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A FORMAL SYNTHESIS OF BRUCEANTIN

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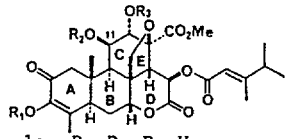
Summary: A 15-deoxybruceolide derivative (**3**) whose total synthesis had been achieved previously was converted into bruceantin (**1**).

Bruceantin (**1**)[1] and its related quassinoids[2] have attracted much attention as synthetic targets[3] because of their significant in vivo activity against P388 leukemia[4] and highly oxygenated complex carbon frameworks. However none of them has been synthesized. In this paper, we would like to report the conversion of 15-deoxybruceolide derivative **3** derived from naturally occurring brusatol (**2**) into bruceantin (**1**). The compound **3** has been synthesized in racemic form by the authors,[5] therefore, the first total synthesis of bruceantin (**1**) has now been formally achieved.

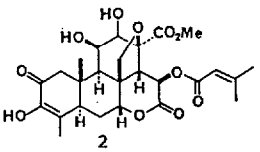
Conversion of **3** into **1** requires (i) oxygenation at C-15[6] and (ii) selective esterification of the resulting alcohol. Direct oxygenation at C-15 by enolate oxidation methods, which were successfully applied for similar compounds in the literatures,[6] gave no product or a complex mixture. Therefore, we examined indirect multistep methods similar to those which were developed by us for preparation of 15-hydroxyquassin from quassin.[7]

Reduction of the lactone **3** with 1 equiv of $NaBH_4$ in EtOH-CH_2Cl_2 (2:1) at 0 °C for 5 h gave hemiacetal (**4**)[8] as a mixture of diastereomers at C-16 (ca. 2:3 by ^{1}H-NMR) in 87% yield, which were treated with $POCl_3$ in pyridine at 100 °C for 4 h to give vinyl ether (**5**) in 67% yield. Although in the case of anhydroneoquassin osmium tetraoxide oxidized the double bond of the ring D with high selectivity,[7] in the case of **5** the reagent reacted with the double bond of the ring A primarily and the desired 15-hydroxyhemiacetal (**6**) was not obtained. Therefore, introduction of an oxygen function into C-15 via 15,16-epoxide was investigated as an alternative method. Treatment of **5** with MCPBA in CH_2Cl_2 at room temperature afforded unexpected m-chlorobenzoylated hemiacetal (**7**) in 85% yield. This result suggested the corresponding epoxide was extremely unstable and reactive toward nucleophile. On epoxidation with MCPBA in two-phase system (1:1 CH_2Cl_2-aq.$NaHCO_3$), **5** yielded **6**[9] in 61% yield along with a small amount of **7**. The hemiacetal **6** was oxidized with excess silver(I) oxide in refluxing acetonitrile to give a bruceolide derivative (**8**) in 65% yield. The configuration of the hydroxyl group at C-15 of **8** was shown to be β by the coupling constant (12.5 Hz) between C-14 and C-15 protons.

On alkaline hydrolysis **8** afforded monoacetate (**9**) under mild reaction



1: $R_1=R_2=R_3=H$
10: R_1=TBS, $R_2=R_3$=Ac
11: $R_1=R_3=H$, R_2=Ac



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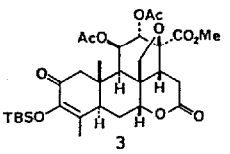
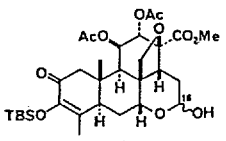


3



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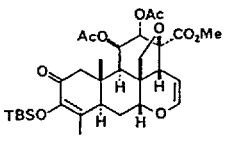
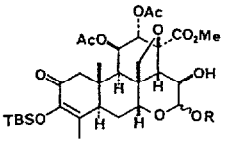
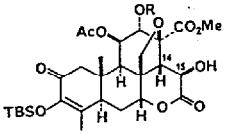


5



6: R=H
7: R=*m*ClC$_6$H$_4$CO



8: R=Ac
9: R=H

conditions and was decomposed under forcing conditions. As hydrolysis of the acetyl group at C-11 was found to be possible under acidic conditions, **8** was esterified with (E)-3,4-dimethyl-2-pentenoic acid[7] (1.5 equiv of acid, 1.5 equiv of DCC, 2 equiv of DMAP in CH_2Cl_2 at room temperature, ca. 72% yield) to yield **10**, which was subsequently hydrolyzed with 3N H_2SO_4-MeOH (1:1, reflux, 29 h) to give rise to bruceantin (**1**) (15%) along with 11-O-acetylbruceantin (**11**) (47%). The synthetic bruceantin (**1**) was identified with an authentic sample chromatographically and spectroscopically.

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References and Notes

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7) Murae, T.; Takahashi, T., Bull. Chem. Soc. Jpn., 54, 941 (1981).
8) The spectroscopic properties (270 MHz ^{1}H NMR, IR and MS) of all new compounds were fully consistent with the assigned structures.
9) A compound which seems to be 3,4-epoxide of **6** was obtained as an inseparable by-product, which coexisted until the acid hydrolysis of **10**.

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