) Thines, E.; Arendholz, W.-R.; Anke, H.; Sterner, O. *J. Antibiot.* **1997**, *50*, 13–19.

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

(3) Clive, D. L. J.; Minaruzzaman; Yang, H. *Org. Lett.* **2005**, *7*, 5581–5583.

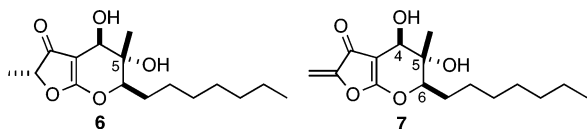
a modified version of the classical Kochi oxidative decarboxylation⁴ (Scheme 1). With this method available for

Scheme 1. Generation of Ketene Acetal System



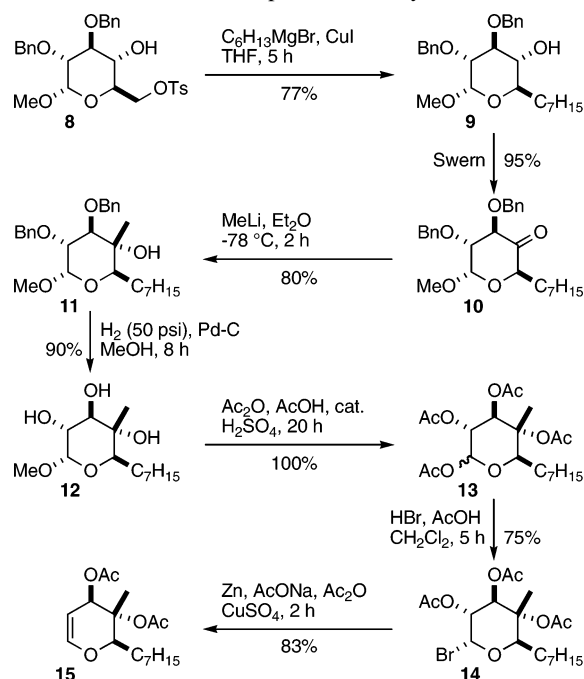
introducing the characteristic C(3a)–C(7a) double bond—at least into a simple model—we began a synthesis of benesudon itself. During that work, isolation of the marine fungal metabolite aigialone (**6**) was reported.⁵ The similarity of its structure, which was deduced by spectroscopic means and X-ray analysis, to that proposed for benesudon prompted a reconsideration⁵ of the original¹ NOE data. This led to the suggestion⁵ 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*-C₆H₁₃MgBr (Scheme 2). Swern oxidation then afforded ketone **10**, and reaction with MeLi gave mainly (24:1) the equatorial alcohol **11** (80%),^{7,8} The stereochemistry⁹ of this step (**10**→**11**) depends on the reagent and temperature; with MeMgI in Et₂O 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 acetoxyl 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 Et₃SiOSO₂CF₃. 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 PCC¹² 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 (Me₃Si)₂NK and 2-[*N,N*-bis(trifluoromethyl)sulfonylamino]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

(4) Kochi, J. K.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746–2754.

(5) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaree, 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.

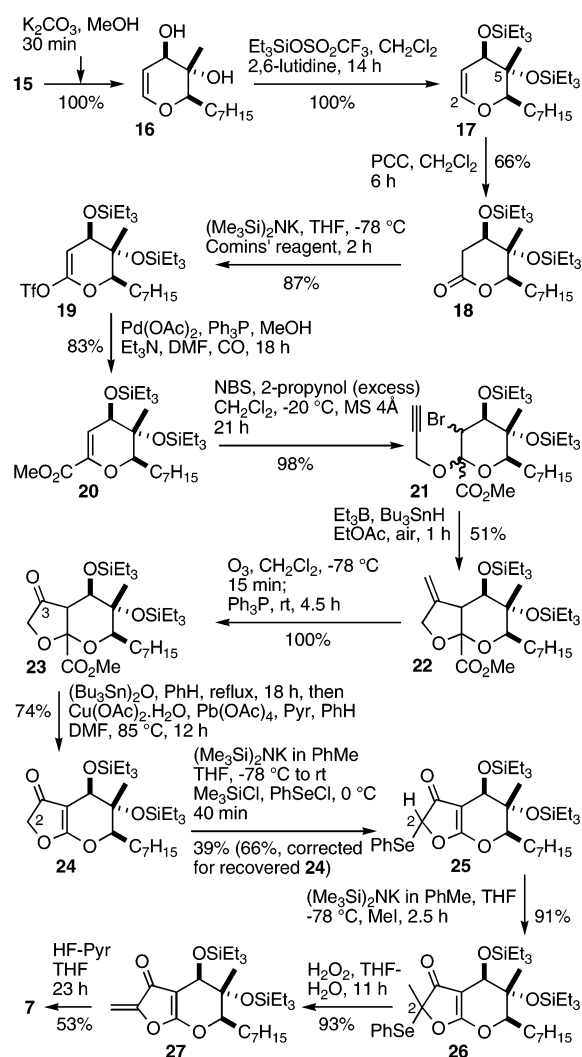
(10) In the sequence leading to **1**, the reaction with NBS in MeOH places a methoxy group at C(2) and a bromine at C(3); the anomeric methoxy group was then replaced by CN, using Me₃SiCN in the presence of BF₃·OEt₂. Base treatment (DBU) served to generate the C(2)–C(3) double bond and the C(2) CN was then hydrolyzed to CO₂H, which was esterified.

(11) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259–265.

(12) Rollin, P.; Sinay, P. *Carbohydr. Res.* **1981**, *98*, 139–142.

(13) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

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 method¹⁵ 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

$(\text{Bu}_3\text{Sn})_2\text{O}$. Accordingly, this reagent¹⁶ 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 bond¹⁷ (**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 published¹ values. Fortunately, the original material¹ 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 $[\alpha]_{\text{D}} = -120.5$ ($c = 0.1$, CHCl_3), while **7** has $[\alpha]_{\text{D}} = +124.2$ ($c = 0.11$, CHCl_3); accordingly, the absolute configuration of benesudon is *4S,5R,6S*, 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.

Acknowledgment. We thank Crompton Co. and NSERC for financial support, and Dr. H. Yang for assistance. We are extremely grateful to Professors O. Sterner (Lund University, Sweden) and H. Anke (University of Kaiserslautern, Germany) for their sample of natural benesudon.

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>.

OL702509A

(14) McKay, C.; Simpson, T. J.; Willis, C. L.; Forrest, A. K.; O'Hanlon, P. J. *Chem. Commun.* **2000**, 1109–1110.

(15) Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440–5442.

(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.