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Synthetic Approach to the Quassinoid Klaineanone—The Synthesis of a Potential Intermediate by Intramolecular Cycloaddition[1]

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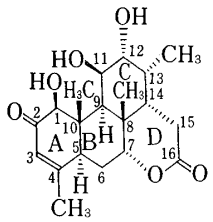
Thermolysis of 4-acetoxymethylene-2-[2-benzyloxy-2-(5-methoxy-3-methylbenzocyclobuten-1-yl]ethyl-2-methylcyclopentan-1,3-dione 1-ethylene ketal (**21**) gave the stachane-type tetracyclic compound (**24**), whose deketalization afforded **26**, a potential synthetic intermediate to the quassinoid klaineanone (**1**).

Keywords——thermolysis of benzocyclobutene derivative; intramolecular cycloaddition; synthetic approach to quassinoid; stereoselective synthesis of stachane-type compound; klaineanone

The bitter principles of *Simarubaceae* species, *e.g.* klaineanone (**1**),[3] are now known as "quassinoids",[4] and constitute a larger part of terpenoid chemistry. This group is of interest from three different points of view. Firstly, with regard to biological activity, this type of terpene can show anticancer activity as exemplified by bruceantin (**2**), isolated by Kupchan.[5] From the biogenetic point of view, quassinoids belong to the triterpenoid group of isoprenoids,[6] although they have only twenty carbons in the basic skeleton. Lastly, from the viewpoint of organic chemistry, the group is of interest because of its complicated stereostructure and high level of oxygenation.



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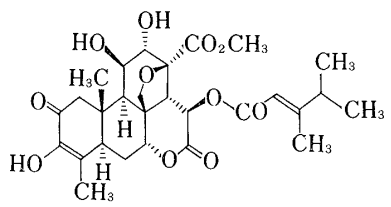

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Chart 1

In spite of the fact that quassinoids are of interest in several respects, as mentioned above, there are few reports on synthetic studies.[7] We began synthetic studies towards this type of terpene by using intramolecular cycloaddition reaction of *o*-quinodimethane derivatives, as developed in our laboratory,[8] and here wish to describe the synthesis of a potential intermediate to klaineanone (**1**).

1) This constitutes part 9 of "Synthetic Studies on Diterpenoid," by T. Kametani. Part 8, T. Kametani, T. Honda, and K. Fukumoto, *Heterocycles*, **14**, 419 (1980).
2) Location: *Aobayama, Sendai 980, Japan.*
3) J. Polonsky and N. Bourguinon-Zylber, *Bull. Soc. Chim. France*, **1965**, 2793.
4) J. Polonsky, *Fortschr. Chem. Org. Naturstoffe*, **30**, 101 (1973).
5) S.M. Kupchan, R.W. Britton, J.A. Lacadie, M.F. Ziegler, and C.W. Sigel, *J. Org. Chem.*, **40**, 648 (1975).
6) J. Moron and J. Polonsky, *Tetrahedron Lett.*, **1968**, 385; *idem*, *Eur. J. Biochem.*, **3**, 488 (1968).
7) J.R. Dias and R. Ramachandra, *J. Org. Chem.*, **42**, 1613 (1977).
8) T. Kametani and K. Fukumoto, *Heterocycles*, **8**, 465 (1977); *idem*, "Chemistry of Natural Products," Vol., 4, ed. by S. Ito, T. Goto, and S. Nozoe, Nankodo, Tokyo, 1980, p. 81.

Previously we reported the synthesis of hibaol (**6**) from the benzocyclobutene (**3**) through the tetracyclic compounds (**4**) and (**5**).[9] In this sequence, the formation of **4** by the thermolysis of benzocyclobutene (**3**) indicates that this type of reaction should provide a good method for constructing the ABC ring system of **1**. Namely, the stereochemistry at C_8, C_9, and C_{13} in **4** is the same as that in klaineanone (**1**),[10] so that a synthetic intermediate to **1** formed by an analogous reaction would be expected to have the requisite stereochemistry for conversion to the natural quassinoid. Moreover, the already accomplished conversion of **4** into hibaol (**6**) suggets that formation of the *trans* AB ring system and introduction of the C_{10}-methyl group are feasible in a synthesis of klaineanone (**1**).

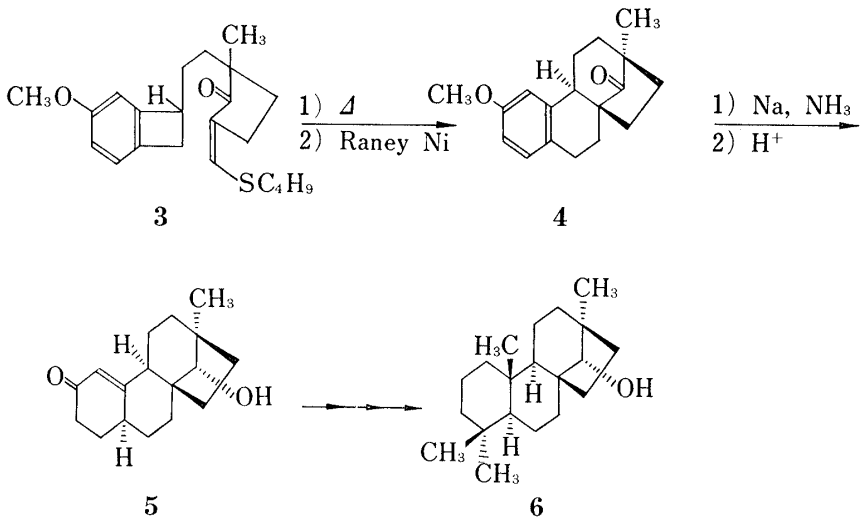


Chart 2

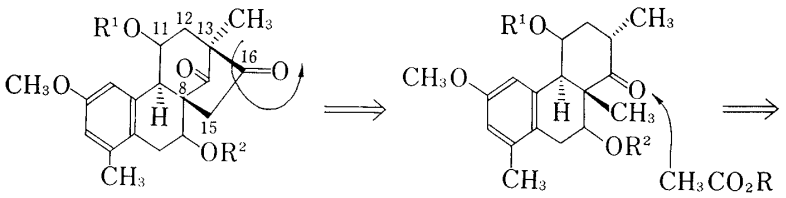
Thus, if the tetracyclic compound (**7**) can be obtained from an appropriate benzocyclobutene derivative, its transformation into klaineanone (**1**) can be envisaged as shown in Chart 3. Namely, removal of the C_{16}-carbonyl group of **7**, through an α-diketone monothioketal, by the method of Marshall[11] should give the tricyclic compound (**8**), which could be converted into the lactone (**9**) by the sequence of Wittig reaction, reduction and cyclization. Birch reduction of **9** should provide the enone (**10**). The presence of the C_2-carbonyl group in (**10**) should permit the introduction of a hydroxy group and a methyl group at the C_1 and C_{10} positions, respectively, and the hydroxy function already on C_{11} is expected to provide access to the ring C diol system of **1**.

On the basis of the above analysis we considered the tetracyclic compound (**26**) to be a potential synthetic intermediate to klaineanone (**1**), and we have investigated the synthesis of **26** by intramolecular cycloaddition[9] following thermolysis of the benzocyclobutene derivative (**21**).

The preparation of the requisite benzocyclobutene (**21**) was straightforward and was carried out along the convergent route illustrated in Chart 4.

1-Cyano-5-methoxy-3-methylbenzocyclobutene (**11**)[12] was condensed with 2-formylmethyl-2-methylcyclopentane-1,3-dione diethylene ketal (**12**)[13] in the presence of sodium

9) T. Kametani, K. Suzuki, H. Nemoto, and K. Fukumoto, *J. Org. Chem.*, **44**, 1036 (1979).
10) The numbering system used for tetracyclic compounds in this paper is based on that of stachane.
11) J.A. Marshall and D.E. Seitz, *J. Org. Chem.*, **39**, 1814 (1974).
12) T. Kametani, Y. Kato, T. Honda, and K. Fukumoto, *J.C.S. Perkin I*, **1975**, 2001.
13) T. Kametani, H. Nemoto, M. Tsubuki, G.E. Purvaneckas, M. Aizawa, and M. Nishiuchi, *J. C. S. Perkin I*, **1979**, 2830.



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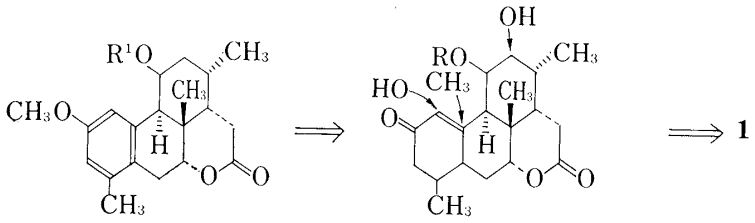

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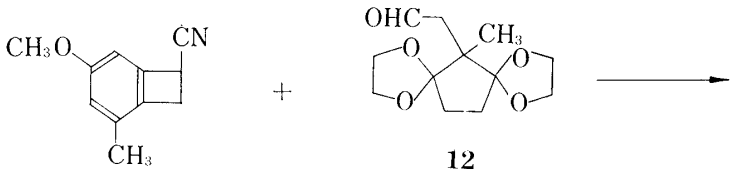
Chart 3



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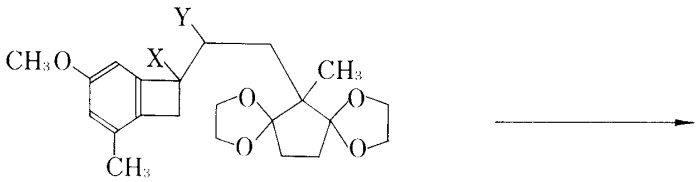
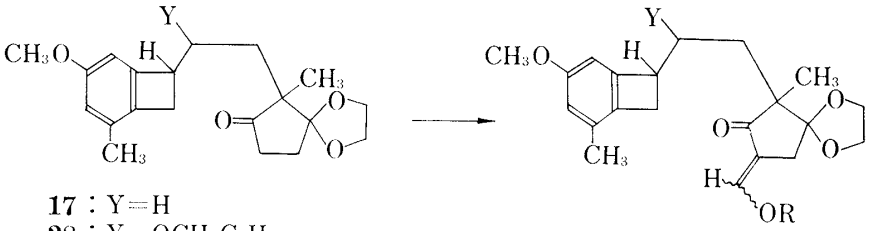


13 : X=CN, Y=OH
14 : X=H, Y=OH
15 : X=Y=H
16 : X=H, Y=$OCH_2C_6H_5$



17 : Y=H
28 : Y=$OCH_2C_6H_5$

18 : R=Y=H
19 : R=$COCH_3$, Y=H
20 : R=H, Y=$OCH_2C_6H_5$
21 : R=$COCH_3$, Y=$OCH_2C_6H_5$

Chart 4

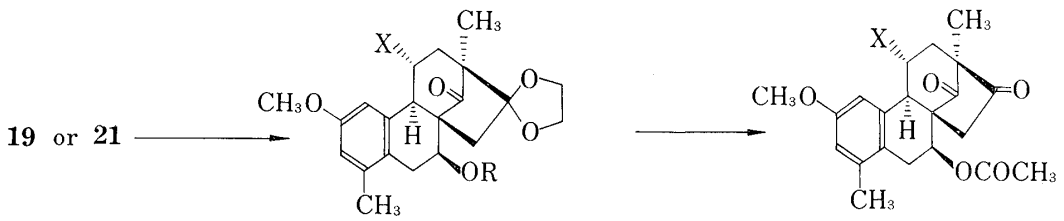
amide in liquid ammonia at −78°, affording in 66% yield the β-cyanohydrin (**13**) [mp 188°; *m/e* 416 ($M^+ +1$)] as a single diastereoisomer showing hydroxy and cyano group absorptions at 3440 and 2225 cm^{-1}, respectively, in the infrared (IR) spectrum. The stereochemistry of this product (**13**) could not however, be determined at this stage. In order to remove the unnecessary cyano group, the β-cyanohydrin (**13**) was treated with sodium in liquid ammonia at −78°.[9,14] This process, however, resulted in the formation of a mixture of the expected alcohol **14**) [*m/e* 390 (M^+); $\nu_{max}^{CHCl_3}$ 3475 cm^{-1}] in 60% yield and the undesired dehydroxylated product (**15**) [*m/e* 374 (M^+)] in 22% yield, which was separated by chromatography on alumina. An attempt to achieve exclusive formation of the decyanated alcohol (**14**) through the sodium salt of the β-cyanohydrin (**13**) gave approximately the same result.[15] We first used this dehydroxylated by-product (**15**) in a model study, *i.e.* to investigate the preparation and thermolysis of the benzocyclobutene (**19**). As there is no example in the literature of the cycloaddition of an *o*-quinodimethane with an acetoxymethylene residue acting as a dienophile,[16] a reaction we envisaged as being the key step in our planned synthesis, it was considered prudent to carry out such a model reaction.

Treatment of compound (**15**) with 10% hydrochloric acid in tetrahydrofuran at room temperature gave, in 87% yield, the cyclopentane-1,3-dione 1-monoethylene ketal (**17**) [$\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; δ ($CDCl_3$) 3.93 ppm (4H, singlet, $-OCH_2CH_2O-$)] as a result of selective hydrolysis of one of the ketal groups. Reaction of **17** with ethyl formate in the presence of sodium hydride in dry benzene afforded the 4-hydroxymethylene derivative (**18**) [δ ($CDCl_3$) 9.80 (1H, singlet, $=CH\cdot O-$)], which without purification was treated with acetic anhydride in dry benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid to produce, in 78% yield, the vinyl acetate (**19**) [*m/e* 400 (M^+)]. Absorption bands at 1725 and 1770 cm^{-1} in the IR spectrum of this derivative indicated the presence of two types of carbonyl group, and the acetoxymethylene moiety was seen in the nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) as resonances at δ 2.18 (3H, singlet, $COCH_3$) and 8.26 (1H, distorted triplet, $J=2$ Hz, $-CH=$).

Having thus obtained the desired functionalized benzocyclobutene (**19**), the key step of thermolysis and intramolecualr cycloaddition was then carried out as follows. Heating the benzocyclobutene (**19**) in *o*-dichlorobenzene at 180° for 15 hr under a nitrogen stream gave the new compound (**22**) [mp 212°; *m/e* 400 (M^+)] in 43% yield, which showed acetoxy group absorption at 1730 cm^{-1} and five-membered ketone absorption at 1750 cm^{-1} in its IR spectrum. That this product has the desired tetracyclic structure was indicated by the absence of olefinic proton resonance (occurring at δ 8.26 in **19**) in its NMR spectrum. Moreover, the observation of C_{13}-methyl group resonance at the normal position of δ 0.98 in $CDCl_3$ suggested this group to be in a *cis* relationship with the C_9-hydrogen,[9] and the appearance of the C_7-hydrogen as a double doublet ($J=7$ and 12 Hz) at δ 5.50 suggested that this C_7-hydrogen was also on the same side at the C_9-hydrogen. Stereoisomers of **22** could not be found in this reaction product. This result can be explained by assuming that the olefin moiety in **19** adopted the (*E*)-configuration as depicted in Chart 4. Hydrolysis of the tetracyclic compound (**22**) was carried out by treatment with 10% sodium hydroxide at 50° to give in 97% yield the alcohol (**23**) [mp 192°; *m/e* 358 (M^+); $\nu_{max}^{CHCl_3}$ 3650 and 1750 cm^{-1}; δ ($CDCl_3$) 4.50 (1H, double doublet, $J=6$ and 12 Hz, $>C\underline{H}OH$)], a compound which is a potential synthetic intermediate to gibbane-type diterpenes. Treatment of **22** with boron trifluoride etherate in methylene chloride at room temperature afforded the diketone monoacetate (**25**) [mp 151°; $\nu_{max}^{CHCl_3}$ 1780, 1745 and 1735 cm^{-1}] in 95% yield.

Since this model experiment showed that we could obtain the expected tetracyclic compounds by intramolecular cycloaddition in which an acetoxymethylene group functions as

14) T. Kametani, M. Kajiwara, T. Takahashi, and K. Fukumoto, *J. C. S. Perkin I*, **1975**, 737.
15) T. Kametani, M. Aizawa, and H. Nemoto, *J. C. S. Perkin I*, in press.
16) W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); *idem*, *Synthesis*, **1978**, 793.



22 : R=$COCH_3$, X=H
23 : R=X=H
24 : R=$COCH_3$, X=$OCH_2C_6H_5$

25 : X=H
26 : X=$OCH_2C_6H_5$

Chart 5

the dieneophile, we directed our attention to intramolecular cycloaddition of the derivative (**21**), with the aim of preparing the potential klaineanone synthetic intermediate (**26**).

Protection of the hydroxyl group in the decyanated alcohol (**14**) was achieved by its conversion to the benzyl ether (**16**) [*m/e* 480 (M^+); δ ($CDCl_3$) 4.51 and 4.83 (each 1H, d, J=11 Hz, $PhC\underline{H}_2O$), in tetrahydrofuran. In the manner already described for the preparation of **19**, this benzyl ether was hydrolyzed using 10% hydrochloric acid to produce the monoketone (**28**) [*m/e* 436 (M^+); $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}] in 86% yield, which was converted to the enol acetate (**21**) in 64% yield [$\nu_{max}^{CHCl_3}$ 1775 cm^{-1}; δ ($CDCl_3$) 8.20 (1H, distorted triplet, J=2 Hz, CH_2-$COOC\underline{H}$=)] by treatment with ethyl formate in the presence of sodium hydride and acetylation of the resulting hydroxymethylene derivative (**20**) using acetic anhydride. The site-selective

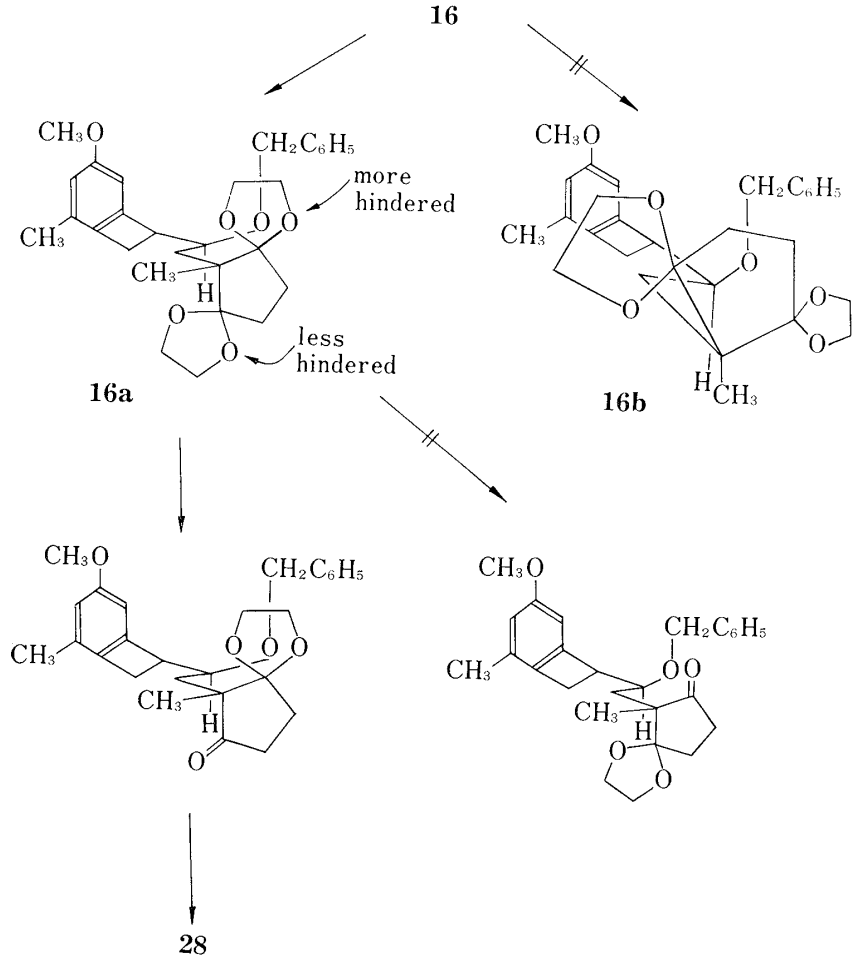
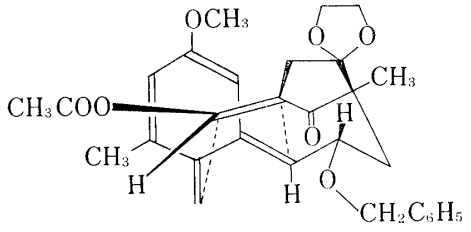


Chart 6

hydrolysis of the diketal (**16**) to the monoketone (**28**) can be explained by assuming the reaction sequence summarized in Chart 6. Of the two possible conformers (**16a** and **16b**), the latter is the unstable one because of severe steric repulsion between the cyclopentane and benzocyclobutene moieties. On the other hand, the conformer (**16a**) has no such severe steric interactions and the reaction, therefore, proceeded along this route to form **28** by the hydrolysis of the less hindered ketal group.

Thermolysis of the benzocyclobutene (**21**) was carried out by heating it in *o*-dichlorobenzene at 190° for 15 hr to provide stereoselectively, in 41% yield, the tetracylic compound (**24**) [mp 197°; $\nu_{max}^{CHCl_3}$ 1750 and 1730 cm^{-1}]; no stereoisomer was observed at this stage. The tetracyclic structure and stereochemistry of this derivative were easily determined from the NMR spectrum, which showed C_{13}-methyl group singlet resonance at δ 1.00 and C_7-hydrogen double doublet (J=7 and 9 Hz) resonance at δ 5.60, but lacked olefinic and cyclobutenyl proton resonances. Moreover, that the benzyloxy group on C_{11} was on the same side as the C_9-hydrogen was suggested by the observation of O-methyl group resonance at abnormally high field (δ 3.53). This abnormal value is assumed to be due to the shielding effect of the benzyloxy group ring-current, which can only occur when this group is on the α-side as depicted in formula **24**. This stereoselective formation of **24** can reasonably be explained by assuming that the intermediate *o*-quinodimethane adopts the most favorable conformation (**27**), as proposed in a previous paper.[9]



27

Chart 7

Finally, the tetracyclic compound (**24**) was treated with 10% hydrochloric acid in tetrahydrofuran at 80° to give, in 53% yield, the diketone (**26**) [mp 168°; $\nu_{max}^{CHCl_3}$ 1770 and 1730 cm^{-1}; *m/e* 462 (M^+)] which ia a potential synthetic intermediate to klaineanone (**1**).

Thus we have achieved the synthesis of tetracyclic compounds with the necessary level of oxygenation for conversion to quassinoids, and we are currently investigating the transformation of such compounds into klaineanone (**1**) and gibbane-type diterpenes.

Experimental

All melting points were measured with a Yanagimoto micro melting point apparatus (MP-22) and are uncorrected. IR spectra were recorded on a Hitachi 125 grating spectrophotometer and NMR spectra on a JEOL JUN PMX-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were taken on a Hitachi M-52 spectrometer.

2-[2-(1-Cyano-5-methoxy-3-methyl)benzocyclobuten-1-yl]-2-hydroxyethyl-2-methylcyclopentane-1,3-dione Diethylene Ketal (13)——2-Formylmethyl-2-methylcyclopentane-1,3-dione diethylene ketal (**14**)[13] (1.4 g) in dry THF (2 ml) was added in a single portion to a stirred solution of 1-cyano-5-methoxy-3-methylbenzocyclobutene (**11**)[12] (1 g) and $NaNH_2$ [prepared from Na (200 mg)] in liquid NH_3 (50 ml) at −78°, and the mixture was stirred for 2 hr at −78°. After addition of excess solid NH_4Cl, the solvent was evaporated off to give a grey residue which was treated with 10% aqueous NH_4Cl solution. The resulting mixture was extracted with $CHCl_3$ and the extract washed with water, dried over Na_2SO_4 and concentrated to afford the β-cyanohydrin (**13**) (1.58 g, 66%) as colorless needles, mp 188°, after recrystallization from benzene. *Anal.* Calcd for $C_{23}H_{29}NO_6$: C, 66.49; H, 7.04; N, 3.37. Found: C, 66.38; H, 7.03; N, 3.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3440 (OH), 2225 (CN). NMR ($CDCl_3$) δ: 1.13 (3H, singlet, >C–CH_3), 2.00 (4H, singlet, >C–CH_2CH_2–C<), 2.17 (3H, singlet, ArCH_3), 3.85 (3H, singlet, OCH_3), 4.00 (8H, broad singlet, 2×OCH_2CH_2O), 6.53—6.87 (2H, broad singlet, ArH), MS *m/e*: 416 (M^++1).

Reductive Decyanation of 13——Sodium (232 mg) was added to a stirred solution of the β-cyanohydrin (**13**) (1.4 g) in dry THF (20 ml) and liquid NH_3 (40 ml) at −78° under a current of N_2 and the mixture was stirred for 50 min at −78°. After addition of excess solid NH_4Cl followed by removal of NH_3 by evaporation, the residue was diluted with 10% aqueous NH_4Cl solution and extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Removal of the solvent afforded a

yellow oil which was subjected to alumina column chromatography using hexane–ethyl acetate (v/v 4: 1) as an eluant. The first fraction gave the dehydroxylated compound (**15**) (280 mg, 22.2%) as a colorless oil. NMR ($CDCl_3$) δ: 1.15 (3H, singlet, >C–CH_3), 2.00 (4H, singlet, >C–CH_2CH_2–C<), 2.22 (3H, singlet, $ArCH_3$), 3.80 (3H, singlet, OCH_3), 4.00 (8H, broad singlet, $2\times OCH_2CH_2O$), 6.40—7.00 (2H, ArH). MS *m/e*: 374 (M^+).

The second fraction afforded the alcohol (**14**) (792 mg, 60%) as a colorless oil. *Anal.* Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.36; H, 7.80. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (OH). NMR ($CDCl_3$) δ: 1.15 (3H, singlet, >C–CH_3), 2.00 (4H, singlet, >C–CH_2CH_2–C<), 2.22 (3H, singlet, $ArCH_3$), 3.80 (3H, singlet, OCH_3), 4.00 (8H, broad singlet, $2\times OCH_2CH_2O$), 6.40—7.00 (2H, ArH). MS *m/e*: 390 (M^+).

4-Acetoxymethylene-2-(5-methoxy-3-methylbenzocyclobuten-1-yl)ethyl-2-methylcyclopentane-1,3-dione 1-Ethylene Ketal (19)——A mixture of the dehydroxylated compound (**15**) (2.85 g), 10% HCl (10 ml) and THF (50 ml) was stirred for 2 hr at room temperature, and then basified with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with benzene and the extract washed with water, dried over Na_2SO_4 and concentrated to give the monoketone (**17**) (2.18 g, 86.7%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (C=O). NMR ($CDCl_3$) δ: 1.03 (3H, singlet, >C–CH_3), 2.20 (3H, singlet, $ArCH_3$), 3.76 (3H, singlet, OCH_3), 3.93 (4H, singlet, OCH_2CH_2O), 6.57 (2H, broad singlet, ArH).

NaH (559 mg, 50% oil dispersion) was added to a stirred solution of the monoketone (**17**) (2.18 g) and ethyl formate (1.73 g) in dry benzene at room temperature, and the mixture stirred for 0.5 hr under N_2. After addition of water to the reaction mixture, the aqueous layer was acidified with 10% H_2SO_4 and extracted with ether. This extract was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. Removal of the solvent afforded the crude hydroxymethylene derivative (**18**) (2.03 g) as an oil which was used for the next reaction without further purification. NMR ($CDCl_3$) δ: 9.80 (1H, singlet, =C<u>H</u>–O).

A solution of the crude compound (**18**) (2.03 g), acetic anhydride (10 ml) and a catalytic amount of *p*-toluenesulfonic acid in dry benzene (10 ml) was stirred at room temperature for 3 hr under a stream of N_2. The solution was then washed with saturated aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated *in vacuo* to give the vinyl acetate (**19**) (1.81 g, 77.7%) as a pale yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (CO), 1725 (CO), 1660 (C=C–O). NMR ($CDCl_3$) δ: 1.90 (3H, singlet, >C–CH_3), 2.18 (3H, singlet, $COCH_3$), 2.23 (3H, singlet, $ArCH_3$), 3.79 (3H, singlet, OCH_3), 4.03 (4H, singlet, OCH_2CH_2O), 6.60 (2H, broad singlet, ArH), 8.26 (1H, distorted triplet, J=2 Hz, –CH=). MS *m/e*: 400 (M^+).

Thermolysis of 19——A solution of the vinyl acetate (**19**) (1.80 g) in dry *o*-dichlorobenzene (90 ml) was heated with stirring under a stream of N_2 for 15 hr at 180°. After removal of the solvent *in vacuo*, the residue was recrystallized from ethanol to afford the tetracyclic compound (**22**) (774 mg, 43%) as colorless needles, mp 212°. *Anal.* Calcd for $C_{23}H_{28}O_6$: C, 69.98; H, 7.05. Found: C, 69.92; H, 7.05. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (C=O), 1730 (C=O). NMR ($CDCl_3$) δ: 0.98 (3H, singlet, >C–CH_3), 2.05 (3H, singlet, $COCH_3$), 2.18 (3H, singlet, $ArCH_3$), 3.75 (3H, singlet, OCH_3), 3.97 (4H, singlet, OCH_2CH_2O), 5.50 (1H, double doublet, J=7 and 12 Hz, C<u>H</u>OCOCH$_3$), 6.63 (2H, broad singlet, ArH). MS *m/e*: 400 (M^+).

Hydrolysis of the Tetracyclic Compound (22)——A mixture of the tetracyclic compound (**22**) (451 mg), 10% aqueous NaOH solution (13 ml) and THF (25 ml) was heated with stirring at 50° for 6 hr. After cooling to room temperature, the mixture was neutralized with 10% HCl and the THF was removed *in vacuo*. The residue was extracted with benzene and the extract washed with water, dried over Na_2SO_4 and concentrated to give the alcohol (**23**) (392 mg, 97.1%) as colorless needles, mp 192°, after recrystallization from EtOH. *Anal* Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.37; H, 7.32. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650 (OH), 1750 (C=O). NMR ($CDCl_3$) δ: 1.00 (3H, singlet, >C–CH_3), 2.25 (3H, singlet, $ArCH_3$), 3.80 (3H, singlet, OCH_3), 3.97 (4H, singlet, OCH_2CH_2O), 4.50 (1H, double doublet, J=6 and 12 Hz, >C<u>H</u>OH), 6.70 (2H, broad singlet, ArH). MS *m/e*: 358 (M^+).

Deketalization of the Tetracyclic Compound (22)——Three drops of boron trifluoride etherate were added to a solution of the tetracyclic compound (**22**) (73 mg) in dry CH_2Cl_2 (7 ml). After stirring at room temperature for 16 hr, the mixture was washed with saturated aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4, and concentrated to give the diketone (**25**) (62 mg, 95.4%) as colorless needles, mp 151°, from EtOH. *Anal.* Calcd for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79. Found: C, 70.68; H, 6.68. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (C=O), 1745 (C=O), 1735 (C=O). NMR ($CDCl_3$) δ: 1.19 (3H, singlet, >C–CH_3), 2.15 (3H, singlet, $COCH_3$), 2.27 (3H, singlet, $ArCH_3$), 3.82 (3H, singlet, OCH_3), 5.75 (1H, double doublet, J=7 and 11 Hz, >C<u>H</u>OCOCH$_3$), 6.68 (1H, broad singlet, ArH), 6.75 (1H, broad singlet, ArH). MS *m/e*: 356 (M^+).

2-[2-Benzyloxy-2-(5-methoxy-3-methyl)benzocyclobuten-1-yl]ethyl-2-methylcyclopentane-1,3-dione Diethylene Ketal (16)——Benzyl bromide (5.56 g) was added dropwise to a stirred mixture of the decyanated alcohol (**14**) (6.34 g), NaH (6.0 g, 50% oil dispersion) and dry THF (100 ml) at room temperature, and the mixture refluxed for 15 hr under a stream of N_2. After cooling to room temperature, the mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and concentrated to leave an oil which was chromatographed on silica gel using benzene as an eluent to give the benzyl ether (**16**) (6.1 g, 78.3%) as a colorless oil. NMR ($CDCl_3$) δ: 1.25 (3H, singlet, >C–CH_3), 1.93 (4H, singlet, >C–CH_2CH_2–C<), 2.20 (3H, singlet, $ArCH_3$), 3.78 (3H, singlet, OCH_3), 3.94 (8H, broad singlet, $2\times OCH_2CH_2O$), 4.51 and 4.83 (each 1H, doublet, J=11 Hz, OCH_2Ar), 6.63 (2H, broad singlet, ArH), 7.35 (5H, broad singlet, OCH_2C_6<u>H</u>$_5$). MS *m/e*: 480 (M^+).

4-Acetoxymethylene-2-[2-benzyloxy-2-(5-methoxy-3-methyl)benzocyclobutene-1-yl]ethyl-2-methylcyclopentan-1,3-dione 1-Ethylene Ketal (21)——10% HCl (20 ml) was added to a solution of the diketal (**16**) (6.0 g) in THF (100 ml) and the mixture was stirred at room temperature for 4 hr. After neutralization with saturated aqueous $NaHCO_3$ solution, the reaction mixture was extracted with benzene. The extract was washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to afford the monoketone (**28**) (4.67 g, 85.7%) as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$: 1740 (C=O). NMR ($CDCl_3$) δ: 1.08 (3H, singlet, $>C-CH_3$), 2.20 (3H, singlet, $ArCH_3$), 3.88 (3H, singlet, OCH_3), 4.00 (4H, singlet, OCH_2CH_2O), 4.40 and 4.70 (each 1H, doublet, $J=10$ Hz, $OC\underline{H}_2Ar$), 6.70 (2H, broad singlet, ArH), 7.43 (5H, broad singlet, $OCH_2C_6\underline{H}_5$. MS *m/e*: 436 (M^+).

A mixture of the monoketone (**28**) (1 g), ethyl formate 764 mg), NaH (248 mg, 50% oil dispersion) and dry benzene (10 ml) was stirred at room temperature for 0.5 hr under a stream of N_2. Acetic anhydride (3 ml) and dry benzene (20 ml) were added and the mixture was stirred at room temperature for 1 hr, then poured onto ice. The organic layer was separated and washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and concentrated to leave an oil which was subjected to column chromatography in silica gel using hexane–ethyl acetate (v/v 9: 1) as an eluent to give the enol acetate (**21**) (750 mg, 64.7%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (C=O), 1725 (C=O), 1660 (C=C). NMR ($CDCl_3$) δ: 1.17 (3H, singlet, $>C-CH_3$), 2.20 (6H, singlet, $ArCH_3$ and $OCOCH_3$), 3.78 (3H, singlet, OCH_3), 4.00 (4H, singlet, OCH_2CH_2O), 4.50 and 4.63 (each 1H, doublet, $J=9$ Hz, $OC\underline{H}_2Ar$), 6.68 (2H, broad singlet, ArH), 7.23 (5H, singlet, $OCH_2C_6\underline{H}_5$), 8.20 (1H, distorted triplet, $J=2$ Hz, $-C\underline{H}=$). MS *m/e*: 506 (M^+).

Thermolysis of the Benzocyclobutene (21)——A solution of the benzocyclobutene (**21**) (520 mg) in dry *o*-dichlorobenzene (25 ml) was heated at 190° for 15 hr under a stream of nitrogen and the solvent was then removed *in vacuo* to give the tetracyclic compound (**24**) (216 mg, 41%) as colorless prisms, mp 197°, after recrystallization from ether. *Anal.* Calcd for $C_{30}H_{34}O_7$: C, 71.13; H, 6.77. Found: C, 71.77; H, 6.70. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750 (C=O), 1730 (C=O). NMR ($CDCl_3$) δ: 1.00 (3H, singlet, $>C-CH_3$), 2.06 (3H, singlet, $COCH_3$), 2.19 (3H, singlet, $ArCH_3$), 3.53 (3H, singlet, OCH_3), 4.00 (4H, singlet, OCH_2CH_2O), 4.63 and 4.90 (each 1H, doublet, $J=12$ Hz, $OC\underline{H}_2Ar$), 5.60 (1H, double doublet, $J=7$ and 9 Hz, $>C\underline{H}-OCOCH_3$), 6.78 (1H, doublet, $J=2$ Hz, ArH), 7.47 (6H, broad singlet, ArH and $OCH_2C_6\underline{H}_5$). MS *m/e*: 446 ($M^+-CH_3CO_2H$).

Deketalisation of the Tetracyclic Compound (24)——A mixture of the tetracyclic compound (**24**) (100 mg), THF (3 ml) and 10% HCl (2 ml) was heated with stirring at 80° for 9 hr. After neutralization with solid $NaHCO_3$, the reaction mixture was extracted with ether, and the extract washed with saturated aqueous NaCl solution, dried over Na_2SO_4, and concentrated to give the diketone (**26**) (49 mg, 53%) as colorless needles, mp 168°, from MeOH. *Anal.* Calcd for $C_{28}H_{30}O_6$: C, 72.72; H, 6.54. Found: C, 72.68; H, 6.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (C=O), 1730 (C=O). NMR ($CDCl_3$) δ: 1.17 (3H, singlet, $>C-CH_3$), 2.05 (3H, singlet, $COCH_3$), 2.20 (3H, singlet, $ArCH_3$), 3.55 (3H, singlet, OCH_3), 4.58 and 4.82 (each 1H, doublet, $J=11$ Hz, $OC\underline{H}_2Ar$), 5.75 (1H, double doublet, $J=7$ and 10 Hz, $>C\underline{H}-OCOCH_3$), 6.77 (1H, doublet, $J=2$ Hz, ArH), 7.42 (6H, broad singlet, ArH and $OCH_2C_6\underline{H}_5$). MS *m/e*: 462 (M^+).

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