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BIOMIMETIC REACTIONS OF SOME MACROCYCLIC DITERPENES

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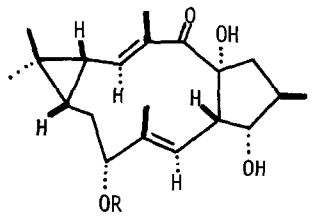
Summary: Some macrocyclic diterpenes derived from euphohelioscopin A and euphornin have been stereoselectively converted into the jatropholane- and daphnane-type compounds and the known tricyclic compound which has been treated with PhCOCl - pyridine to afford euphohelionone, the new type of diterpene isolated from Euphorbia helioscopia L.

A number of toxic diterpenes isolated from Euphorbiaceae have attracted increasing attention because of their antitumor or tumor promoting activity,[1] including the lathylane-, daphnane-, and ingenane-type diterpenes and others. However, these three types of euphorbia diterpene have not yet been synthesized and any chemical interconversion to one another has not been carried out.

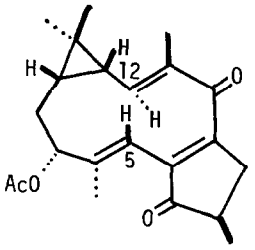
On the basis of biogenetic consideration together with conformational analysis using molecular mechanics calculations, biomimetic reactions of some macrocyclic diterpenes derived from euphohelioscopin A[2] and euphornin[3] have been carried out, giving stereoselectively the jatropholane- and daphnane-type compounds and the known tricyclic compound[3] which has been treated with PhCOCl - pyridine to afford euphohelionone, the first diterpene with stereochemistry different from that of the known lathylane-type diterpenes, as described herein.

The known acetate (1)[2] derived from euphohelioscopin A was subjected to oxidation using Ac_2O (5 equiv.) - DMSO (room temp., 17 h) followed by dehydration with $SOCl_2$ - pyridine in CH_2Cl_2 containing catalytic amount of DMAP (0 C° - room temp., 50 min) to give the corresponding diketotriene (2)[4] in 49% yield. Molecular mechanics calculations[5] of this compound (2) indicate that 2 adopts the most stable conformation [A] (steric energy: 28.1497 Kcal/mol) and its relative population at 25 °C is 99.7% of several possible ones. In addition, the nonbonded distance between C_5 and C_{12} is 2.8075 Å in [A]. In the light of the conformation [A], when treated with $AlCl_3$ (5.6 equiv.) in ether under argon atmosphere (0 °C - room temp., 30 min), 2 was stereoselectively converted into the jatropholane-type compounds (3a and 3b)[6] in 41% yield (3a/3b = 1), in addition to an aldehyde (4)[7] in ca. 20% yield. This experiment strongly suggests the formation process of jatropholone B (5)[8] and crotofolin A (6)[9] in vivo.

Of many euphorbia diterpenes, tetracyclic diterpene esters of the daphnane-type are quite interesting because of their irritant and tumor promoting activity in mice.[1] On catalytic hydrogenation on PtO_2 in MeOH (room temp., 30 min), the trihydroxy compound (7)[2] derived from euphohelioscopin A was converted into a tetrahydro compound (8)[10] in ca. 50%



1 R = Ac
7 R = H



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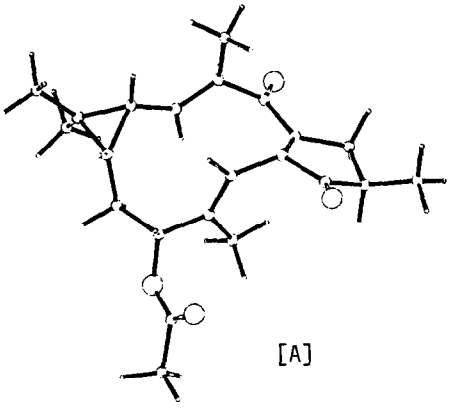
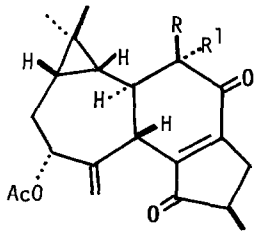
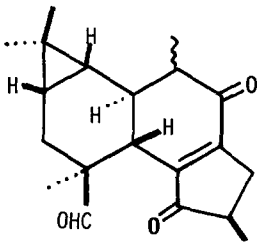


[A]



3a R = H, R^1 = Me
3b R = Me, R^1 = H



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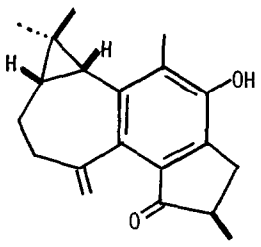

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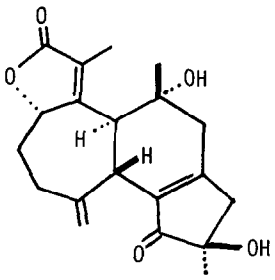

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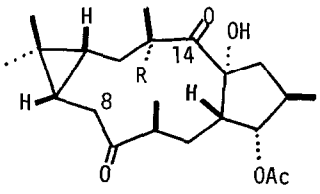
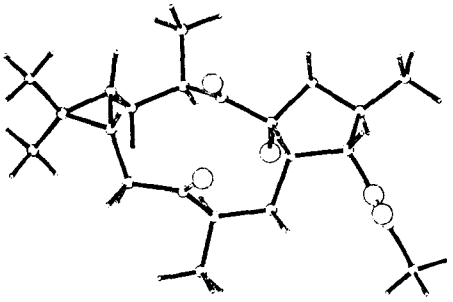
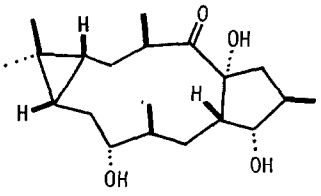


9 R = H
10 R = OH



[B]



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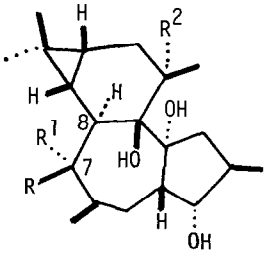
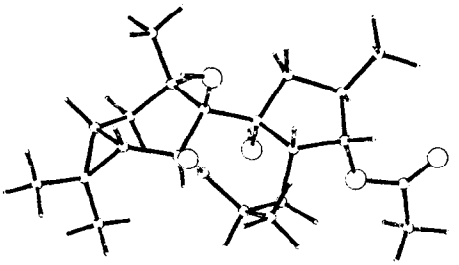


11 R·R^1 = O, R^2 = H
12 R = OH, R^1 = R^2 = H
13 R·R^1 = O, R^2 = OH

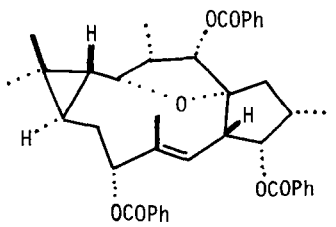


[C]

yield, which was further subjected to acetylation[11] using Ac_2O - pyridine followed by PCC oxidation on celite in CH_2Cl_2 (room temp., 28 h) to afford a desirable diketone (9)[12] in 20% yield, together with an oxygenated diketone (10)[13] in ca. 20% yield. In consideration of the most favorable conforamtion [B][14] (steric energy: 52.5856 Kcal/mol) based on molecular mechanics calculations, the diketone (9) was treated with K_2CO_3 in MeOH (room temp., 2.5 h) to afford a daphnane-type compound (11),[15] in 82% yield, which was further reduced with $LiAlH_4$ in THF (0 °C - room temp., 20 min) to give a tetrahydroxy compound (12)[16] having a newly formed secondary OH group [δ 4.20 (1H, br.s)] in addition to the secondary one at C_3-position. The tetracyclic compound (11) so far obtained has the same stereochemistry as that of many naturally occurring diterpenes of the daphnane-type and adopts the most favorable conformation, as depicted in [C][15] (steric energy: 60.8682 Kcal/mol). According to the same procedure as described above, the compound (10) was also converted into the corresponding daphnane-type compound (13)[17] in high yield.

The lathylane-type diterpenes, which have a cyclopropane ring containing gem-dimethyl group, are regarded as an important precursor of the daphnane- and ingenane-types of diterpene. Interestingly, our considerable efforts have been made to search for new types of euphorbia diterpenes, resulting in the isolation of euphohelionone (14), whose stereochemistry is different from that of the hitherto known lathylane-type diterpenes at the cyclopropane moiety, as described below.

The MeOH extract of the fresh leaves and roots of the plant Euphorbia helioscopia L. (ca. 50 Kg) was partitioned between ether and water. The ethereal extract was further partitioned between 90% aq.MeOH and isooctane. The methanolic extract was subjected to repeated column chromatography on silica gel using a gradient solvent of $CHCl_3$ - MeOH (20~1 : 1) and then hexane - AcOEt (8~2 : 1), and further separated by repeating preparative TLC [Kieselgel PF_{254}; 1) hexane - AcOEt (6 : 1), 2) hexane - AcOEt (3 : 1)] to give 5.2 mg of euphohelionone (14) as a colorless oil: $C_{41}H_{44}O_7$ [m/z 648.3103(M^+)]; IR (film) 1720, 1600, 1580, 1265, and 1110 cm^{-1} (no OH absorption band); ^1H NMR ($CDCl_3$) δ0.10(1H, dd, J= 5.5, 6Hz), 0.90(1H, m), 0.97(3H, d, J= 6.5Hz), 1.01(3H, s), 1.09(3H, s), 1.14(3H, d, J= 7Hz), 1.25(1H, m), 1.84(3H, br.s), 1.93(1H, d, J= 12.5Hz), 2.05(1H, m), 2.28(1H, br.d, J= 15Hz), 2.40(1H, m), 2.46(1H, dd, J= 5.5, 12.5Hz), 3.24(1H, dd, J= 5.5, 10.5Hz), 3.74(1H, dd, J= 3.5, 6Hz), 5.47 - 5.38(2H, complex), 5.59(1H, d, J= 5.5Hz), 5.85(1H, br.d, J= 10.5Hz), and 8.14 - 6.85(15H, complex). Fortunately, deacetyleuphornin (15) was subjected to stereospecific cyclization using p-TsOH in acetone (room temp., 5.5 h)[3] followed by benzoylation with PhCOCl - pyridine (room temp., 2 days) to give euphohelionone (14) in 74% yield.



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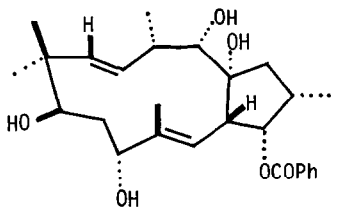

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Calculations were performed at Nagoya University Computation Center. This research has been supported in part by grants from the Ministry of Education, Science and Culture.

References and Notes

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3. Y. Shizuri, S. Kosemura, J. Ohtsuka, Y. Terada, S. Yamamura, S. Ohba, M. Ito, and Y. Saito, Tetrahedron Lett., 25, 1155 (1983).
4. 2: 163.5-166.5 °C (from hexane-AcOEt); $C_{22}H_{28}O_4$ [m/z 356.1968(M^+)]; IR (film) 1730, 1710, 1665, 1240br., and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.85-1.05(2H, complex), 1.13(3H, s), 1.20 (3H, s), 1.25(3H, d, J= 6.5Hz), 1.57(3H, br.s), 1.86(3H, br.s), 2.07(3H, s), 5.16(1H, dd, J= 2, 9Hz), 6.02(1H, br.d, J= 9Hz), and 6.03(1H, br.s).
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6. 3a as a white powder: $C_{22}H_{28}O_4$ [m/z 356.1975(M^+)]; IR (film) 1740, 1715, 1690, 1640, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.6-0.9(2H, complex), 0.94(3H, s), 1.15(3H, s), 1.16(3H, d, J= 6Hz), 1.23(3H, d, J= 6Hz), 2.09(3H, s), 2.95-3.35(2H, complex), 4.33(1H, s), 5.06(1H, s), and 5.30(1H, br.d, J= 10.5Hz). 3b as a white powder: $C_{22}H_{28}O_4$ [m/z 356.1981(M^+)]; IR (film) 1740, 1715, 1690, 1640, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.45-0.75(2H, complex), 0.88(3H, s), 1.11(3H, s), 1.12(3H, d, J= 6Hz), 1.18(3H, d, J= 6Hz), 2.07(3H, s), 2.8-3.3 (2H, complex), 4.30(1H, s), 5.05(1H, s), and 5.32(1H, br.d, J= 10.5Hz).
7. 4 as an oil: $C_{20}H_{26}O_3$ [m/z 314.1880(M^+)]; IR (film) 1720br., 1700br., and 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.55-0.85(2H, complex), 0.89(3H, s), 0.98(3H, s), 1.10(3H, s), 1.17(3H, d, J= 7Hz), 1.22(3H, d, J= 6.5Hz), 2.9-3.3(2H, complex), and 9.72(1H, s).
The stereochemistry of the CHO group is based on the cyclization process of the conformer [A] followed by neighboring participation of the AcO group at C_7-position.
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10. 8: mp 169-173 °C (from hexane-AcOEt); $C_{20}H_{34}O_4$ [m/z 338.2439(M^+)]; IR (film) 3450br. and 1700 cm^{-1}; ^1H NMR (acetone-d_6) δ0.5-0.8(2H, complex), 0.80(3H, s), 0.90(3H, d, J= 6Hz), 1.00(3H, s), 1.03(3H, d, J= 6Hz), 1.10(3H, d, J= 6Hz), 3.20(1H, m), and 4.27(1H, br.d, J= 3Hz).
11. The diacetate as a by-product was quantitatively converted to 8 on hydrolysis with K_2CO_3.
12. 9: mp 141.5-142 °C (from hexane-AcOEt); $C_{22}H_{34}O_5$ [m/z 378.2404(M^+)]; IR (film) 3500, 1740, 1710, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.83(3H, s), 1.00(3H, d, J= 6Hz), 1.10(3H, d, J= 6 Hz), 1.13(3H, d, J= 6Hz), 2.10(3H, s), and 4.92(1H, br.d, J= 5Hz).
13. 10: mp 140-141 °C (from hexane-AcOEt); $C_{22}H_{34}O_6$ [m/z 394.2364(M^+)]; IR (film) 3430, 1735, 1710, and 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.87(3H, s), 0.96(3H, d, J= 6.5Hz), 1.05(3H, s), 1.14(3H, d, J= 6.5Hz), 1.47(3H, s), 2.10(3H, s), and 4.90(1H, br.d, J= 5.5Hz).
14. Of the possible conformers of 9, relative population of [B] is 99.3%.
15. 11: mp 156-156.5 °C (from hexane-AcOEt); $C_{20}H_{32}O_4$ [m/z 336.2288(M^+)]; IR (film) 3600, 3500, 3400, 1700sh., and 1680 cm-1; ^1H NMR ($CDCl_3$) δ0.6-?(2H, some parts of the signal are overlapped with Me signals), 0.96(3H, d, J= 6Hz), 1.03(3H, d, J= 6Hz), 1.05(6H, s), 1.14(3H, d, J= 6Hz), 2.75(1H, m), 3.06(1H, d, J= 8.5Hz), 3.74(1H, br.d, J= 4.5Hz). The conformation [C] is supported by J-value of the doublet at δ3.06 due to C_8-H together with the broad singlet at δ4.20 due to C_7-H in 12 (see ref. 16).
16. 12: mp 218.5-220 °C (from hexane-$CHCl_3$); $C_{20}H_{34}O_4$ [m/z 338.2458(M^+)]; IR (film) 3400 cm^{-1}; ^1H NMR (pyridine-d_5) δ0.8-?(2H, some parts of the signal are overlapped with Me signals), 1.08(3H, s), 1.10(3H, s), 1.10(3H, d, J= 6Hz), 1.22(3H, d, J= 6Hz), 1.43(3H, d, J= 6Hz), 4.02(1H, d, J= 5Hz), and 4.20(1H, br.s).
17. 13 as a colorless oil: $C_{20}H_{32}O_5$ [m/z 352.2268(M^+)]; IR (film) 3400br., 1695, 1070, 1055, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.55-?(2H, some parts of the signal are overlapped with Me signals), 0.87(3H, d, J= 6Hz), 1.00(3H, s), 1.08(3H, s), 1.10(3H, d, J= 6Hz), 1.38(3H, s), 2.80(1H, m), 3.28(1H, d, J= 9Hz), and 3.59(1H, d, J= 4.5Hz).

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