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SYNTHESIS OF BRUCEANTIN SKELETON

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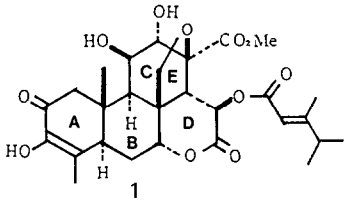
Abstract: A stereoselective synthesis of a compound (**3**), which satisfies all requirements for bruceantin skeleton and has preferable functional groups at suitable positions for the total synthesis of bruceantin, is described.

Among a large number of quassinoids,[1] several compounds bearing skeleton related to bruceantin (**1**) exhibit remarkable potent in vivo antineoplastic activity.[2] Therefore, after completion of synthesis of quassin (**2**)[3], many efforts[4] have been focussed on construction of a skeleton of bruceantin (**1**) and related quassinoids. However none of the works concerning construction of bruceantin skeleton has accomplished to synthesize a complete skeleton of bruceantin or its analogs. In this paper we would like to report the synthesis of a compound (**3**) which has a complete bruceantin skeleton and desirable functional groups at suitable positions for further synthesis toward bruceantin (**1**) and its analogs.



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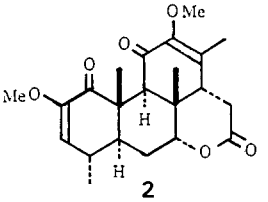

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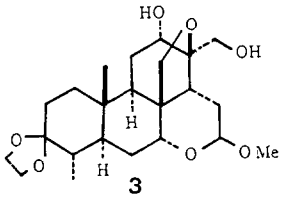

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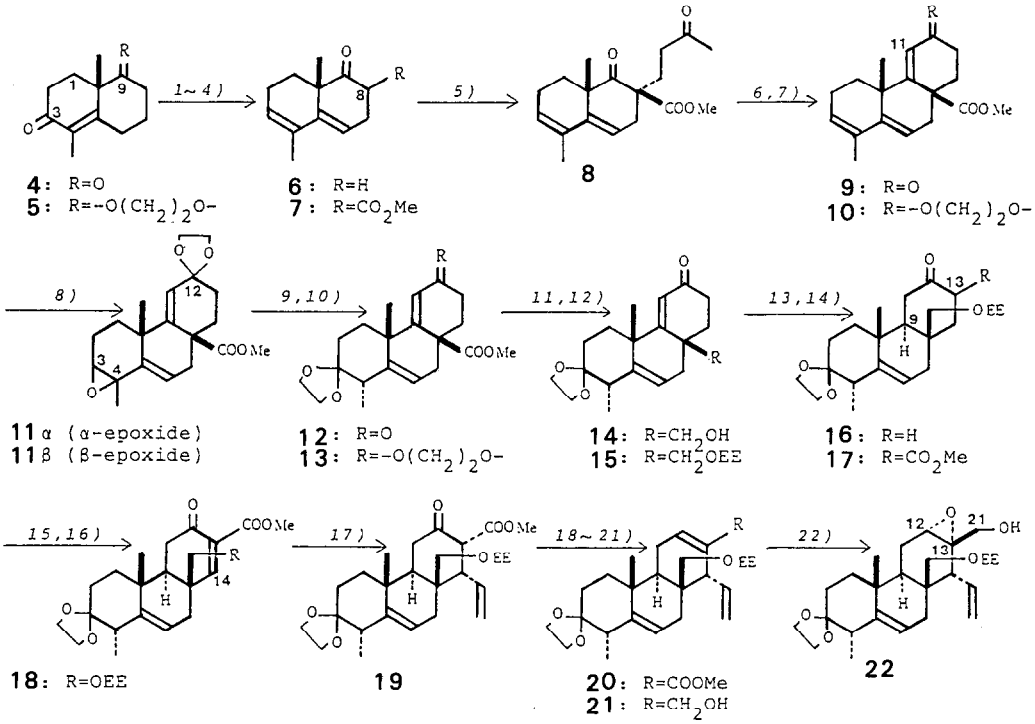
On reduction and successive treatment by acids, the acetal (**5**)[5] which was obtained by partial acetalization of dione (**4**)[6] yielded the diene (**6**) in a quantitative yield. The Michael addition product (**8**) was obtained in a quantitative yield by carbomethoxylation of **6** and following treatment of the product (**7**) with methyl vinyl ketone.

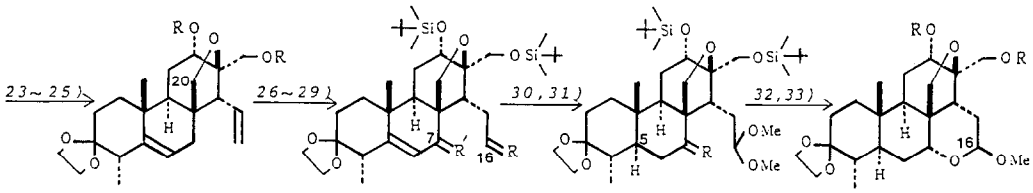
Although difficulty of cyclization of compounds which have a structure closely similar to **8** has been reported,[7] **8** gave a tricyclic compound (**9**) in 80% yield by treatment with 1.2 eqiv. of metatoluic acid and 0.2 eqiv. of pyrrolidine in refluxing benzene passing through a column of molecular sieves 4A. Epoxidation of the acetal (**10**) derived from **9** gave a 6:1 mixture of α- and β-epoxides (**11**-α and -β), which was treated with $BF_3 \cdot Et_2O$ in benzene without separation to yield an acetal exchanged product (**12**) in 64% yield from **9**. The



1) $(CH_2OH)_2$-TsOH/PhH, reflux 2) $NaBH_4$/MeOH 3)HCl-AcOH/MeOH, reflux 4) $(MeO)_2CO$-NaH-KH/DME, reflux 5) MVK-NaOMe/MeOH 6) 1.2eq.mMeC6H4COOH-0.2eq.pyrrolidine/PhH, molecular seaves 4A, reflux 7) $(CH_2OH)_2$-TsOH/PhH, reflux 8) mCPBA/CH_2Cl_2, -20 °C, 20 m 9) $BF_3 \cdot Et_2O$/PhH 10) $(CH_2OH)_2$-TsOH/PhH, reflux 11) LAH/THF; PPTS/Me_2CO 12) CH_2=CHOEt-PPTS/CH_2Cl_2 13) NaHTe/EtOH, reflux, 17h 14) $(MeO)_2CO$-NaH-KH/DME, reflux 15)NaH-PhSeCl/THF, 0°C 16) H_2O_2/CH_2Cl_2, 0°C 17) CH_2=CHMgBr-CuI(nBu_3P)/THF, -45°C~-20°C, 4h 18) $NaBH_4$/EtOH 19) MsCl-Et_3N/CH_2Cl_2 20) DBU/PhH, reflux 21) DIBAH/PhMe 22) tBuOOH-$Ti(OiPr)_4/CH_2Cl_2$, -20°C, 3.5h

alchohol (**14**) was given by successive reduction of the diacetal (**13**)[8] and partial hydrolysis of the product. α-Ethoxyethyl ether (**15**) derived from **14** gave the saturated ketone (**16**) on heating with NaHTe[9] in refluxing ethanol in a quantitative yield. The ester (**17**) was obtained as a sole product in 90% yield on carbomethoxylation[10] of **16**. On phenylselenenylation and successive oxidative elimination,[11] **17** afforded **18** (R=OEE) in 68% yield.

Difficulty for introduction of alkyl group by usual methods at 14-C[12] of a compound (**18**: R=H) closely related to our compound **18** (R=OEE) has been suggested.[13] However the compound **18** (R=OEE) easily afforded a conjugated addition product (**19**) on treatment with vinylmagnesium bromide in the presence of catalytic amount of CuI(nBu_3P)[14] in 80% yield. On reduction with $NaBH_4$, mesylation, and treatment with DBU, **19** gave conjugated ester (**20**) in 75% yield. Epoxidation with t-BuOOH and $Ti(OiPr)_4$[15] was carried out on the alchohol (**21**: derived by reduction of **20** with DIBAH) giving the epoxide (**22**) regio-



23) PPTS/EtOH 24) $tBu(Me)_2SiCl$-imidazole/DMF, 2h 25) $tBu(Me)_2SiCl$-KH/THF-DMF, 1h 26) (i) $(Me)_2CHC(Me)_2CBH_2$/THF (ii) H_2O_2-NaOH 27) CrO_3:Pyr/CH_2Cl_2,1h 28) $HC(OMe)_3$-PPTS/CH_2Cl_2, 48h 29) CrO_3:DMP/CH_2Cl_2, -20°C, 4h 30) Li-NH_3-tBuOH/THF, -78°C, 20m, -33°C, 20m 31) $LiBH(Et)_3$/THF, -78°C~r.t., 16h 32) PPTS/MeOH, 1h 33) Bu_4NF/THF

and stereoselectively. The epoxide (**22**) yielded the diol (**23**), which has A, B, C, and E rings of bruceantin skeleton, by treatment with pyridinium p-toluenesulfonate (PPTS). The yield of **23** from **20** was almost quantitative.

On treatment with $tBu(Me)_2SiCl$ and imidazole in DMF, only primary hydroxyl group of the diol (**23**) reacted to give monosilyl derivative (**24**) in 82% yield. As migration of the silyl group in **24** to the hydroxyl group at 12-C[12] on treatment with KH in a mixed solvent of THF and DMF was observed, **24** was treated with $tBu(Me)_2SiCl$ and KH in the same mixed solvent and a disilyl derivative (**25**) was obtained in 96% yield. Oxidation of the alchohol (**26**: obtained by hydroboration of **25** with thexylborane) yielded the aldehyde (**27**), whose aldehyde group was protected as dimethylacetal (**28**). The yield of **28** from **25** was 77%. The allylic position (C-7)[12] of **28** was oxidized with complex of chromic anhydride and 3,5-dimethylpyrazole[16] yielding an α,β-unsaturated ketone (**29**) in 68% yield. The saturated ketone (**30**), which was obtained by Birch reduction of **29** in 70% yield, was reduced with super-hydride[17] to give the α-alchohol (**31**) in 90% yield. On treatment with PPTS in methanol **31** afforded the protected hemiacetal (**32**: inseparable 1:1 mixture of stereoisomers at 16-C[12]), whose silyl protecting group was removed by treatment with nBu_4NF giving the diol (**3**: hardly separable 1:1 mixture of stereoisomers at 16-C) in a quantitative yield.

The structure of **3** including stereochemistry was confirmed by decoupling (Table 1) and NOE (Fig. 1) experiments using a 270 MHz ^{1}H-NMR for one of the stereoisomers of the diol (**3**) (colorless needles, mp 213~6 °C, M^+ 424.2446; calcd. for $C_{23}H_{36}O_7$ 424.2462, IR(KBr) 3420 cm^{-1}). Further syntheses toward bruceantin (**1**) and its analogs utilizing **3** are under way.

Table 1. Chemical shifts (in $CDCl_3$) and coupling constants of the protons of **3**; a) determined by differential NOE, b) could not be determined because of overlapping with other signals.

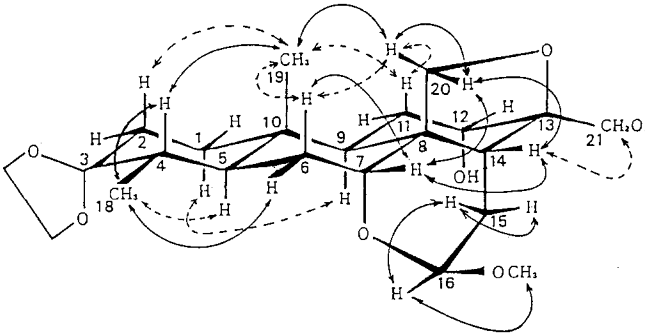
Protons(δ:PPM)

1C-αH(~1.3)[a)]	1C-βH[b)]	2C-αH[b)]	2C-βH(~1.6)[a)]	4C-H(1.72)	5C-H(1.92)
6C-αH(~1.7)[a)]	6C-βH(1.20)	7C-H(3.73)	9C-H(2.06)	11C-αH(~1.6)[a)]	11C-βH(1.85)
12C-H(4.00)	14C-H(2.02)	15C-αH(2.43)	15C-βH(1.71)	16C-H(4.80)	18C-H_3(0.82)
19C-H_3(0.93)	20C-αH(3.31)	20C-βH(4.23)	21C-H_2(3.77)	Ethylenedioxy-H_4(3.93)	

J(protons)=Coupling constant(Hz)

J(4-5)=12	J(4-18)=6	J(5-6α)=3	J(5-6β)=12	J(6α-6β)=14	J(6α-7)=2	J(6β-7)=2
J(9-11α)=4	J(9-11β)=14	J(11α-11β)=14	J(11α-12)=~0	J(11β-12)=4	J(14-15α)=14	J(14-15β)=4
J(15α-15β)=14	J(15α-16)=3	J(15β-16)=~0	J(20α-20β)=8			

Fig. 1. Results of differential NOE spectra for **3** in $CDCl_3$.
⟵⟶ : Strong NOE was observed.
⟵ - - - ⟶ : Weak but clear NOE was observed.



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5) The spectral data (NMR, IR, MS) for all derivatives were satisfied with their structures.
6) The dione (**4**) was obtained by heating 2-methylcyclohexan-1,3-dione with 1-chloro-3-pentanone and catalytic amount of p-TsOH in dioxane under reflux using Dean-Stark water separator packed with molecular sieves 3A.
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