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BIOMIMETIC TRANSFORMATION OF DEHYDROCURDIONE INTO CURCUMENOL AND ISOCURCUMENOL AND THEIR STEREOCHEMISTRIES

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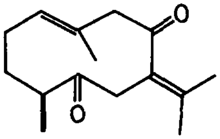
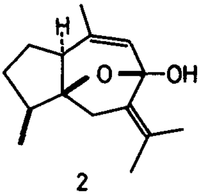
Abstract: Dehydrocurdione, a sesquiterpene isolated from *Curcuma zedoaria*, was converted to curcumenol, isocurcumenol or new spirolactones in a highly selective manner and their absolute configurations were determined.

From the rhizome of *Curcuma zedoaria* Roscoe, various biogenetically related sesquiterpenes have been isolated.$^{1)}$ Dehydrocurdione$^{2)}$ (1), one of the components of *C. zedoaria*, is a unique sesquiterpene having a germacrenedione structure and is considered to be the biogenetic precursor of curcumenol$^{3)}$ (2) and isocurcumenol$^{4)}$ (3) isolated from the same plant.

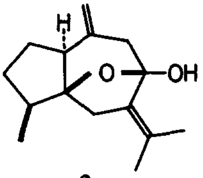
In this communication we wish to report the biomimetic transformations of 1 into 2 and 3. Furthermore, since no stereochemistry has been assigned to these sesquiterpenes, we determined the absolute configurations of dehydrocurdione (1), curcumenol (2) and isocurcumenol (3) as shown below.



1



2



3

Conversion of 1 to 2 or 3 is quite simple and highly selective. When 1 was treated with K_2CO_3 in MeOH or alumina in benzene, curcumenol (2) ($[\alpha]_D$ +385°, lit.$^{3)}$ +397°) was obtained as the sole product in 80% and 87% yields, respectively. On the other hand, pyrolysis of 1 at 230°C under argon afforded isocurcumenol (3) ($[\alpha]_D$ +39.8°, lit.$^{4)}$ +34.0°) in 73% yield together with a small amount of 2. The optical rotations of synthetic 2 and 3 revealed that essentially no racemization took place during the conversions. Interestingly, when treated with acids such as *p*-TsOH, $BF_3 \cdot Et_2O$ or $AlCl_3$, 1 underwent a different type of cyclization giving raise to two spirolactones 4 and 5 (ca. 1:1) in quantitative yield. Extensive spectral analysis$^{5)}$ revealed that 4 and 5 have the same functionalities, namely a sec-Me, a β,β-dimethyl-α,β-unsaturated-γ-lactone and an isopropenyl group. The spiro structures were assigned based on the presence of a quaternary oxygen-bearing carbon by CMR.[5)] In the case of 4 NOE difference spectra revealed the proximity of i) the 14-Me group and H-6, and ii) H-1 and H-4. In 5, however, NOEs were observed between the 14-Me group and both H-6 and H-1 indicating that these compounds are epimeric at C-1. It is noteworthy that the same spirolactones were isolated from the crude drug zedoary, the dried rhizomes of C. zedoaria, although they have not been detected in the fresh plants.

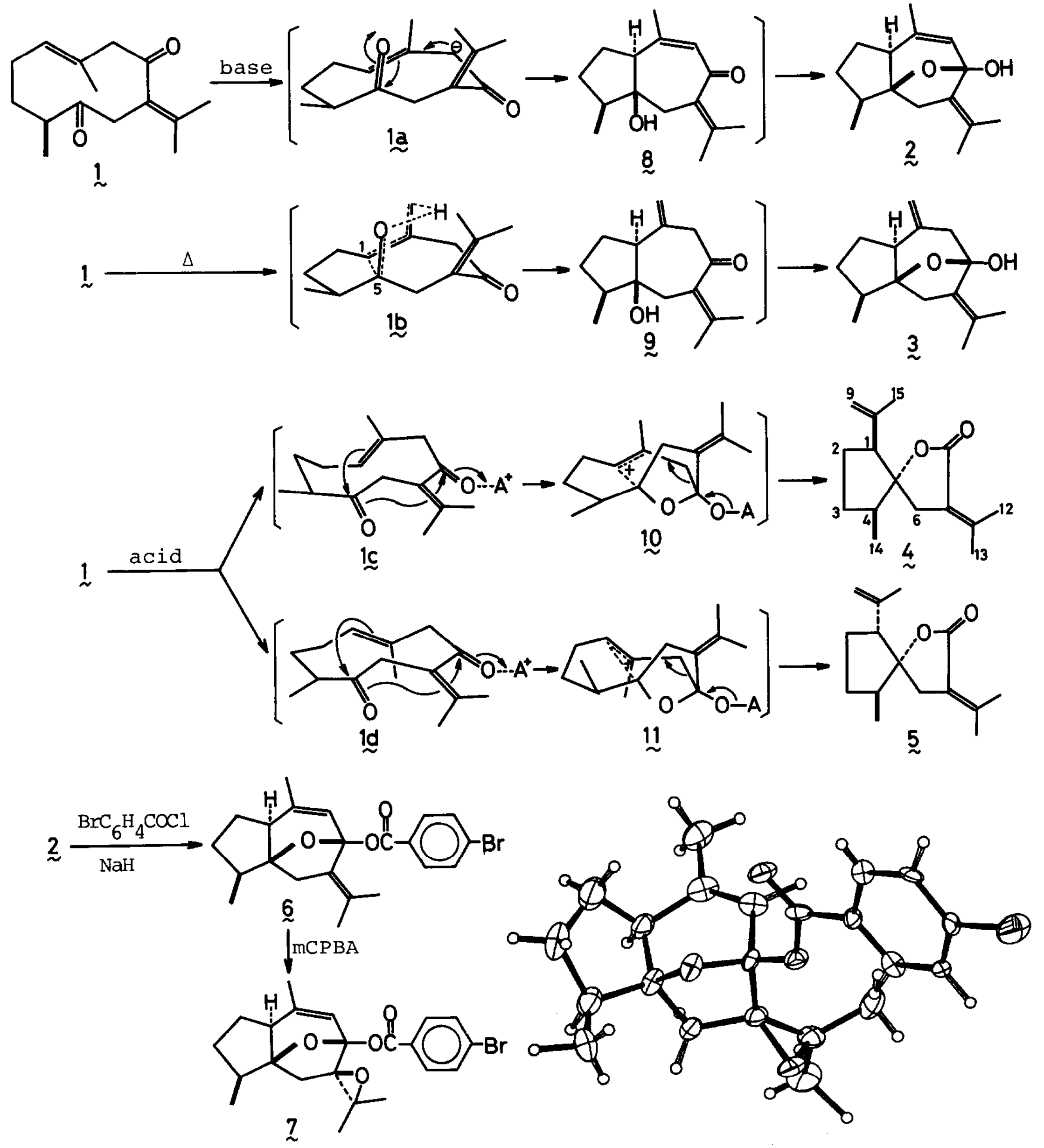


Figure 1

We now turned our attention to the stereostructures of 1, 2 and 3 and the rationalization of the above highly selective conversions. For this purpose, 2 was first converted to the p-bromobenzoate (6), m.p. 99.5-101°C. Since, however, the attempted X-ray analysis was unsuccessful, 6 was transformed into the epoxide[6] (7), m.p. 234-236°C, and the absolute stereochemistry determined by X-ray analysis.[7] The computer generated perspective drawing is illustrated in Figure 1. Since curcumenol (2) and isocurcumenol (3) have already been correlated chemically,[4] the absolute configurations of these sesquiterpenes as well as those of the spirolactones have been determined unequivocally.[9]

The stereostructure suggests that the cyclizations leading to 2 and 3 take place from the same conformation (i.e. 1a[10]) in which the 15-Me and C_5-carbonyl have the same orientation. In the case of base treatment, the anion generated at C-9 initiates the cyclization to give intermediate 8 where the endocyclic double bond is introduced regioselectively. The selective formation of the exocyclic double bond on pyrolysis can be rationalized by assuming that the reaction proceeds through a six-membered ring transition state (1b) and that hydrogen is transferred intramolecularly as in the pyrolysis of preisocalamenediol.[11,12] In contrast, the spirolactones 4 and 5 should be formed independently from different conformations (i.e. 1c and 1d) because no interconversion is observed under the reaction conditions. In this case, coordination of the acid to the carbonyl group of the enone system induces the cyclization and concomitant C-C bond cleavage resulting in the formation of the novel ring system.

We are indebted to Prof. T. Takahashi and Dr. T. Murae, The University of Tokyo, for the measurement of high resolution mass spectra.

References and Notes

1) H. Shibuya, Y. Yamamoto, I. Miura and I. Kitagawa, Heterocycles, **17**, 215 (1982) and references cited therein.

2) H. Hikino, C. Konno and T. Takemoto, Chem. Pharm. Bull. (Tokyo), **20**, 987 (1972).

3) H. Hikino, Y. Sakurai, S. Numabe and T. Takemoto, Chem. Pharm. Bull. (Tokyo), **16**, 39 (1968).

4) H. Hikino, K. Agatsuma and T. Takemoto, Chem. Pharm. Bull. (Tokyo), **17**, 959 (1969).

5) 4: colrless oil, $[\alpha]_D$ -33.0° (c=1.17, $CHCl_3$), m/z 234.1617 ($C_{15}H_{22}O_2$), λ_{max} 235 nm (ε 14000), ν 1738, 1666 cm^{-1}, PMR; δ 0.87(3H, d, J=6.8; 14-Me), 1.18(1H, m), 1.65(1H, m), 1.73(3H, br.s; 15-Me), 1.80(1H, m), 1.84(3H, br. s; 13-Me), 1.92(1H, m), 2.24(3H, br.s; 12-Me), 2.32(1H, m; H_4), 2.47(2H, br.s; H_6), 2.82(1H, dd, J=11.8, 8.8; H_1), 4.76(1H, br.s; H_9), 4.95(1H, br. s; H_9), CMR; δ 13.1(q), 19.9(q), 23.3(t), 23.9(q), 24.3(s), 26.5(t), 27.6 (t), 42.8(d), 52.3(d), 89.6(s), 112.7(t), 120.9(s), 143.8(s), 149.1(s), 169.9(s). 5: colorless oil, $[\alpha]_D$ +24.2° (c=1.44, $CHCl_3$), m/z 234.1612(C_{15}

$H_{22}O_2$), λ_{max} 235 nm (ε 14000), ν 1740, 1644 cm^{-1}, PMR; δ 0.97(3H, d, J=6.4; 14-Me), 1.48-1.64(2H, m), 1.67(3H, br.s; 15-Me), 1.84(3H, br.s; 13-Me), 1.81-1.91(2H, m), 2.02(1H, m), 2.25(3H, br.s; 12-Me), 2.49(1H, br.d, J=16.6 ; H_6), 2.85(1H, t, J=7.8; H_1), 2.87(1H, br.d, J=16.6; H_6), 4.76(1H, br.s; H_9), 4.89(1H, br.s; H_9), CMR; δ 13.1(q), 19.9(q), 22.0(q), 24.4(q), 27.4 (t), 30.8(t), 33.8(t), 45.2(d), 56.0(d), 91.6(s), 114.0(t), 120.8(s), 145.3 (s), 148.9(s), 169.8(s).

6) Spectral properties of **7**: ν 1739, 1667, 1588 cm^{-1}, δ 1.07(3H, d, J=6.3), 1.34(3H, s), 1.37(3H, s), 1.75(3H, d, J=1.3), 1.98(1H, d, J=13.9), 2.14(1H, d, J=13.9), 5.68(1H, br.s), 7.56(2H, d, J=8.7), 7.94(2H, d, J=8.7).

7) Crystal data: $C_{22}H_{25}O_4Br$, orthorhombic prisms, $P2_12_12_1$, $\underline{a}$=12.222(4), $\underline{b}$=12.641(3), $\underline{c}$=13.389(4) Å, V=2068.6(9) Å^3, Z=4. Intensities with 2θ≤55.0 were collected by ω-scan technique on a Syntex P3 diffractometer with graphite-monochromated MoKα radiation. Of the 2686 independent reflections measured, 1583 had $|F_o|>3\sigma(|F_o|)$. The structure was solved by direct and heavy atom methods and refined by the block-diagonal least-squares method to the final R-value of 8.64%.[8] The absolute configuration was determined using the anomalous dispersion of bromine for MoKα radiation.

8) All computations were carried out using the UNICSIII program system (T. Sakurai and K. Kobayashi, *Rep. Inst. Phys. & Chem. Res.*, **55**, 69 (1979).

9) The result showed that **2** is a dehydro derivative of curcumol, the absolute configuration of which has been assigned recently (S. Inayama, J.-F. Gao, K. Harimaya, T. Kawamata, Y. Iitaka and Y.-T. Guo, *Chem. Pharm. Bull.* (Tokyo), **32**, 3783 (1984).

10) Molecular mechanics calculations showed that **1a** is one of the stable conformations. Discussions of the conformations of **1** will be reported elsewhere.

11) M. Niwa, M. Iguchi and S. Yamamura, *Bull. Chem. Soc. Jpn.*, **49**, 3148 (1976).

12) The formation of **2** as a minor product is explained by the fact that the C=O bond tends to be directed towards 9β-H when C_1 approaches C_5 during the bond formation.

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