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BIOMIMETIC SYNTHESES OF OPPOSITOL, OPLOPANONE, AND APHANAMOL II FROM GERMACRENE-D

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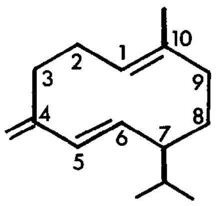
Summary: Biomimetic reaction of germacrene-D induced with bromonium ion has been carried out to give several bromo compounds, from which (±)-oppositol and (±)-oplopanone have been synthesized. (±)-Aphanamol II has also been synthesized from epoxygermacrene-D.

(-)-Germacrene-D (1) was first isolated by Yoshihara et al. from Pseudotsuga japonica S., and they carried out acid-catalyzed reaction of 1 leading to a variety of products including (+)-γ-muurolene, (-)-α-amorphene, α-muurolene, (+)-cadinene, and (+)-γ-cadinene.[1] In contrast, both selinane- and oppositol-type compounds have been obtained on acid-catalyzed reaction of epoxygermacrene-D (2).[2] On the basis of these two experiments together with molecular mechanics calculations, we carried out biomimetic reaction of germacrene-D (1) induced with bromonium ion in order to synthesize oppositol (3),[3] oplopanone (4),[4] aphanamol II (5)[5] and others.



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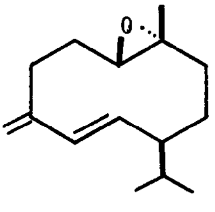

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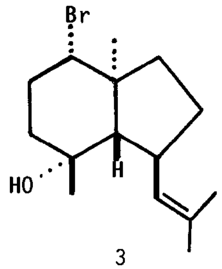

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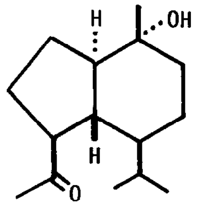

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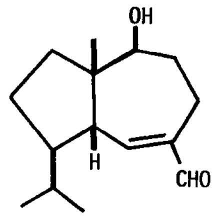

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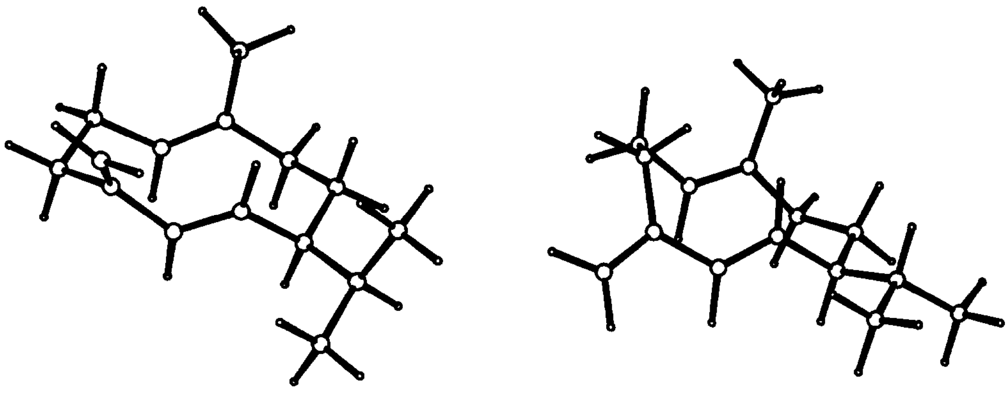
As judged from molecular mechanics calculations[6] of germacrene-D (1), 1 adopts two main conformations (relative ratio at 25 °C: CC : TC : others = 82 : 17 : 1) as shown in Fig. 1. Epoxygermacrene-D (2) also adopts the same two conformations (CC and TC). Interestingly, the relative ratio of these two conformers at 25 °C (CC : TC : others = 16 : 83 : 1) in 2 is reversed, suggesting that some different results may be obtained between 1 and 2 on acid-catalyzed reaction. As seen in Fig. 1, however, the two double bonds at C_1-C_{10} and C_5-C_6

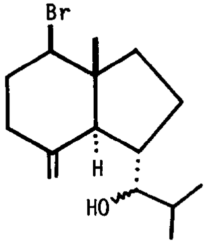


CC (S.E., 23.8291 Kcal/mol) TC (S.E., 24.7557 Kcal/mol)

Fig. 1. The two main conformations of germacrene-D (1)

occupy the same situation in both CC and TC conformations and the same stereochemistry is expected in both the cyclization products derived from 1 and 2.

When treated with NBS (1.0 equiv.) in THF - H_2O (3 : 2)^7 at room temperature for 30 min, germacrene-D (1)^8 was converted into several bromo compounds (6, 7, 8, 9, 10, 11, and 12)^9 in 13.3, 2.7, 4.2, 4.9, 7.0, 7.2, and 11% yields, respectively. 2,4,4,6-Tetrabromocyclohexadienone was used as a reagent generating bromonium ion instead of NBS. However, any good result has not yet been obtained as compared with the latter. Anodic oxidation of 1 was also carried out at a constant potential (+1.3 V vs. SCE; 8 - 6 mA) in aqueous THF containing NaBr as a supporting electrolyte to afford the same bromo compounds as



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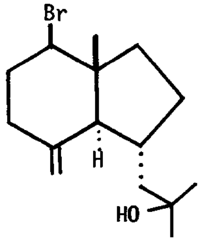

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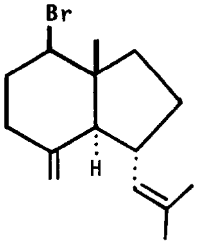

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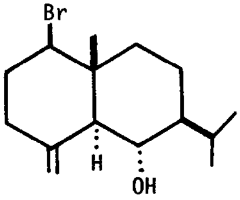

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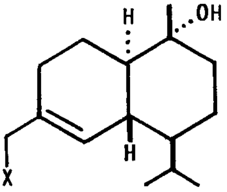
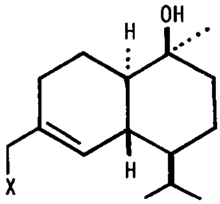


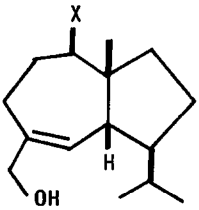
10 X = Br

16 X = H



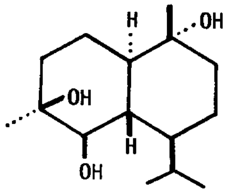
11 X = Br

17 X = H



12 X = Br

19 X = OH



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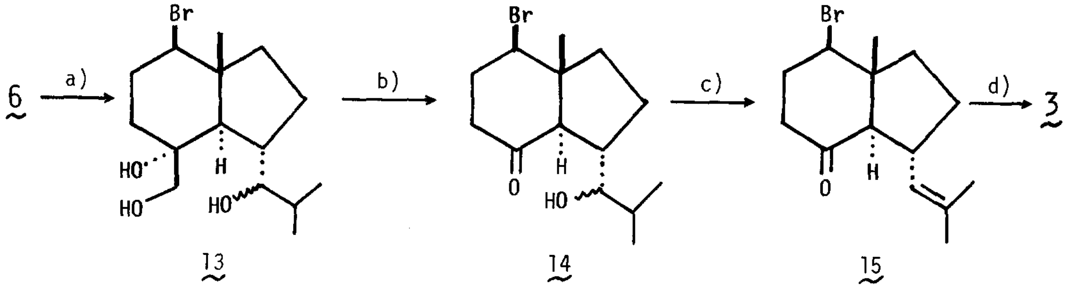
obtained in the case of NBS. However, yields of each compound were relatively low.

Of these bromo compounds (6 - 12), 6 was readily converted into (±)-oppositol (3) [mp 71.5 - 72.5 °C; (-)-3: mp 54 - 55 °C[3]], in 4 steps, as shown in Fig. 2.



a) OsO_4 (1.8 equiv.) - pyridine/dioxane (room temp., 20 h) (~100%). b) $NaIO_4$ (1.5 equiv.)/ aqueous EtOH (88%). c) $POCl_3$ - excess pyridine/CH_2Cl_2 (0 °C - room temp., 2 h) (58%). d) MeMgI (3 equiv.)/Et_2O (0 °C, 30 min) (81%)

Fig. 2. Synthesis of (±)-oppositol (3).

The bromo compounds (10 and 11) were treated with $LiAlH_4$ in THF (0 °C, 30 min) to afford the known α- and T-cadinol (16 and 17) in almost quantitative yields, respectively. The former was subjected to oxidation using OsO_4 (14 equiv.) - pyridine in dioxane to give a triol (18),[10] in 93% yield, which was further treated with MsCl (3 equiv.) in pyridine containing catalytic amount of DMAP to afford (±)-oplopanone (4) [mp 98 - 99 °C; (±)-4: mp 101.5 - 102 °C (lit.)[11]; (-)-4: mp 96 - 97 °C (lit.)[4]] in 63% yield.

The bromo compound (12) with a cis hydroazulene-type carbon skeleton is quite similar to aphanamol I and II, toxic principles of the plant *Aphanamixis grandifolia*.[5] Inspite of our considerable efforts, we have not succeeded in chemical transformation of 12 into aphanamol I and II. However, epoxygermacrene-D (2) was stirred with active Al_2O_3 (20 times in weight) in THF - H_2O (2 : 3) at 40 °C for 3 days to afford a cis hydroazulene (19)[9] in 5.4% yield, in addition to the known oppositol- and selinane-type compounds[2] as main products. The compound (19) was further treated with MnO_2 (11 equiv.) in benzene (refluxing temp., 1 h) under argon atmosphere to give (±)-aphanamol II (5)[5] in 43% yield.

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REFERENCES AND NOTES

1. K. Yoshihara, Y. Ohta, T. Sakai, and Y. Hirose, Tetrahedron Lett., 1969, 2263.
2. M. Niwa, M. Iguchi, and S. Yamamura, Tetrahedron Lett., 1978, 4043.
3. S. S. Hall, D. J. Faulkner, J. Fayos, and J. Clardy, J. Am. Chem. Soc., 95, 7178 (1973).
4. K. Takeda, H. Minato, and M. Ishikawa, Chem. Commun., 1965, 4043.

5. M. Nishizawa, A. Inoue, Y. Hayashi, S. Sastrapradja, S. Kosela, and T. Iwashita, J. Org. Chem., 49, 3660 (1984).
6. Program MM2: N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977); QCPE #395.
7. The yield of **6** varied with relative ratio of the two solvents.
8. The sample ($[\alpha]_D^{30}$ -8.6° (c 3.0, $CHCl_3$)) was obtained from the plant Solidago altissima L. collected in Yokohama late in July, which contained a mixture of (-)- and (+)-germacrene-D in a ratio of 51.4 : 48.6. See M. Niwa, M. Iguchi, and S. Yamamura, Chem. Pharm. Bull., 28, 997 (1980).
9. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: **6** as an oil: $C_{15}H_{25}OBr^{79}$ [m/z 300.1075(M^+)]; $\delta(CDCl_3)$ 0.89 (3H, s), 0.97(3H, d, J= 8Hz), 1.03(3H, d, J= 8Hz), 3.21(1H, dd, J= 2, 10Hz), 4.12(1H, dd, J= 5, 10Hz), 4.81(1H, s), 4.93(1H, s). **7** as an oil: $C_{14}H_{22}OBr^{79}$ [m/z 285.0898(M^+ - Me)]; $\delta(CDCl_3)$ 0.82(3H, s), 1.27(6H, s), 4.05(1H, m), 4.62(1H, s), 4.85(1H, s). **8** as an oil: $C_{15}H_{23}Br^{79}$ [m/z 282.0968(M^+)]; $\delta(CDCl_3)$ 0.85(3H, s), 1.67(6H, s), 4.05(1H, m), 4.48(1H, s), 4.78(1H, s), 4.96(1H, br.d, J= 9Hz). **9**: mp 121.5 - 122 °C; $C_{15}H_{25}OBr^{81}$ [m/z 302.1039(M^+)]; $\delta(CDCl_3)$ 0.84(3H, s), 0.87(3H, d, J= 7Hz), 0.95(3H, d, J= 7Hz), 3.71(1H, t, J= 10Hz), 4.05(1H, dd, J= 5, 12Hz), 4.77(1H, s), 5.05(1H, s). **10**: mp 104 - 105 °C; $C_{14}H_{22}OBr^{79}$ [m/z 285.0843(M^+ - Me)]; $\delta(CDCl_3)$ 0.87(3H, d, J= 7Hz), 0.92(3H, d, J= 7Hz), 1.12(3H, s), 3.93 (2H, s), 5.96(1H, br.s). **11** as an oil: $C_{15}H_{25}OBr^{81}$ [m/z 302.1055(M^+)]; $\delta(CDCl_3)$ 0.80(3H, d, J= 7Hz), 0.93(3H, d, J= 7Hz), 1.24(3H, s), 3.93(2H, s), 6.01(1H, br.s). **12** as an oil: $C_{15}H_{25}OBr^{79}$ [m/z 300.1074(M^+)]; 0.88(6H, d, J= 6Hz), 1.13(3H, s), 4.03(2H, br.s), 4.06 (1H, dd, J= 8, 14Hz), 5.37(1H, br.d, J= 5Hz). **13**: mp 72 - 74 °C; $C_{14}H_{24}O_2Br^{79}$ [m/z 303.0979(M^+ - CH_2OH)]; $\delta(CDCl_3)$ 3.33(1H, dd, J= 3, 11Hz), 3.58(1H, d, J= 12Hz), 3.73(1H, d, J= 12Hz), 3.97(1H, dd, J= 6, 10Hz). **14**: mp 92 - 94 °C; $C_{14}H_{23}O_2Br^{79}$ [m/z 302.0921(M^+)]; IR (film) 3450, 1715 cm^{-1}. **15**: mp 76 - 77 °C; $C_{14}H_{21}OBr^{79}$ [m/z 284.0757(M^+)]; IR (film) 1705 cm^{-1}; $\delta(CDCl_3)$ 1.68(3H, s), 1.85(3H, s), 4.85(1H, br.d, J= 9Hz). **19**: mp 107 - 108 °C; $C_{15}H_{26}O_2$ [m/z 238.1923(M^+)]; $\delta(CDCl_3)$ 0.91(6H, d, J= 7Hz), 1.00(3H, s), 3.45(1H, dd, J= 6, 11Hz), 4.04(2H, br.s), 5.35(1H, br.d, J= 5Hz).
10. (±)-**18**: mp 156 - 157 °C; $C_{15}H_{26}O_2$ [m/z 238.1902(M^+ - H_2O)]; $\delta(CDCl_3)$ 0.81(3H, d, J= 7Hz), 0.92(3H, d, J= 7Hz), 1.11(3H, s), 1.21(3H, s), 3.06(1H, d, J= 8Hz). See Y. T. Lin, Y. S. Cheng, and Y. H. Kuo, J. Chin. Chem. Soc., 17, 111 (1970).
11. D. Caine and F. N. Tuller, J. Org. Chem., 38, 3663 (1973).

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