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Synthesis of the Core Structure of the Fungal Metabolite Benesudon: Use of Oxidative Decarboxylation

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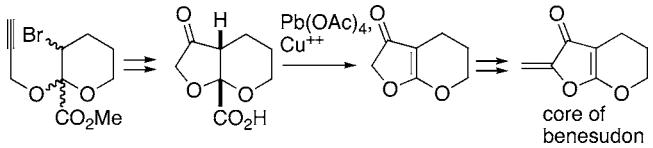
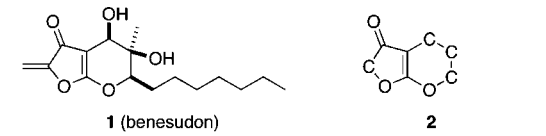
ABSTRACT



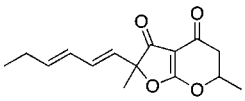
The core structure (5) of the fungal metabolite benesudon (1) was synthesized, the key step being oxidative decarboxylation of acid 17.

Benesudon (**1**)[1] is a fungal metabolite with a wide range of biological properties covering antifungal, antibacterial, cytotoxic, phytotoxic, and nematicidal activity. The compound represents a very rare structural type, and a literature search based on substructure **2**[2] retrieved only **3** (cyclogregatin)[3] and **4** (aigialone),[4] besides benesudon.



1 (benesudon)

2



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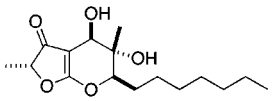
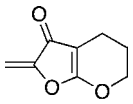


4

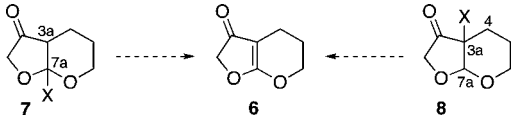
No synthetic work has been reported on any of these substances. Apart from its rarity, the core structure **5** of benesudon is very densely functionalized in that several subunits (α-methylene carbonyl, ketene acetal, vinylogous ester, enol ether) are incorporated within its compact framework. The corresponding cores of **3** and **4** share all these features, except for the exocyclic double bond. We describe here the first synthesis of **5**, which we have prepared as a preliminary study for the synthesis of benesudon.



5

Our plan was to attach the exocyclic methylene unit last, so the immediate objective became the ketene acetal **6**, which we felt might be reached from **7** or **8** by a proper choice of X (Scheme 1). To restrict double bond formation to C(3a)−C(7a) (see Scheme 1), the route via **8** would probably require that, in the intended synthesis of benesudon, the group X

Scheme 1



7 **6** **8**

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

(2) A search of the Beilstein database located only **1**, but use of SciFinder Scholar retrieved **1**, **3**, and **4**.

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

(4) Vongvilai, P.; Isaka, M.; Kittakoop, P.; Srikitikulchai, P.; Kongsaeree, P.; Thebtaranonth, Y. *J. Nat. Prod.* **2004**, *67*, 457−460.

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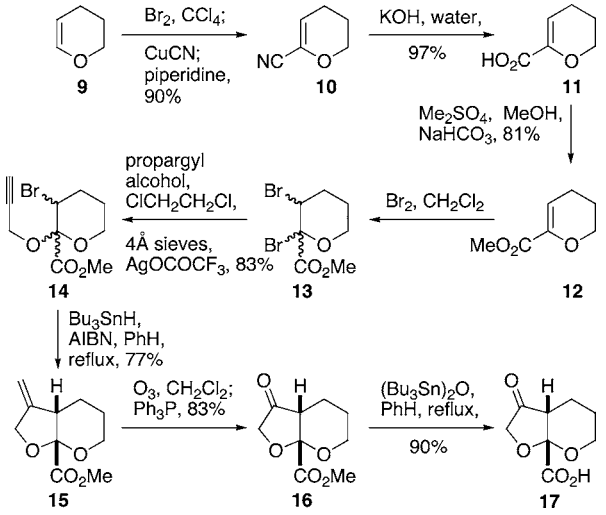
should have a particular stereochemistry (which would depend on the nature of X) relative to both the single hydrogen that would be present at C(4) and to the hydrogen at C(7a). On the other hand, a route via **7** might have less demanding stereochemical requirements because the stereochemical relationship between X and only a single hydrogen—that at C(3a)—might be important. In the event, this was the route we used in the present work, with X = CO_2H.

The acid corresponding to **7** (X = CO_2H) was made, as summarized in Scheme 2. Dihydropyran (**9**) was converted

Scheme 2

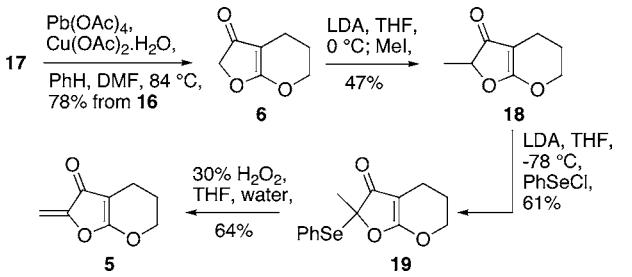


efficiently into the unsaturated nitrile **10**[5] by bromination, displacement by cyanide, and elimination of HBr, following a published[5] procedure. Base hydrolysis then gave the corresponding acid **11**[5] (97%), which was esterified (**11** → **12**,[6] Me_2SO_4, $NaHCO_3$, 81%).

Bromination of ester **12**, followed by addition of the resulting dibromides **13**[7] to a mixture of propargyl alcohol, 4 Å molecular sieves, and $AgOCOCF_3$, led efficiently (83% overall) to the two isomeric bromides **14**. Although these could be separated, it was more convenient to process them as a mixture. Radical cyclization occurred smoothly in the presence of Bu_3SnH, under standard conditions,[8] to afford the desired bicyclic skeleton **15** (77%). Then, ozonolysis with reductive workup (Ph_3P) liberated keto ester **16** (83%), from which the desired acid **17** was obtained (90%) by the action of $(Bu_3Sn)_2O$[9] in refluxing PhH for a controlled time (5 h). This acid is not particularly stable and should be used promptly—preferably within an hour of isolation. Attempts to generate the acid by classical hydrolysis (LiOH, MeOH–water) were unsuccessful.

With the acid in hand, we first considered the possibility of Barton decarboxylation and trapping of the intermediate radical with a chalcogenide,[10] the intention being to place a PhSe, PhS, or 2-pyridylthio group at the ring junction (see **7**, X = SePh, SPh, C_5H_4NS), so that oxidation to the corresponding selenoxide or sulfoxide would lead to the desired alkene. To our surprise, trial experiments directed along these lines were unpromising, and so we turned our attention to the process of oxidative decarboxylation, which can be effected by the action of $Pb(OAc)_4$ in the presence of a cuprous salt.[11] When we first treated acid **17** with $Pb(OAc)_4$ and $Cu(OAc)_2 \cdot H_2O$ in the presence of pyridine, closely following a published general procedure,[11a] the result was again disappointing, but a very small amount of the desired alkene **6** was indeed produced. From this point, we were able to modify the reaction conditions so as to afford **6** in acceptable yield (78% from ester **16**) (Scheme 3). In

Scheme 3



our optimized procedure, $Cu(OAc)_2 \cdot H_2O$ is added to a solution of freshly prepared acid **17** in dry PhH, followed, after 5 min, by $Pb(OAc)_4$, which is added in portions, in the

(5) Hoffmann, H. M. R.; Giesel, K.; Lies, R.; Ismail, Z. M. *Synthesis* **1986**, 548–551.

(6) Faivre, V.; Lila, C.; Saroli, A.; Doutheau, A. *Tetrahedron* **1989**, *45*, 7765–7782.

(7) The bromination product was not characterized; we assume it is a mixture of cis and trans dibromides.

(8) A solution of Bu_3SnH (0.3 M) in PhH, containing a catalytic amount of AIBN, was added over 10 h to a stirred and heated (85 °C) solution of **14** (0.05 M) in PhH. Heating was continued for 2 h after the end of the addition.

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

(10) (a) Replacement of carboxyl by PhSe or PhS: Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Heterocycles* **1987**, *25*, 449–462. (b) Replacement of carboxyl by thiopyridyl unit: Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3942.

(11) (a) Bacha, J. D.; Kochi, J. K. *Tetrahedron* **1968**, *24*, 2215–2226. (b) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279–421. (c) Kochi, A. J.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746–2754.

(12) $Cu(OAc)_2 \cdot H_2O$ (56 mg, 0.28 mmol) was added to a stirred solution of the crude acid **17** [from ester **16** (96 mg, 0.48 mmol)] in dry PhH (2.5 mL) (N_2 atm), and stirring was continued for 5 min. The flask was then wrapped in aluminum foil, and $Pb(OAc)_4$ (118 mg, 0.27 mmol) was tipped in. Stirring was continued for 30 min, and another portion of $Pb(OAc)_4$ (55 mg, 0.13 mmol) was added, followed by PhH (1.5 mL). Stirring was again continued for 30 min, and again a further portion of $Pb(OAc)_4$ (88 mg, 0.20 mmol) was added, followed by PhH (1 mL) and dry DMF (0.4 mL). The flask was fitted with a reflux condenser and flushed well with N_2 for 30 min (in some experiments, the apparatus was evacuated with the house vacuum and then filled with N_2, and the process was repeated twice more). The mixture was refluxed for 11 h (oil bath at 84 °C). The aluminum foil was removed, and refluxing was continued for 1 h. The resulting green solution was cooled to room temperature, evaporated to a small volume, and applied directly to a flash chromatography column. Flash chromatography over silica gel (1.5 × 26 cm), using 1:1 EtOAc–hexane, and then pure EtOAc, gave **6** (52 mg, 78% over two steps) as a white solid.

dark, and with a short (30 min) period of stirring between each addition. Finally, a small amount of DMF[11b,c] is added, the mixture thoroughly purged with N_2, and refluxed for 11 h. Under these conditions (described more fully in ref 12), the oxidative decarboxylation reliably generates alkene **6** on a 100 mg scale, and it was then a comparatively simple matter to attach the exocyclic methylene group.

Deprotonation of **6** (LDA, THF, −78 °C) and alkylation with MeI gave the expected product **18**, although the yield was poor (47%) because of loss through extensive dimethylation (ca. 42% yield). From that point, phenylselenation (LDA, THF, −78 °C, PhSeCl) led to selenide **19**, and finally, oxidation (H_2O_2) gave the core of benesudon (**19** → **5**). The compound is a white, sharp-melting (63−64 °C) solid.[13] It is not especially sensitive and could, for example, be chromatographed over silica gel without any noticeable hydrolytic damage; it appeared to be more robust than the parent acid **17**, which must be processed very promptly.

(13) Compound **5** had: FTIR (CH_2Cl_2, cast) 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.97−2.02 (m, 2H), 2.37 (t, J = 6.3 Hz, 2H), 4.53 (t, J = 5.8 Hz, 2H), 5.12 (d, J = 2.8 Hz, 1H), 5.53 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 9 (t), 21.5 (t), 72.0 (t), 90.4 (s), 95.8 (t), 152.8 (s), 178.4 (s), 180.7 (s); exact mass m/z calcd for $C_8H_8O_3$ 152.04735, found 152.04742.

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Supporting Information Available: Preparation of **17**; characterization data for **14**, **15**, **16**, **17**, **6**, **18**, **19**; ^{13}C NMR spectra of **5**, **6**, **14** (less polar isomer), **14** (more polar isomer), and **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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