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A Facile Entry into the Ring System of Sativene

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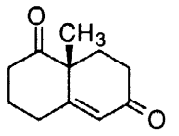
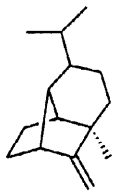
Abstract: *The mechanism of the dehydrobromination of two isomeric dibromo-cis-4a-methyldecalin-2,5-diones and tribromo-cis-4a-methyldecalin-2,5-dione is described. Treatment of dione (2), with 2 equiv of bromine gave a mixture of dibromides (3) and (4) in a 1:1 ratio. Treatment of (2) with 3.2 equiv of bromine gave tribromide (5) as the major product. Dehydrobromination of (3) and (4), independently with DBU in THF, resulted in the loss of HBr and the exclusive formation of two isomeric tricyclic compounds (6) and (7) respectively. Dehydrobromination of tribromide (5) with DBU gave a mixture of two tricyclic compounds (6) and (8) in an approximate ratio of 1:1. The mechanisms of the formation of the isomeric tricyclic bromoketones (6) and (7) from compounds (3) and (4), and that of (6) and (8) from the tribromide (5) are discussed. Both tricyclic compounds (6) and (8), readily available in good yields from Wieland Miescher ketone (1), have the same carbon skeleton as the sesquiterpene hydrocarbon sativene.*

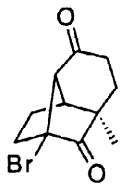
Intramolecular carbon-carbon bond formation has attracted the attention of many synthetic organic chemists.[1] As an extension of our recently reported syntheses of several polycyclic systems involving a novel intramolecular ring-opening of cyclopropanones by enolate anions,[2] we envisioned an entry into the ring system of sativene, a tricyclic sesquiterpene hydrocarbon, from the readily available Wieland-Miescher ketone **1**.[3] In this article we report the results of our investigation on the bromination of the *cis*-4a-methyldecalin-2,5-dione **2**, and the subsequent dehydrobromination of the two isomeric dibromoketones **3** and **4** as well as the tribromoketone **5**, with DBU. Although ring closures involving intramolecular alkylation on substituted *cis*-decalones have been employed for a number of terpene syntheses,[4] McMurry's notable synthesis of sativene[5] is the work most similar to that discussed in this paper.



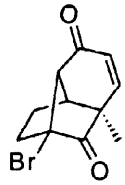
Wieland Miescher Ketone **(1)**



Sativene



6



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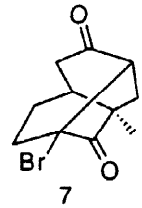

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Catalytic hydrogenation of Wieland-Miescher ketone in ethanol with 5% Pd/C as catalyst gave the authentic sample of cis-4a-methyldecalin-2,5-dione **2**,[6] identical with that first prepared by Nazarov.[7] Treatment of **2** with either 2 equiv of bromine in chloroform or with 4.5 equiv of $CuBr_2$ in ethyl acetate/chloroform[8] gave a mixture of dibromides **3** and **4** as the major products (Scheme 1). These dibromides could be separated either by fractional crystallization using dichloromethane/hexane mixture, or through column chromatography using 10% ethyl acetate/hexane. The stereochemistry of **3** and **4** was in each case unambiguously established through single crystal X-ray structure determination. Compound **2** upon treatment with 3.2 equiv of Br_2 in chloroform or 9 equiv of $CuBr_2$ in ethyl acetate/chloroform gave rise to the formation of tribromide **5** as the major product (Scheme 1). The stereochemistry of the tribromide **5** was proven by a single crystal X-ray structure determination.

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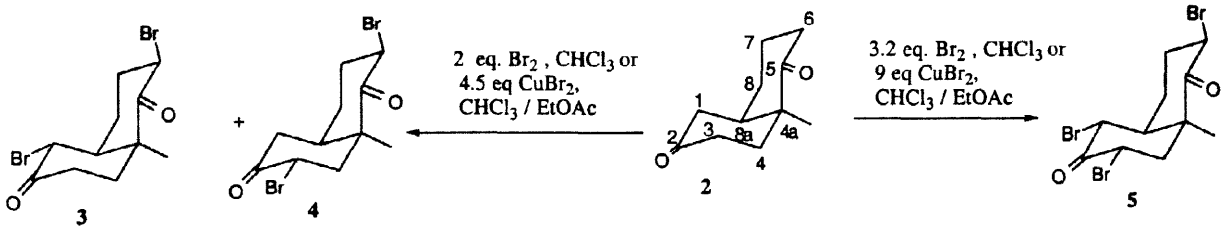
Scheme 1

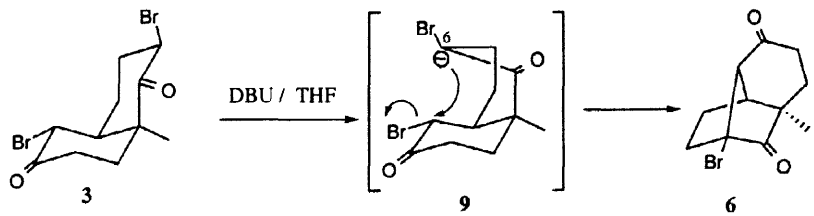


The ^{1}H NMR spectrum of **3** reveals both the location and orientation (both equatorial) of the two bromines in the molecule. For example, a doublet at δ=4.5 with $J_{1(ax)}$-$J_{8a(ax)}$ = 12.7 Hz[9] is observed for the proton at C-1 corresponding to 1,2 diaxial coupling. A set of doublets of doublets centered at δ = 5 with $J_{6(ax)-7(ax)}$ = 12.7 Hz, and $J_{6(ax)-7(eq)}$ = 7 Hz, is indicative of the axial proton at C-6. The ^{1}H NMR spectrum of **4** displayed for the protons at C-3 and C-6 the typical doublets of doublets, at δ = 4.97 and 5.1 while lacking the doublet at δ = 4.5 observed for **3**. A 500 MHz COSY spectrum allowed the assignment of all protons in **4**. The triplet at δ = 1.95 corresponds to $H_{4(ax)}$ coupling with $H_{4(eq)}$ and $H_{3(ax)}$ with the same coupling constant $J_{gem} = J_{vic\ ax}$ = 13 Hz. The doublet of doublets at δ = 3.2 corresponds to $H_{4(eq)}$, coupling to $H_{3(ax)}$ and $H_{4(ax)}$. The X-part of the ABX system at δ = 5.14 corresponds to $H_{6(ax)}$ with $J_{6(ax)-7(ax)}$ = 13 Hz, and $J_{6(ax)-7(eq)}$ = 6.3 Hz, indicating the axial position of both hydrogens H_3 and H_6 and thus the equatorial positions of both bromines in these positions.[10] The IR comparison between **3** and **4** reveals that in **3**, two stretching vibrations for the carbonyl groups were observed at 1744 and 1728 cm,$^{-1}$ while in **4**, the two carbonyl groups have bands at nearly the same frequency, at 1724 cm.$^{-1}$

The ^{1}H NMR spectrum of the tribromide **5** showing a triplet at δ = 1.8, a doublet at 4.5 and, the X-parts of two very close ABX systems centered at δ = 4.95 and 5.05 is essentially a combination of the ^{1}H NMR spectra of dibromides **3** and **4**.

Dehydrobromination of **3** with DBU in THF first at 0 °C and later between 55-60 °C under N_2 for 16 hr yielded the tricyclic bromoketone **6** in nearly quantitative yield. A single crystal X-ray structure determination confirmed **6** as 1-bromo-3-methyl-tricyclo-[4.4.0.0^{1,7}]-decane-2,8-dione. The transannular cyclization of **3** to **6** may involve a direct S_N2 attack by the enolate ion **9** with displacement of bromine attached to C-1 as outlined in (Scheme 2).

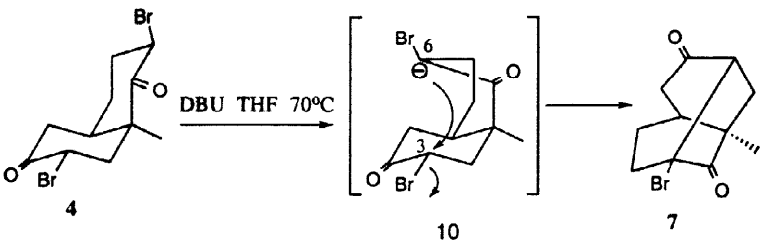
Scheme 2



Treatment of **4** with DBU under the same reaction conditions led to the formation of tricyclic dione **7**, an isomer of **6**, in 76% yield. A single crystal X-ray structure determination clearly established **7** as 1-bromo-3-methyltricyclo[4.4.0.0^{1,9}]-decane-2,8-dione (Scheme 3). The mechanistic pathway leading to the tricyclic compound **7** from cis-3,6(dieq)-dibromo-4a-methyldecalin-2,5-dione **4** may be the result of an intramolecular

S_N2 reaction via bromoenolate ion (**10**), similar to that proposed for the cyclization of **3** to **6** as depicted in Scheme 2.

Scheme 3



A comparison of the spectral data for **6** and **7** is quite interesting. In the ^1H NMR of compound **6**, the proton at the bridgehead C-7 appears as a singlet due to the near zero coupling with the proton at the bridgehead C-4. The same protons at the bridgehead C-9 in compound **7** however couples significantly (J = 5.5 Hz) with one of the two protons of the neighboring CH_2 group (C-10), due to a smaller dihedral angle.[10] The IR spectra show for both compounds **6** and **7** two different carbonyl groups:

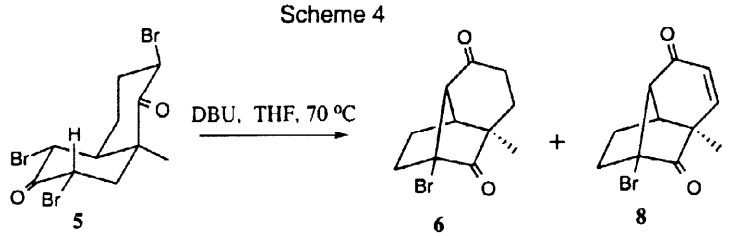
6 : ν C=0 1766 & 1712 cm^{-1}

7: 1761 & 1727 cm^{-1}

While there is very little difference for the C_2=O stretching frequencies in **6** and **7**, the values for the C_8=O stretching frequency of **7** is 15 wavenumbers greater than that for compound **6**, suggesting a somewhat more strained system being present in **7**.

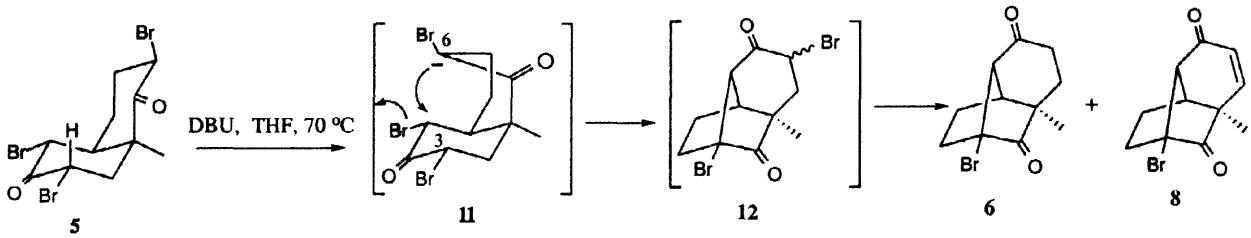
Dehydrobromination of the tribromide **5** with DBU in dry THF yielded **6** (previously obtained from **3**), and a second UV active compound **8** in a 1:1 ratio as determined by GC/MS and ^1H NMR spectra (Scheme 4). Separation of compounds **6** and **8** was achieved by chromatography using 10% ethyl acetate in hexane. Compound **8** showed a molecular ion with m/z = 254/256 (10%). The ^1H NMR spectrum displayed prominently an AB system at δ = 6.08 and 6.72 with J_{AB} = 9.5 Hz . The IR spectrum with an absorption at 1684 cm^{-1} as well as the ^{13}C NMR spectrum displaying signals at δ = 151.9 and 130.1 further support the presence of an α,β-unsaturated ketone. A single crystal X-ray structure determination clearly established **8** as 1-bromo-3-methyltricyclo-[4.4.0.$0^{1,7}$]-9-decene-2,8-dione.

Scheme 4



Both reaction products **6** and **8** from **5** in Scheme 4 can most conveniently be explained by an S_N2 reaction pathway. Nucleophilic intramolecular attack by the C-6 bromoenolate ion (**11**) at the C-1 bromine affords intermediate (**12**). Upon further reaction with DBU, the common intermediate (**12**) can undergo either reductive debromination or dehydrobromination to afford **6** and **8** (Scheme 5).

Scheme 5



Dehydrobromination of the dibromide **3** and the tribromide **5** with DBU, provides an easy access to the ring system of sativene. The two isomeric dibromides **3** and **4** and the tribromide **5**, upon treatment with DBU, appear to react via a direct S_N2 mechanism. The results of dehydrohalogenation of bromo-cis-decalindiones described in this paper as well as our previous findings, seem to represent a general method for the generation of tricylo[4.4.0.0]decane ring systems. Further studies, extending this concept to include the facile assembly of the structurally related terpenes are under investigation.

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