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BIOMIMETIC REACTIONS OF GERMACRENES

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Summary: The biomimetic reactions of epoxygermacrene-D (1) with basic alumina afforded three new interesting compounds (4, 5, and 6), two of which (4 and 6) have the same carbon skeleton as that of periplanone-A (3), a sexual stimulant for the American cockroach. The remaining one (5) is a bicyclo[3.1.0]hexane derivative, from which an axisonitrile-3 type compound (14) has been produced. Finally, preisocalamendiol (2) was also converted into 6.

In the previous paper,[1] we reported the acid-catalyzed cyclization of epoxygermacrene-D (1), leading to the formation of the new interesting compounds having the same carbon skeleton as that of oppositol, in addition to the selinane-type compounds related to (+)-junenol. In these cases using 80% aq.AcOH and $AlCl_3$ - ether, the transannular reactions take place, resulting in only the C_5-C_{10} bond formation. In the present paper, we wish to describe the biomimetic reactions of epoxygermacrene-D (1) with basic alumina, affording the biogenetically interesting compounds (4, 5, and 6) in contrast to the case of the previous experiments.[1]

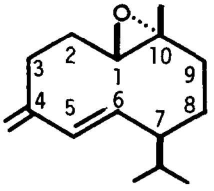
A solution of epoxygermacrene-D in hexane was adsorbed on basic alumina (Nakarai Chemicals, 300 mesh) at room temperature for 2.5 h, and then eluted with hexane-ether (1 : 1) to give two new ketones (4 and 5) in 11 and 10% yields, respectively. Further elution with AcOEt afforded a diene (6) in 3.5% yield. The structures of these reaction products were determined on the basis of their spectral data coupled with some chemical evidences.

4 as a colorless oil: $C_{15}H_{24}O$ [m/e 220(M^+)]; ν_{max}(film) 3070, 1700, and 1650 cm^{-1}; $\delta(CDCl_3)$ 0.89(3H, d, J= 6Hz), 0.98(3H, d, J= 6Hz), 1.18(3H, s), 4.66(1H, br.s), and 4.70(1H, br.s).

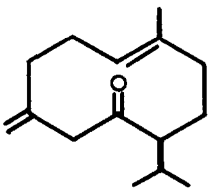
5 as a colorless oil: $C_{15}H_{24}O$ [m/e 220(M^+)]; ν_{max}(film) 3070, 3020, 1720, and 1650 cm^{-1}; $\delta(CDCl_3)$ 0.60(2H, m), 0.93(6H, d, J= 7Hz), 2.14(3H, s), 4.55(1H, br.s), and 4.84 (1H, br.s).

6 as a colorless oil: $C_{15}H_{24}O$ [m/e 220(M^+)]; ν_{max}(film) 3350br., 3070, and 1635 cm^{-1}; $\delta(CDCl_3)$ 0.91(3H, d, J= 7Hz), 0.92(3H, s), 0.93(3H, d, J= 7Hz), 3.45(1H, dd, J= 4.5 and 10.5Hz), 4.64(1H, t, J= 2Hz), 4.82(1H, t, J= 2Hz), and 5.58(1H, br.s).

As judged from the NMR spectrum, 4 has one tertiary Me group derived from the Me group at C_{10}-position in 1, in addition to one exocyclic double bond and one isopropyl group. Furthermore, the newly formed CO group must be included in a partial structure $-CH_2CO-\overset{|}{\underset{|}{C}}-$ or $-\overset{|}{C}H-CO-\overset{|}{C}H-$: when heated with CD_3ONa-CD_3OD under reflux for 9 h, 4 afforded a deutero compound (7) in quantitative yield, whose molecular ion peak was observed at m/e 222 (M^+ for $C_{15}H_{22}D_2O$). From these data and co-occurrence of the diene (6), the structure of this ketone can be



1



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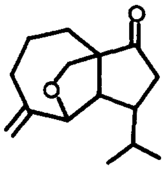

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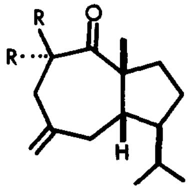
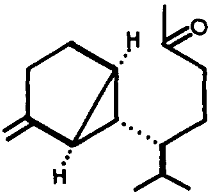


4 R = H

7 R = D



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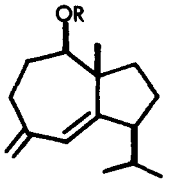
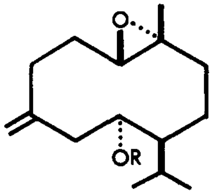


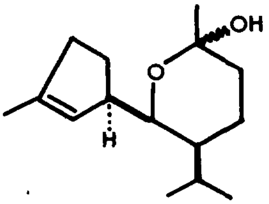
6 R = H

8 R = Ac

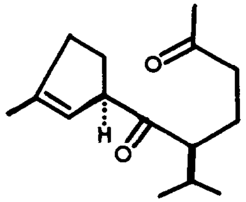


9 R = H

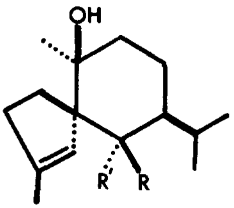
10 R = Ms



11a,b

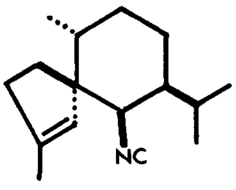


12



13 R,R' = O

14 R = OH, R' = H



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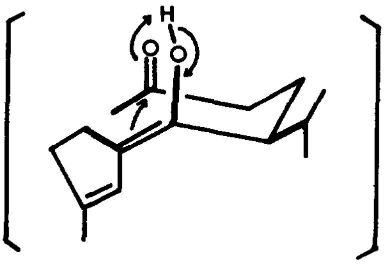


[A]

represented by 4,[2] the formation process of which is quite reasonable,[3] *as shown in Scheme 1.*

The structure of the diene (6)[2] was unambiguously determined on the basis of its NMR spectrum, as follows. The conjugated diene system $H_2C=\overset{|}{C}-CH=\overset{|}{C}-$ is confirmed by its NMR signals at δ4.64, 4.82, and 5.58. In addition, the NMR signal at δ3.45 is assignable to the methine proton in a $-CH_2-CH(OH)-\underset{|}{\overset{|}{C}}-$ *grouping*, which is shifted to a lower magnetic field on acetylation with Ac_2O-pyridine (room temp., overnight) [**8**: $C_{17}H_{26}O_2$ (m/e 262(M^+)); ν_{max}(film) 1740 and 1250 cm^{-1}; $\delta(CDCl_3)$ 0.88(3H, d, J= 7Hz), 0.90(3H, d, J= 7Hz), 0.99(3H, s), 2.04(3H, s), 4.55-4.70(3H, complex), and 5.58(1H, br.s)]. It is noteworthy that this compound (**6**) is produced from preisocalamendiol (**2**)[4] in four steps.

On reduction[5] with $LiAlH_4$ in ether followed by epoxidation with *m*-chloroperbenzoic acid in ether (-15°, overnight), **2** was readily converted into a hydroxyepoxide (**9**) in a good yield [$C_{15}H_{26}O_2$ (m/e 238(M^+)); ν_{max}(KBr) 3400br. and 1645 cm^{-1}]. This compound was then treated with MsCl-pyridine (0°, 3 h) to afford the corresponding mesylate (**10**) in 70% yield [mp 93-94° (from hexane); $C_{16}H_{28}O_4S$ (m/e 316(M^+)); ν_{max}(film) 1650, 1325, and 1175 cm^{-1}; $\delta(CDCl_3)$ 3.01(3H, s) and 4.93(1H, dd, J= 3.5 and 11Hz)], which was further treated with excess NaI in HMPA (80°, 6 h) to give **6** in 20% yield. In this reaction, epoxygermacrene-D (**1**) as an intermediate must be produced from **10**.

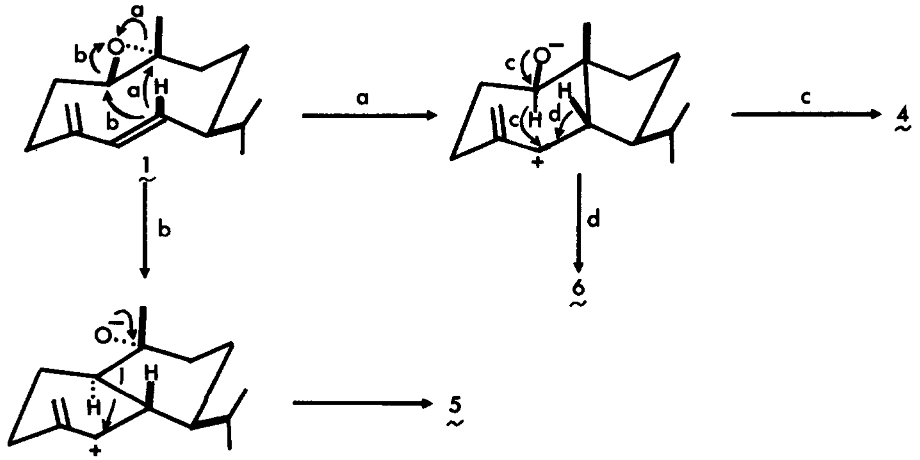
The structure of the remaining product (**5**) was also based on its physical and chemical properties, as follows. From the NMR spectrum of **5**, it has a cyclopropane ring (δ 0.60) and one acetyl group [ν_{max}(film) 1720 cm^{-1}; δ2.14] in addition to the original exocyclic double bond and isopropyl group.

On treatment with 10% H_2SO_4-acetone (room temp., overnight), **5** afforded a mixture of two isomers [**11a**,b: ν_{max}(film) 3400br.cm^{-1} and no CO band], which was directly oxidized with Jones reagent (room temp., 3 h) to give a diketone (**12**) and a hydroxyketone (**13**) in 31 and 12% yields, respectively [**12**: $C_{15}H_{24}O_2$ (m/e 236(M^+)); ν_{max}(film) 1720 cm^{-1}; $\delta(CDCl_3)$ 0.87(3H, d, J= 6Hz), 0.92(3H, d, J= 6Hz), 1.75(3H, d, J= 1Hz), 2.09(3H, s), 3.65(1H, br.s), and 5.22(1H, m). **13**: mp 119-120° (from hexane); $C_{15}H_{24}O_2$ (m/e 236(M^+)); ν_{max}(KBr) 3480 and 1690 cm^{-1}; $\delta(CDCl_3)$ 0.88(3H, d, J= 6Hz), 0.91(3H, d, J= 6Hz), 1.17(3H, s), 1.72(3H, br.s), and 5.28(1H, br.s)]. The former was also converted into **13** in 40% yield, when treated with 10% H_2SO_4-acetone (under reflux, 5 h). From the spectral data of **12** and **13**, the former has a Me-C=CH-CH- grouping (δ1.75, 3.65, and 5.22) and an acetyl group (δ2.09), while **13** has a Me-C=CH-C- grouping (δ1.72 and 5.28) and Me-C(OH)- grouping (δ1.17), indicating that the latter has a partial structure Me-C=CH-C-CMe(OH). Furthermore, when treated with $LiAlH_4$-ether (room temp., overnight), the spiro compound (**13**) was readily converted into a diol [**14**: mp 171-173° (from benzene-hexane); $C_{15}H_{26}O_2$ (m/e 238(M^+)); ν_{max}(KBr) 3370br.cm^{-1}; $\delta(CDCl_3)$ 0.91(3H, d, J= 6Hz), 0.94(3H, d, J= 6Hz), 1.02(3H, s), 1.72(3H, br.s), 3.43(2H, br.s, <u>OH</u>), 3.60(1H, d, J= 2Hz), and 5.09(1H, br.s)]. Clearly, the newly formed secondary OH group is in an axial configuration, as judged from a J-value of the doublet at δ3.60. In addition, the δ-value (1.17) assignable to the tertiary Me group in **13** is shifted to a higher magnetic field in **14** (δ1.02), indicating that the tertiary Me group must be in an equatorial configuration. The δ-value at 5.28 in **13** is also shifted to a higher magnetic field in **14** (δ5.09), suggesting that the double bond is placed on an opposite side against the secondary OH group. Thus, the stereochemistry of the spiro compound may be represented by **13**. In fact, the NMR signals of **14** are quite similar to those of axisonitrile-3 (**15**) [**14**, δ1.72(3H, br.s) and 5.09(1H, br.s); **15**, δ1.73(3H, br.s) and 5.1(1H, br.s)].[6] Furthermore, the stereostructure (**13**) can be explained well by an enol form [A].

Finally, the formation process of these reaction products are shown in Scheme 1. In the present experiments, it is quite interesting that the C-C bond formation takes place at C_6-

position of the conjugated diene system giving 4, 5, and 6, in contrast to the case of the acid-catalyzed cyclization of epoxygermacrene-D (1).[1]

Scheme 1. Formation process of the cyclization products (4, 5, and 6).



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