BROMINATION AND DEHYDROBROMINATION STUDIES ON SOME CIS-4a- METHYL-DECALINE -2,7- DIONES

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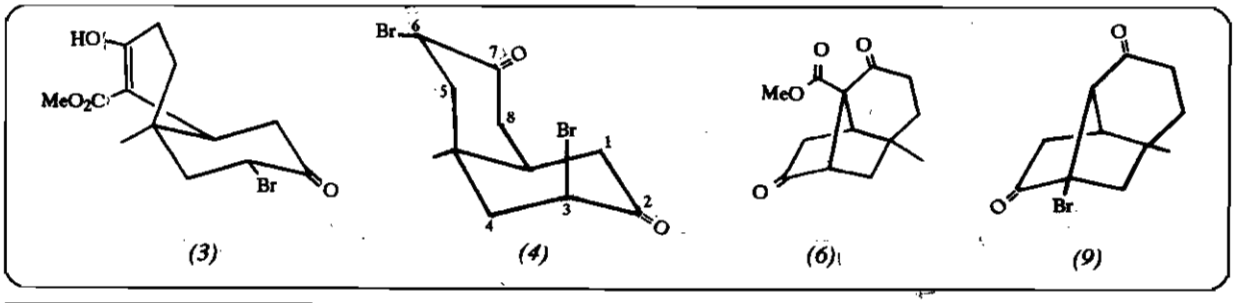
ABSTRACT : *Results of the bromination and dehydrobromination of several angular methylated decalindiones are described. The key reaction, base-induced cyclization of the monobromo keto ester(3),and the dibromo ketone(4), leads to the formation of tricyclic systems(6)and(9) respectively.*

KEY WORDS : *Cis-fused decalin, Favorskii, Intermediate, Dehydrohalogenation,Intramolecular Cyclization, X-ray Analysis.*

INTRODUCTION :

Several reactions of bromination and dehydrobromination of β- keto ester *(1)* and diketone *(2)*, which possess a cis- fused decalin skeleton, have been examined and were found to give contrasting results. The results of this investigation encouraged us to explore its generality toward the synthesis of sativene and related terpenes.



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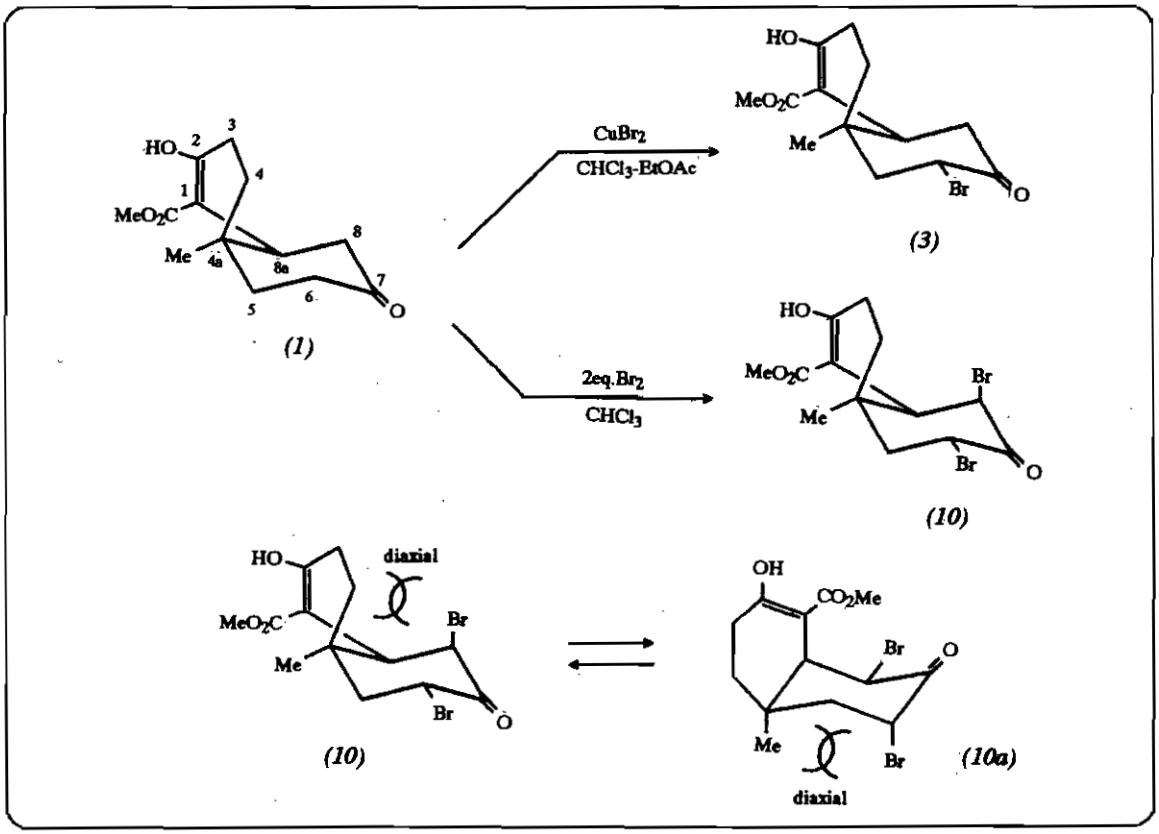
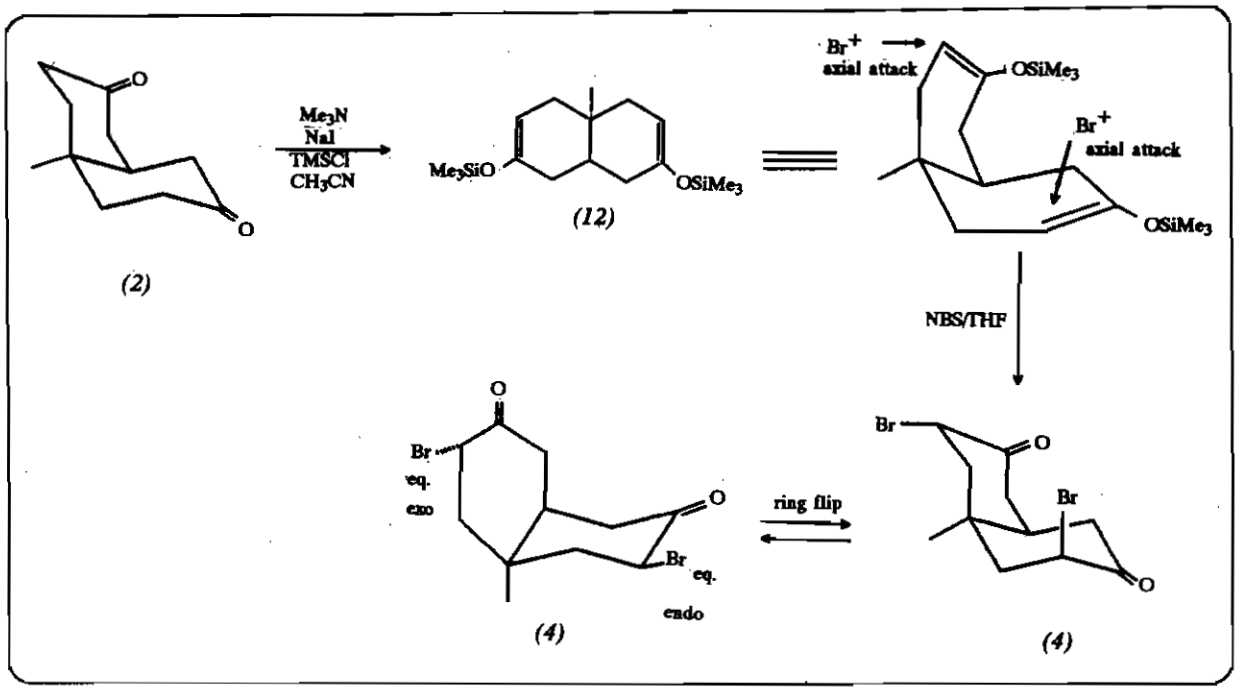
RESULTS AND DISCUSSIONS :

The keto- ester *(1)* was brominated exclusively at C_6 to produce *(3)* in 80% yield when 1 eq. of Copper (II) bromide was used as brominating agent. When 2 eq. of bromine were used instead of Copper(II) bromide, the second bromine was delivered at C_8 and gave *(10)* in 80% yield. It should be noted that compound *(10)* is in equilibrium with its conformer *(10a)*, both with a 1,3- diaxial interaction. That the initial bromination has occurred at C_6, instead of the C_8 position, was confirmed by both the IR and NMR spectra of *(3)* and *(10)*. The carbonyl absorption of ketone *(3)* was shifted ~ 18 cm^{-1} from that of the parent ketone, indicating an equatorial configuration for the bromine atom [1]. Also, in the NMR spectrum of 3, the coupling pattern for the deshielded proton at C_6 δ4.8: (J6(ax)-5(ax)= 13.58Hz,J6(ax)- 5(eq) = 5.83 Hz; JAX + JBX= 20Hz) is characteristic of the axial $\alpha-$ proton of an ABX- type system [2,3], confirming C_6 as the position of the bromine atom.

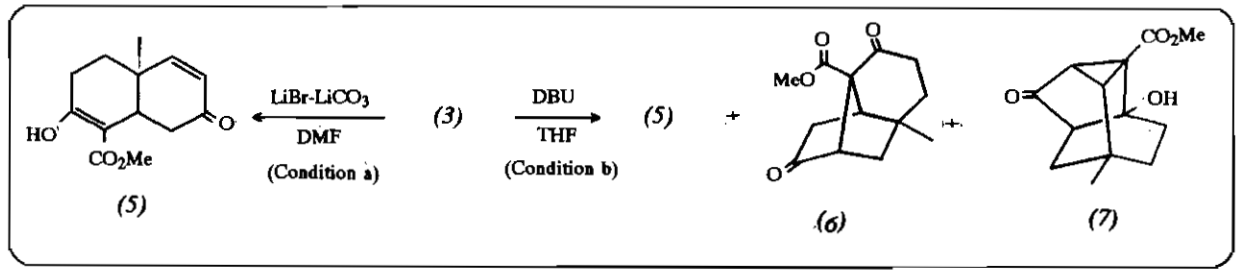
The location and the stereochemistry of the bromine atom at C_8 in compound *(10)* was furnished unambiguously by comparison of its proton NMR spectrum with that of compound *(3)*. In compound *(10)* the axial $\alpha-$ hydrogen at C_6 was moved downfield by 0.73 ppm to δ 5.53 compared to the same hydrogen in structure *(3)*. This downfield chemical shift difference shows that the other bromine atom in the molecule must be in the axial position. The amount of deshielding might be due to a 1,3 diaxial interaction between the axial hydrogen at C_6 and the axial bromine at C_8 [2,3]. Furthermore, a doublet at 4.7 ppm for the C_8 hydrogen atom in *(10)* confirmed the location of the bromine atom. Also the value of its coupling constant (J8(eq) - 8a(ax)- 5 Hz) with the ring junction at C_{8a} is consistent for an equatorial- axial coupling. Further evidence for the structural proof for*(3)* and *(10)* was provided by X-ray crystallographic data which confirmed the stereochemistry of the bromines in both compounds.

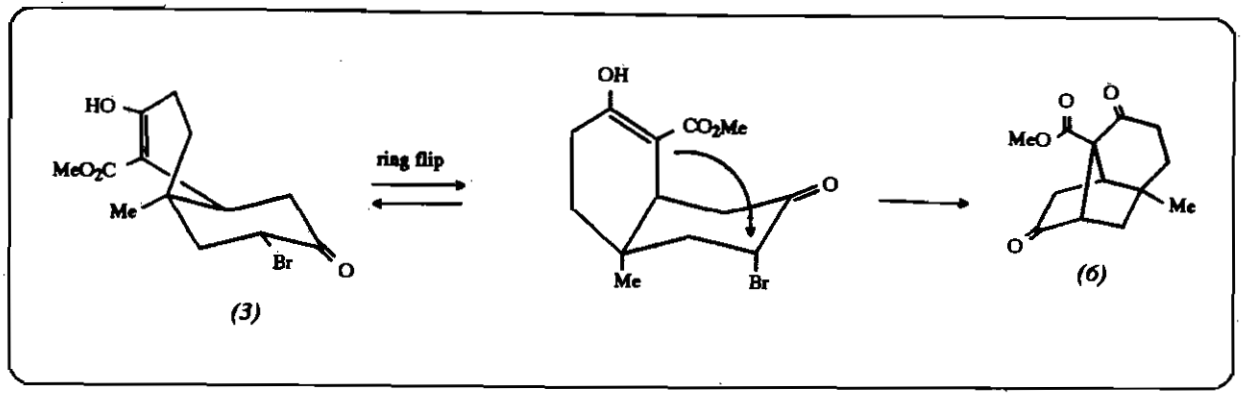




The dione *(2)* available from 4- methyl anisole [4,5] was silylated by the method of Doboudin [6,7] in quantitative yield. From the symmetry and the chemical shifts in the proton NMR spectrum of *(12)*, one finds this structure to be the only product of silylation. Compound *(12)* without purification, on treatment with NBS in THF, afforded the dibromo adduct *(4)* in 62% isolated yield. The stereochemistry of the bromines was assigned on the basis of the well-known propensity of cis- decalins to suffer attack from the convex side. The magnetically non-equivalent $\alpha-$ protons on C_3 and C_6 display two sets of doublets of doublets in the region near 4.9 ppm. The proton NMR coupling pattern of the bromine- substituted carbons (J3(ax) - 4(ax) and J6(ax) - 5(ax) = 13 Hz, J3(ax) - 4(eq) and J6(ax) - 5(eq)= 6.4 Hz; JAX + JBX = 20 Hz) is characteristic of the axial $\alpha-$ protons of an ABX- type system [2,3], thus confirming C_3 and C_6 as the location of the bromine atoms. It should be noted that direct bromination of *(1)* with Copper(II) bromide gives the same result but in lower yield.

Several polycyclic systems involving some complex mechanisms were obtained as a result of dehydrohalogenations of our bromodecalin derivatives. From the dehydrobromination of monobromo ketone *(3)* with DBU (condition b), three compounds were obtained: *(5)*, *(6)* and *(7)* in 18%, 40%, and 40% yields, respectively. These three compounds were separated chromatographically by use of a chromatotron, eluting with 20% ethyl acetate in hexane. Using Condition (a), enone *(5)* was the only product obtained.

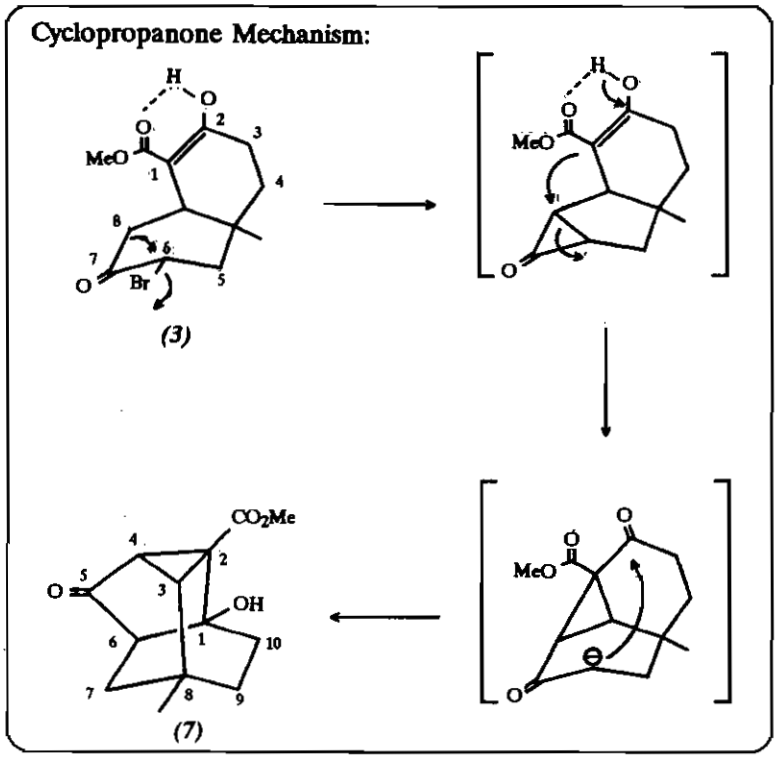


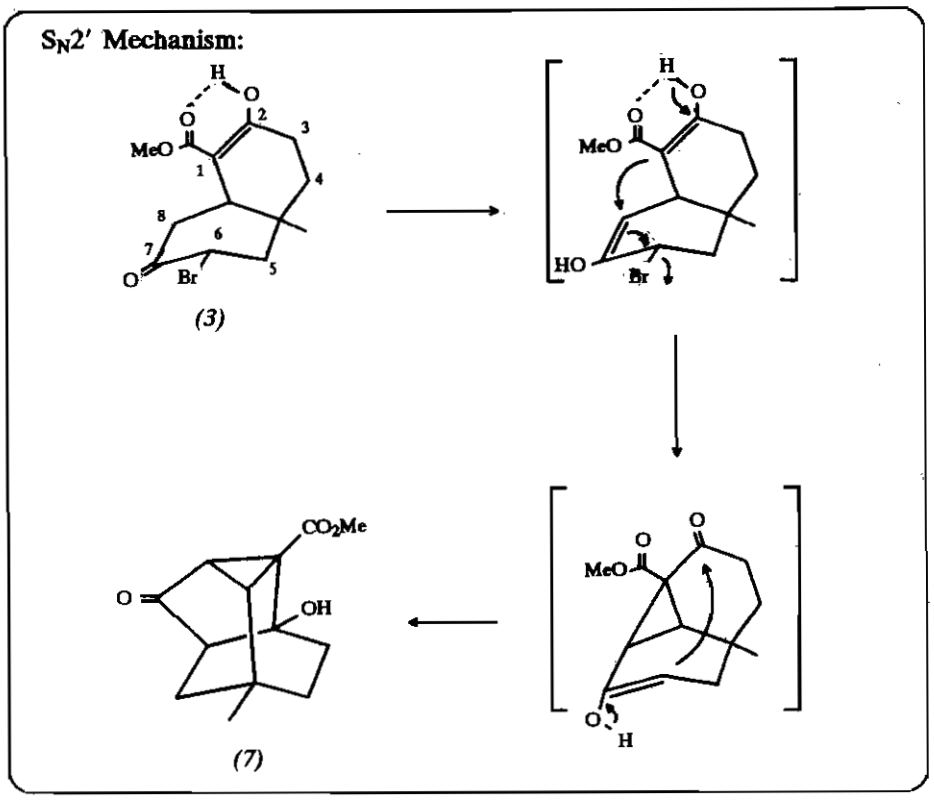


The tricyclic structure *(6)* formed via an intramolecular cyclization, shows that the orbital in leading to the product, is placed directly to the rear of the bromine- bearing carbon C_6 and is oriented at the line of departure of this group.

The third, tetracyclic compound *(7)* formed during this dehydrobromination reaction may involve a cyclopropanone intermediate. The reaction is initiated by a Favorskii- like intramolecular displacement [8] which carries out a nucleophilic substitution to form a cyclopropanone ring. Due to the large strain associated with a trigonal carbon in a three-membered ring of cyclopropanone, nucleophilic attack by the enolate ion becomes feasible in order to relieve this strain. The three membered ring then opens to give a carbanion that attacks the ketone across the ring to give a transient oxygen anion that is protonated by the solvent to produce *(7)*.

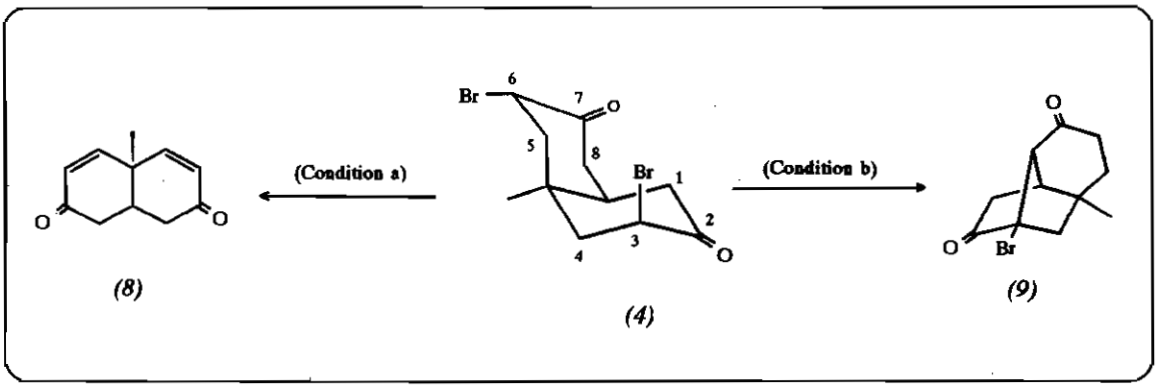
Formation of *(7)* may also involve an S_N2' mechanism. According to this view, in the presence of DBU, the initial step involves enolization between C_7 and C_8. Subsequent ejection of bromine is then feasible by an enolate attack at C_8 via an S_N2'- like mechanism as shown next page.

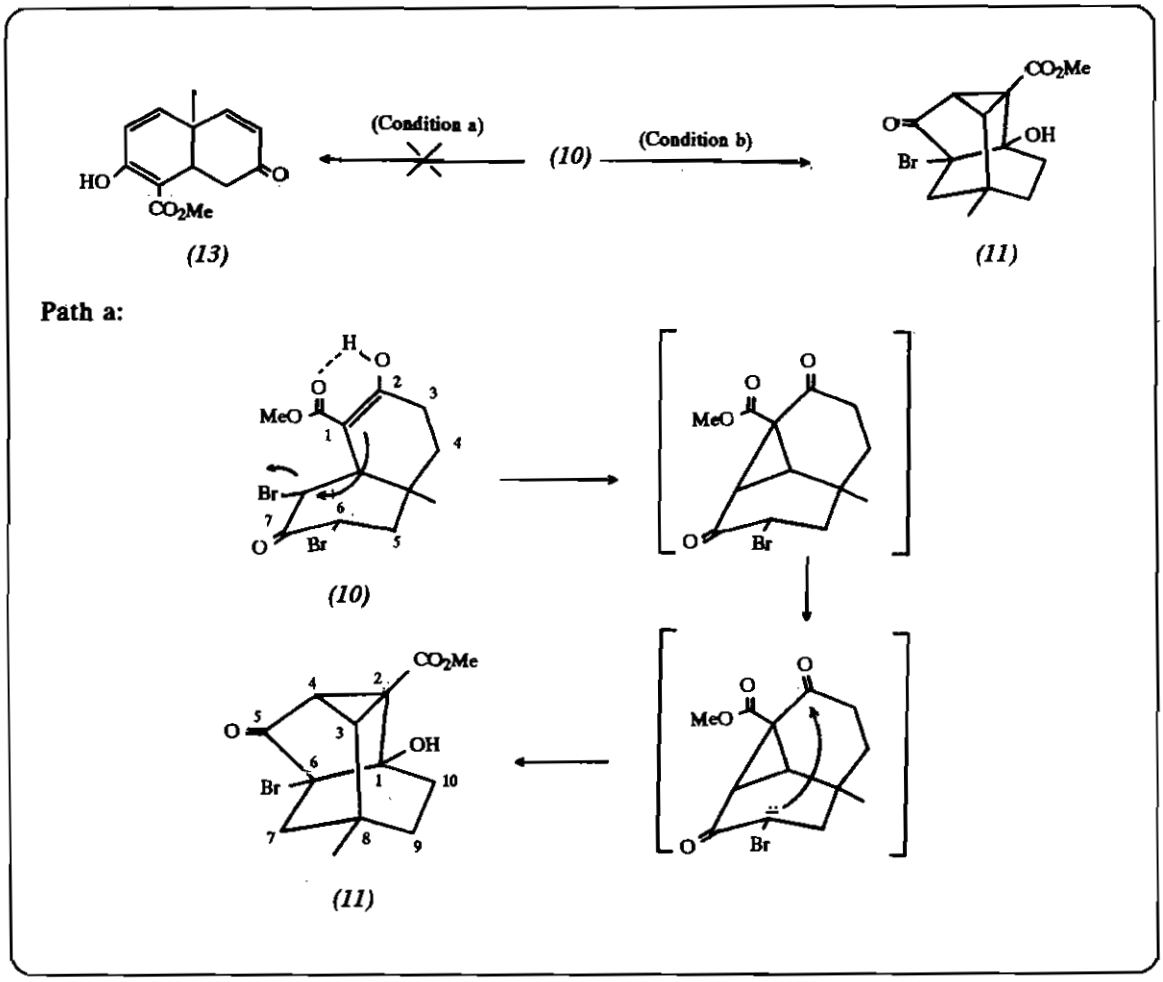




We then investigated the dehydrobromination of *(4)* under both dehalogenating conditions. Treatment of *(4)* under condition (a) affords dienedione *(8)* similar to that of compound *(3)*. A reasonable mechanistic path, involving either a cyclopropanone intermediate or S_N2', may be invoked for the formation of the tricyclic structure *(9)*, upon treatment with DBU.

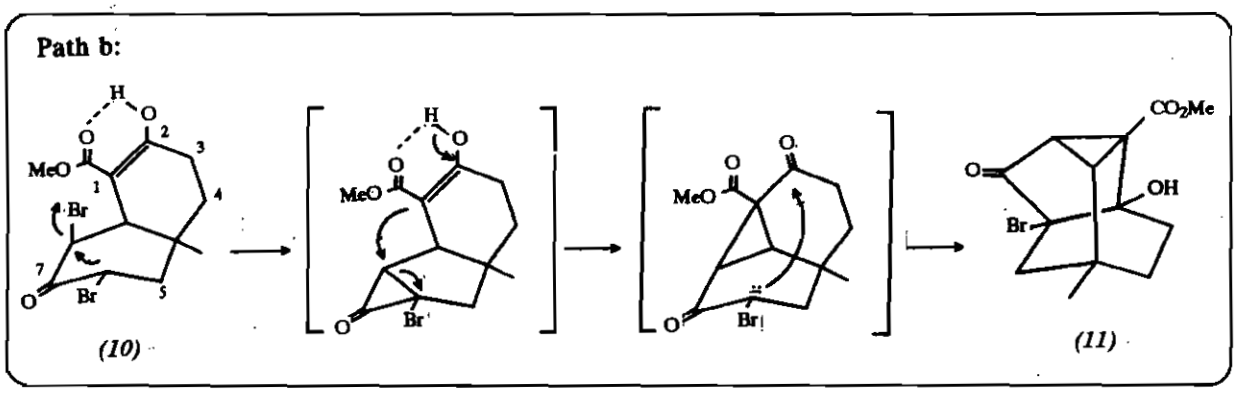
Treatment of compound *(10)* under both dehalogenating conditions did not lead to the expected dienone (13), but instead, an intramolecular dehydrohalogenation with the formation of *(11)* was observed. The transformation of *(10)* to *(11)* may involve: (a) Cyclopropanation by way of an enolate attack on C_8 forming a C_8-C_1 bond, (b) Removal of the $\alpha-$ hydrogen from C_6 bearing bromine followed by an intramolecular cyclization to *(11)* (Path a). Due to ring inversion however, it is not clear whether the location of bromine attached to C_8 at the time of the departure is axial or equatorial.

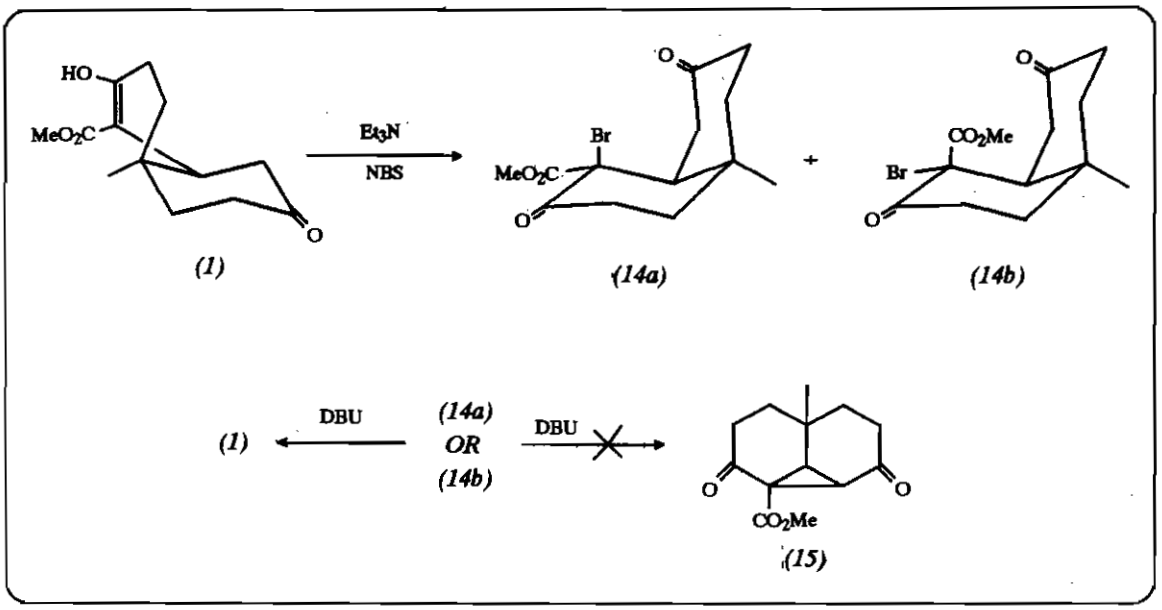




Alternatively, formation of *(11)* may be attributed to a mechanism that involves a cyclopropanone intermediate (Path b). According to this view, the initial step is the removal of a proton from the $\alpha-$ carbon atome (C_6) to give the haloketone enolate anion. Subsequent ejection of halide ion from C_8, leads to a bromocyclopropanone which is rapidly cleaved by the enolate anion from C_1 to produce a transient carbanion that attacks carbonyl C_2 across the ring to afford *(11)*.

We then examined an approach toward base





promoted bromination of compound *(1)* aimed at C_1 position. Bromination of the keto- ester *(1)* in dichloromethane in the presence of an *(1)* in dichloromethane in the presence of an excess of triethylamine with 1 mol-equivalent of NBS or bromine at 0°C gave a bromoester *(14)*, isomeric to monobromoester *(3)*. Compound *(14)* proved to be a mixture of two epimers *(14a)* and *(14b)*, which could be separated by column chromatography and subsequent recrystallization. The NMR spectra of both epimers no longer showed any enol hydrogen. An X-ray structure analysis established for the epimer *(14a)* the structure as cis-1(ax)Br-1(eq) carbomethoxy- 4a- methyl- decaline- 2,7- dione as shown above. All attempts to dehydrohalogenate *(14a)* or its epimer *(14b)* under a variety of conditions did not lead to the expected tricyclic diketo-ester *(15)* but instead resulted in reductive debromination with the formation of *(1)*.

CONCLUSIONS :

Dehydrohalogenation of compounds *(3)* and *(10)* under condition (a) gave different results. Compound *(3)* underwent dehydrohalogenation to the monoene *(5)* exclusively. Compound *(10)* under the same condition afforded the tetracyclic bromo ketone*(11)* and none of the dienone *(13)*. This result perhaps suggests that the acidity of the α- hydrogen on carbon bearing bromine (C_6) facilitates formation of the Favorskii intermediate leading to the product *(11)* as indicated in path (b), although path (a) may be included as an alternative mechanism. Furthermore, attempted dehydrohalogenation of the epimers *(14a)* and *(14b)* led to reductive debromination. These results are somewhat surprising in view of the well documented facile formation of cyclopropane rings by a 1,3- dehydrohalogenation [9]. The intramolecular nucleophilic attack of enolate anions to Favorskii intermediates is a novel flexible synthetic route to functionalized tri- and tetracyclic systems valuble for the synthesis of many natural and unnatural products.

EXPERIMENTAL :

General :

All air- moisture sensitive reactions were performed under a positive pressure of Ar or N_2. All solvents and reagents were distilled, dried and/or recrystallized prior to use according to standard laboratory procedures. Melting points are uncorrected. Proton and carbon NMR spectra were measured in $CDCl_3$ on a GE/*Bruker* QE 300MHz spectrometer. Analytical thin layer

chromatography (TLC) was conducted on *Polygram Sil* G/UV254 plate (0.25mm) from *Machery* and *Nagel*. Flash chromatography was performed using 230-400 mesh silica gel. Mass spectra were obtained on a *Hewlet Packard* 5989A GC Mass spectrometer (EI). X-Ray structures were determined on an *Enraf-Nonius* CAD4 diffractometer (graphite-monochromated Cu Kα radiation). Structures were solved by a multiple solution procedure, and refined by full matrix least squares. In the final refinement, the nonhydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure- factor calculations but their parameters were not refined. The final discrepancy indices are R=0.05 wR=0.06.

Cis- 3,4,5,6,8,8a- hexahydro- 4a- methyl- 2,7-(1H,3H)-naphthalene-dione (2)

A solution of *(1)* (2g, 8mmol), in acetic acid (35mL) and phosphoric acid (3.5mL), was stirred at RT for 1.5h and then refluxed overnight. The mixture was allowed to cool and the acetic acid was evaporated under reduced pressure. The residue was poured into aqueous saturated sodium bicarbonate until neutral. The solution was partitioned between water (100mL) and ether (100mL), and the aqueous layer was extracted with ether (2×100mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Crystallization of the solid residue from ether- hexane gave the diketone *(2)* (1g, 70%): mp 91-93°C.

(2): ^{1}H-NMR: δ 2.47(m,6H), 2.15(m,5H), 1.69(m,2H), 1.34(s, 3H).

^{13}C-NMR : δ 209.88 (C=O, C_2 or C_7), 44.46 (C_1 and C_8 or C_3 and C_6), 43.74 (C_3 and C_6 or C_1 and C_8), 37.27 (C_4 and C_5), 34.19 (C_{8a}), 32(C_{4a}), 25.73 (CH_3).

IR(CCl_4) ν_{max} : 2970, 2940(C-H), 1725 (C=O) cm^{-1}.

Cis-8a, 1,3,4,5,6- hexahydro-6 (eq)- bromo-4a- methyl-2,7- dioxo- (6H, 8H)- [1]- methyl-naphthoate (3)

The copper (II) bromide was grounded in a mortar and pestle to ensure a large surface area for reaction. Copper (II) bromide (0.45g, 2.01mmol) was placed in a round bottom flask fitted with a reflux condensor. Ethyl acetate (10mL) was added and brought to reflux on a hot plate. Compound (1) (0.24g, 1mmol) was dissolved in hot chloroform (10mL) and added to the flask. The resulting reaction mixture was refluxed with stirring for 1h to ensure complete exposure of the copper(II) bromide to the reaction medium until the reaction changed color from green to amber. The mixture was then gravity filtered in order to remove copper(I) bromide and worked up first with sodium thiosulfate, sodium bicarbonate, and then water (2×30mL). The aqueous layer was extracted with ether(2×30mL),and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford *(3)* (0.32g) in quantitative yield. Compound (3) was recrystallized from methylene chloride- hexane mixture into colorless needles: mp 179-181°C.

(3): ^{1}H-NMR: δ12.37 (s, 1H), 4.8(dd, 1H, J= 13.58, 5.83Hz), 3.77(s, 3H), 2.93 (dd, 1H, J=14.17, 4.7Hz), 2.71(m, 1H), 2.45(m, 3H), 2.23(m, 3H), 1.52(m,1H), 1.04(s, 3H).

^{13}C-NMR: δ 200.33(C=O, C_7), 172.2(C_2), 171.87 (C=O of ester), 100.03 (C_1), 52.76 (C_6), 51.79 (C_8 or OCH_3), 51.39 (C_8 or OCH_3), 44.87 (C_{8a}), 41.75(C_3), 35.09(C_{4a}), 26.17(C_5), 26.08 (C_4), 25.08 (CH_3).

IR(CCl_4) ν_{max}: 2950 (C-H), 1620 (C-OH of enol), 1740 (C=O of ester), 1660 (C=O of ketone) cm^{-1}.

Cis-3,6-(eq)- dibromo- 3,4,5,6,8a,8- hexahydro-4a-methyl-2,7-(1H, 3H) naphthalene dione (4) via reaction of (12) with NBS

To a solution of the (silyl enol) ether *(12)* (0.65g, 2mmol) in THF (15mL), was added recrystallized ($CHCl_3$) NBS (0.73g, 4.1mmol) and the reaction was stirred at RT under N_2 for 1h. The reaction was quenched with water and

diluted with ether (2×30mL). The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography(30% ethyl acetate in hexane) afforded *(4)* (0.49g, 62%) as white crystals: mp 127-129°C.

(4): ^{1}H-NMR: δ 4.9(dd, 1H, J=13.0, 6.4Hz), 4.75 (dd, 1H, J=13.63, 6.13Hz), 2.92 (dd, 1H, J=14.5, 4.5Hz), 2.76 (t, 1H, J=13.35), 2.6 (d, 1H, J= 10.14Hz), 2.51 (dd, 1H, J=13.91, 6.18Hz), 2.4(m, 3H), 2.19(t, 1H, J=13.78Hz), 1.45(s, 3H).

^{13}C-NMR: δ 199 (C_2 or C_7), 198.76 (C_2 or C_7), 51.92 (C_3 or C_6), 51.88 (C_3 or C_6), 50.24 (C_1 or C_8), 45.46 (C_{8a}), 43.74 (C_1 or C_8), 42.71 (C_4 or C_5), 38.53 (C_4 or C_5), 25.82 (C_{4a}), 25.56(CH_3).

Compound (4) derived from the reaction of (2) with copper bromide

The copper(II) bromide was grounded in a mortar and pestle to ensure a large surface area for reaction. Copper(II) bromide (0.78g, 3.5mmol) was placed in a round bottom flask fitted with a reflux condensor. Ethyl acetate (20mL) was added and brought to reflux on a hot plate. compound *(2)* (0.18g, 1mmol) was dissolved in hot chloroform (20ml) and added to the flask. The resulting reaction mixture was refluxed with stirring for 1h to ensure complete exposure of the copper(II) bromide to the reaction medium until the reaction changed color from green to amber. The mixture was then gravity filtered in order to remove copper(I) bromide and worked up first with sodium thiosulfate, sodium bicarbonate, and then water (2×60mL). The aqueous layer was extracted with ether (2×60mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford *(4)* in quantitative yield. Compound *(4)* was digested with ether and placed in the refrigerator overnight to yield pure dibromo diketone *(4)* as needles: mp 127-129°C.

(4): ^{1}H-NMR: δ4.9 (dd, 1H, J=13.0, 6.4Hz), 4.75 (dd, 1H, J=13.63, 6.13Hz), 2.92 (dd, 1H, J=14.5, 4.5Hz), 2.76 (t,1H,J=13.35), 2.6(d,1H, J=10.14), 2.51(dd, 1H, J=13.91, 6.18Hz), 2.4(m, 3H), 2.19 (t, 1H, J=13.78), 1.45 (s, 3H).

^{13}C-NMR: δ 199(C_2 or C_7), 198.76 (C_2 or C_7), 51.92 (C_3 or C_6), 51.38 (C_3 or C_6), 50.24 (C_1 or C_8), 45.46 (C_{8a}), 43.74 (C_1 or C_8), 42.71 (C_4 or C_5), 38.53 (C_4 or C_5), 25.82 (C_{4a}), 25.56 (CH_3).

Cis- 8a, 1, 3, 4- tetrahydro- 4a- methyl- 2,7- dioxo- (4aH, 8H)- [1]- methyl-naphthoate (5)

Monobromide 3 (0.64g, 2mmol) was dissolved in THF (20mL) under N_2. To this solution DBU (0.6mL. 4mmol) was added and the mixture was heated to 60°C for 15h. The mixture was allowed to cool slowly to RT, before it was quenched with HCl (1N). The mixture was diluted with ether (2×30mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the monoene *(5)* (0.08g, 17%): mp 97-100°C.

(5): ^{1}H-NMR: δ 12.41 (s, 1H), 6.66 (d, 1H, J=10.12Hz), 5.93(d, J=10.16Hz), 3.78(s, 3H), 2.84 (dd, 1H, J=13.2, 4Hz), 2.72 (dd, 1H, J=17, 4.33Hz), 2.42(m, 2H), 2.2(q, 1H, J=13.25Hz), 1.88 (m, 1H), 1.56(m, 1H), 1.15(s, 3H).

^{13}C-NMR: δ 195.53(C=O,C_2),174.88(C_7), 171.36 (C=O of ester), 96.84 (C_8), 53.75 (C_1 or C_3), 51.91 (C_1 or C_3), 51.00 (OCH_3), 47.9 (C_{8a}), 44.71 (C_6), 35.21(C_{4a}), 27.78(C_4), 27.23 (C_5), 25.96 (CH_3).

Synthesis of (5) by lithium- bromide lithium- carbonate dimethylformamide dehydrobromination

To a stirred suspension of dry LiBr (0.14g, 1.57mmol) and $LiCO_3$ (0.18g, 2.46mmol) in dry DMF (10mL) at 120°C under N_2, was added solid *(3)* (0.32g, 1mmol). Stirring was continued for 75 minutes at the same temperature. The reaction was then cooled, poured into dilute acetic acid, and extracted with ether. The ether extracts were washed with water, brine, dried

over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give monoene *(5)* as the only product (0.15g, 64%).

7- Carbomethoxy- 5- methyl- tricyclo- [4.4.0.0^{1,7}]- decane- 2,8- dione (6)

Monobromide *(3)* (0.64g, 2mmol) was dissolved in THF (20mL) under N_2. To this solution DBU (0.6mL, 4mmol) was added and the mixture was heated to 60°C for 15h. The mixture was allowed to cool slowly to RT before it was quenched with HCl (1N). The mixture was diluted with ether (2×30mL), and the organic layer was wahsed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the keto-ester *(6)* (0.19g, 40%) which was recrystallized from hexane: mp 107-108°C.

(6): ^{1}H-NMR: δ 3.73 (s, 3H), 2.94 (d, 1H, J= 5.44Hz), 2.74 (m, 2H), 2.53 (m, 1H), 2.44 (d, 1H, J= 18.92Hz), 2.05 (m, 3H), 1.81 (m, 1H), 1.44 (d, 1H, J= 14.6Hz), 1.2 (s, 3H).

^{13}C-NMR: δ210.08 (C=O, C_2), 206.18 (C=O, C_8), 169.87 (C=O of ester), 71.15(C_7), 56.25 (C_1), 52.71 (OCH_3), 49.31 (C_4), 38.17 (C_5), 37.55 (C_3 or C_9), 36.32 (C_3 or C_9), 35.47 (C_6 or C_{10}), 34.96 (C_6 or C_{10}), 23.99 (CH_3).

IR(CCl_4) ν_{max}: 2970, 2890 (C-H), 1770 (C=O of C_3 b- keto ester), 1750 (C=O of ester), 1720 (C=O of ketone, C_9) cm^{-1}.

2- Carbomethoxy- 1- hydroxy- 8- methyl- tetracyclo- [4.4.0.0^{1,6}.0^{2,4}]- decane- 5- one (7)

Monobromide *(3)* (0.64g, 2mmol) was dissolved in THF (20mL) under N_2. To this solution DBU (0.6mL, 4mmol) was added and the mixture was heated to 60°C for 15h. The mixture was allowed to cool slowly to RT, before it was quenched with HCl(1N).The mixture was diluted with ether (2×30mL), and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (Chromatotron, 20% ethyl acetate in hexane) afforded the tetracyclic *(7)* (0.19g, 40%) which was recrystallized from hexane into colorless crystals: mp 104-105°C.

(7): ^{1}H-NMR: δ 3.76 (s, 3H), 2.4 (dd, 1H, J= 1.88Hz), 2.26 (dd, 1H, J= 7.62, 7.62, 2.74Hz), 2.16 (dd, 1H, J= 7.85, 1.62Hz), 2.08 (d, 1H, J= 10.78Hz), 1.93 (m, 2H), 1.68 (m, 1H), 1.58 (m, 3H), 1.16 (s, 3H).

^{13}C-NMR: δ 207.85 (C=O, C_5), 171.22 (C=O of ester), 74.2 (C_1), 52.2 (OCH_3), 51.14 (C_{10}), 43.29 (C_6), 40.59 (C_4), 38.58 (C_2), 37.26 (C_7), 35.80 (C_3), 29.12 (C_8), 27.79 (C_9), 25.47 (CH_3).

IR(CCl_4) ν_{max}: 3540(OH), 2970, 2940, 2890 (C-H), 1720(C=O of ester), 1755 (C=O of ketone) cm^{-1}.

1- Bromo- 5- methyl- tricyclo- [4.4.0.0^{1,7}]- decane- 2,8- dione (9)

To a solution of dibromide *(10)* (0.13g, 0.385mmol) dissolved in dry THF (10mL) under N_2 was added DBU (0.15mL) and the mixture was stirred at 50°C overnight. The reaction was quenched with HCl (10%) and diluted with ether (2×20mL). The organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography (15% ethyl acetate in hexane) afforded (9) (47mg, 48%) as white crystals.

(9): ^{1}H-NMR: δ 2.82 (s, 1H), 2.66 (m, 2H), 2.48 (m, 3H), 2.26 (dd, 1H, J= 18.77, 5.2Hz), 1.8 (m, 3H), 1.25 (s, 3H).

^{13}C-NMR: δ 205.7 (C_2), 202.28 (C_8), 66.6 (C_1), 64.85 (C_7), 46.41 (C_4), 42.7 (C_3), 41.21 (C_5), 37.75(C_9), 37.04 (C_6), 36.76 (C_{10}), 22.79 (CH_3).

Cis- 8a- 1,3,4,5,6- hexahydro- 6(eq), 8(ax)- dibromo- 4a- methyl- 2,7- dioxo- (6H, 8H)- [1]- methyl-naphthoate (10)

A solution of bromine (0.4g, 2.5mmol) in chloroform (10mL) was slowly added to β- keto ester *(1)* (0.24g, 1mmol) dissolved in chloroform (10mL) over a period of 15 minutes. The solu-

tion was left to stir overnight at RT. The reaction was quenched with sodium bisulfite (5%), and the layers were separated. The organic layer was washed with aqueous saturated sodium bicarbonate, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (20% ethyl acetate in hexane) gave 10 (0.32g, 80%): mp 178-179°C.
(10): ^{1}H-NMR: δ 12.59 (s, 1H), 5.53 (dd, 1H, J= 14.27, 5.62Hz), 4.79 (d, 1H, J= 5Hz), 3.79(s, 3H), 2.92 (d, 1H, J= 4.86Hz), 2.78(m, 1H), 2.47 (m, 3H), 2.2 (t, 1H), 1.39 (m, 1H), 1.01 (s, 3H).
^{13}C-NMR: δ 195.53 (C=O, C_2), 174.88 (C_7), 171.36 (C=O of ester), 96.84 (C_8), 53.75 (C_1 or C_3), 51.91 (C_1 or C_3), 51.00 (OCH_3), 47.9 (C_{8a}), 44.71 (C_6), 35.21 (C_{4a}), 27.78 (C_4), 27.23 (C_5), 25.96 (CH_3).

6- Bromo- 2- carbomethoxy-1- hydroxy-8-methyl- tetracyclo- [4.4.0.0^{1,6}.0^{2,4}] decane-5-one (11)

To a solution of dibromo ketone *(10)* (0.2g, 0.5mmol) dissolved in dry THF (10mL) under N_2 , was added DBU (0.08g, 1mmol) dropwise using a syringe. Stirring was continued overtnight at 55°C before the reaction was quenched with HCl (10%). The mixture was diluted with ether (2 × 20mL), and the organic layer was washed with saturated sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give *(11)* (0.11g, 70%) as pale yellow crystals. Recrystallization from hexane afforded pure *(11)* as colorless needles: mp 114-116°C.
(11): ^{1}H-NMR: δ 3.81 (s, 1H), 3.75 (s, 3H), 2.56 (d, 1H, J= 7.58Hz), 2.27 (dd, 1H, J= 7.53, 2.45Hz), 2.11 (m, 4H), 1.81 (q, 1H, J= 2Hz), 1.67 (m, 1H), 1.16 (s, 3H).
^{13}C-NMR: δ 199.3 (C_5), 170.14 (C=O of ester), 74.22 (C_1), 69.15 (C_6), 52.53 (OCH_3), 52.33 (C_{10}), 42.47 (C_4), 38.06 (C_2), 37.41 (C_7), 32.82 (C_3), 31.65 (C_8), 26.30 (C_9), 24.92 (CH_3).
IR(CCl_4) ν_{max}: 3540(OH), 2970, 2940, 2890(C-H), 1770(C=O, C5), 1720(C=O of ester) cm^{-1}.

Synthesis of (11) by lithium - bromide lithium- carbonate dimethylformamide dehydrobromination

To a stirred suspension of dry LiBr (0.14g, 1.57mmol) and $LiCO_3$ (0.18g, 2.46mmol) in dry DMF (10mL) at 120°C under N_2 ,was added *(10)* (0.2g, 0.5mmol) as solid. Stirring was continued for 75 minutes at the same temperature. The reaction was then cooled, poured into dilute acetic acid, and extracted with ether. The ether extracts were washed with water, brine, and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the tetracyclic compound *(11)* as the only product (80mg, 50%).

(Silyl enol) ether (12) derived from silylation of (2)

Dione *(2)* (0.36g, 2mmol) was dissolved in dry acetonitrile (12mL). Triethylamine (1.2mL, 8mmol), sodium iodide (1.2g, 8mmol) and trimethylsilyl chloride (1mL, 8mmol) were added sequentially. After 15 minutes at RT, the reaction mixture was heated to 70°C for 1h. Upon consumption of the aldehyde, a cold aqueous saturated $NaHCO_3$(15mL) and ether were added (20mL). The aqueous phase was separated and extracted with ether (2×20mL). The organic layer was dried over K_2CO_3, filtered, and concentrated in vacuo to afford (silyl enol) ether 12 (0.65g) in quantitative yield. The product was carried out to the next step without purification.
(12): ^{1}H-NMR: δ 4.7 (br s, 2H), 2.05(m, 4H), 1.81(m, 4H), 1.5(d, 1H, J= 10.93Hz), 0.96(s, 3H), 0.17(s, 9H), 0.16(s, 9H).

Cis-8a,1,3,4,5,6- hexahydro- 1(ax)- bromo-4a-methyl-2,7-dioxo- (6H,8H)- [1]- methylnaphthoate (14a)

To a solution of the b- keto ester *(1)* (4.76g, 0.02mol) dissolved in dry methylene chloride (150mL) was added (under N_2) triethyl amine (16.72mL). To the resulting solution cooled to 0°C, N- bromo succinimide (7.83g) dissolved in methylene chloride (300mL) was added dropwise. The mixture was stirred at 0°C for 2h

before it was quenched with 10% HCl. The layers were separated and the organic phase was washed with aqueous $NaHSO_4$ (5%), saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silica gel (30% ethyl acetate in hexane) gave *(14a)* (2.28g, 36%) which was recrystallized from ether-hexane mixture as white needles: mp 108-110°C. Compound *(14a)* was obtained together with *(14b)* in a combined yield of 63%.

(14a): ^{1}H-NMR: δ 3.84(s, 3H), 3.1(m, 2H), 2.57 (m, 5H), 2.19(dd, 2H), 1.81(m, 1H), 1.62(m, 1H), 1.16(s, 3H).

^{13}C-NMR: δ 208.53 (s, C=O, C_2), 198.69 (C=O, C_7), 167.68(C=O of ester), 71.78(C_1), 54.04 (OCH_3), 49.11(C_{8a}), 41.34(C_3 or C_6 or C_8), 36.44 (C_3 or C_6 or C_8), 35.17(C_3 or C_6 or C_8), 33.75(C_4 or C_5), 33.33(C_4 or C_5), 33.12(C_{4a}), 27.84(CH_3).

IR(CCl_4) ν_{max}: 2960, 2930(C-H), 1725(C=O of ketone), 1740(C=O of ester), 1270, 1250(C-O of ester) cm^{-1}.

Cis- 8a, 1,3,4,5,6- hexahydro- 1(eq)- bromo- 4a- methyl- 2,7- dioxo- (6H, 8H)- [1]- methyl- naphthoate (14b)

To a solution of the β- keto ester *(1)* (4.76g, 0.02mol) dissolved in dry methylene chloride (150mL) was added (under N_2) triethyl amine (16.72mL). To the resulting solution cooled to 0°C, N- bromo succinimide (7.83g) dissolved in methylene chloride (300mL) was added dropwise. The mixture was stirred at 0°C for 2h before it was quenched with 10% HCl. The layers were separated and the organic phase was washed with aqueous $NaHSO_4$ (5%), saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. Purification by chromatography on silic gel (30% ethyl acetate in hexane) gave *(14b)* (1.68g, 27%) which was recrystallized from methylene chloride- hexane mixture as white needles: mp 115-116°C. Compound *(14b)* was obtained together with *(14a)* in a combined yield of 63%.

(14b): ^{1}H-NMR: δ 3.75(s, 3H), 3.26(dd, 1H, J= 17.93, 1.6Hz), 2.87(ddd, 1H, J= 6, 5.9, 6Hz), 2.65(m, 2H), 2.47(m, 3H), 2.17(m, 1H), 1.91(m, 2H), 1.53(m, 1H), 1.25(s, 3H).

^{13}C-NMR: δ 206.82 (C=O, C_2), 196.91 (C=O, C_7), 168.55(C=O of ester), 72.31(C_1), 54.51(C_{8a}), 53.38(OCH_3), 40.18(C_3 or C_6 or C_8), 38.92(C_3 or C_6 or C_8), 36(C_3 or C_6 or C_8), 35.58(C_4 or C_5), 35.16(C_{4a}), 30.09(C_4 or C_5), 27.46(CH_3).

IR(CCl_4) ν_{max}: 2970, 2950(C-H), 1740(C=O of ketone and ester overlapping), 1255(C-O of ester) cm^{-1}.

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