Two Stable Conformational Isomers of Teucrin P1, a Pentacyclic Clerodane Diterpene

Masaya Morita,[a] Natsuki Kato,*[a] Takashi Iwashita,[b] Koji Nakanishi,[b] Zheng Zeyong,[c] Takashi Yamane,[c] Tamaichi Ashida,[c] and Franco Piozzi[d]

[a] *Department of Agricultural Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan*
[b] *Suntory Institute for Bioorganic Research, Mishima-gun, Osaka 618, Japan*
[c] *Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan*
[d] *Institute of Organic Chemistry, University of Palermo, Via Archirafi, Palermo, Italy*

The cage-structured clerodane diterpene teucrin P1, upon treatment with lithium di-isopropylamide, was converted into another conformational form; both conformers are stable at room temperature and can be isolated as crystals, the *X*-ray crystal structure of form (B) having been determined.

The structure of teucrin P1, m.p. 165—168 °C; $[\alpha]_D$ −13°, has been determined independently by three groups by spectroscopic and *X*-ray studies.[1—3] It is a unique furanoid diterpene with a tetracyclic cage skeleton in which rings B and E adopt boat–boat (b/b) conformations. We have found that this conformational form of teucrin P1 (form A), upon treatment with lithium di-isopropylamide (LDA), is converted into another form (B), m.p. 164—167 °C, the *X*-ray study[4] of which show that rings B/E are now boat–chair (b/c) (Figures 1 and 2).

Treatment of form (A) (0.03 mmol) with LDA (0.06 mmol) in tetrahydrofuran–hexamethylphosphoric triamide, THF–HMPA (10 : 1; 2 ml) at −20 °C and increasing the temperature to 30 °C in 5 min, followed by the usual work-up, purification of the crude product by t.l.c. on Kiesel gel F-254 with EtOAc–n-hexane (50 : 50) as eluant, and recrystallization of the eluted product gave crystals (B), m.p. 164—167 °C (from ether–acetone, 9 : 1), $[\alpha]_D^{22}$ +2.9° (*c* 0.07, $CHCl_3$). The (A) to (B) transformation could not be induced by melting at 170 °C, sublimation at 170 °C *in vacuo*, or by treatment with Bu^{t}OK–Bu^{t}OH or LDA–THF for 30 min at −20 °C.

The ^{1}H n.m.r. spectra ($CDCl_3$) of (A) and (B) were similar except for slight differences in shapes and chemical shifts of the 7β-H and 18-H signals, respectively† (Figure 1) and some nuclear Overhauser enhancement (n.O.e.) values: irradiation of the 12-H signal at δ 5.09 induced 2.8 and 4.9% enhancements, respectively, of the δ 3.95 (18-H in A) and 3.97 (18-H

† N.m.r. data of (A) (360 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* 7.03 Hz, C8-Me), 2.01 (1H, dd, *J* 9.36 and 13.40 Hz, C11β-H), 2.26 (1H, m, *J* 3.99 and 14.57 Hz,[a] C7α-H), 2.28 (1H, m, *J* 3.99, 7.02, and 9.45 Hz,[a] C8β-H), 2.37 (1H, dd, *J* 6.99 and 13.31 Hz, C11α-H), 2.52 (1H, d, *J* 4.34 Hz, C17-H), 2.57 (1H, dd, *J* 1.62 and 4.34 Hz, C17-H), 2.87 (1H, m, *J* 9.45 and 14.57 Hz,[a] C7β-H), 3.95 (1H, d, *J* 11.48 Hz, C18α-H), 4.39 (1H, d, *J* 11.50 Hz, C18β-H), 5.09 (1H, dd, *J* 7.05 and 9.09 Hz, C12α-H), 5.10 (1H, s, C20-H), 6.38 (1H, m, C14-H), and 7.41 (2H, m, C15,16-H). (B) δ 1.06 (3H, d, *J* 7.03 Hz, C8-Me), 2.01 (1H, dd, *J* 9.30 and 13.35 Hz, C11β-H), 2.26 (1H, m, *J* 4.57 and 16.16 Hz,[a] C7α-H), 2.28 (1H, m, *J* 4.57, 7.03, and 10.38 Hz,[a] C8β-H), 2.38 (1H, dd, *J* 6.98 and 13.33 Hz, C11α-H), 2.53 (1H, d, *J* 4.34 Hz, C17-H), 2.57 (1H, dd, *J* 1.67 and 4.34 Hz, C17-H), 2.88 (1H, m, *J* 10.38 and 16.16 Hz,[a] C7β-H), 3.97 (1H, d, *J* 11.50 Hz, C18α-H), 4.39 (1H, d, *J* 11.48 Hz, C18β-H), 5.10 (1H, dd, *J* 7.09 and 9.10 Hz, C12α-H), 5.10 (1H, s, C20-H), 6.38 (1H, m, C14-H), and 7.41 (2H, m, C15,16-H); M^+ *m/z* 344.1645 (calc. 344.1624). [a] *J* values obtained by spectral simulation calculation for higher-order signals.

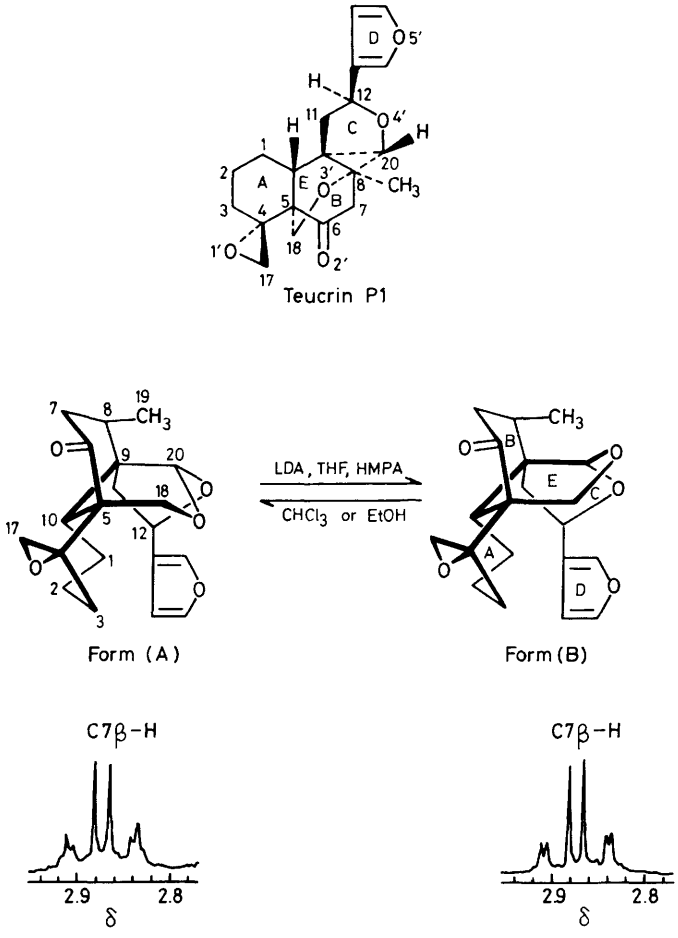

Figure 1. (A) and (B) forms of teucrin P1, and ^{1}H n.m.r. C7β-H. (A) m.p. 165—168 °C, $[\alpha]_D$ −13°; (B), m.p. 164—167 °C, $[\alpha]_D^{22}$ + 2.9°. δ (C18-H_2; 360 MHz, $CDCl_3$) 3.95/4.39 for (A) and 3.97/4.39 for (B), each d, J 11.49 Hz.

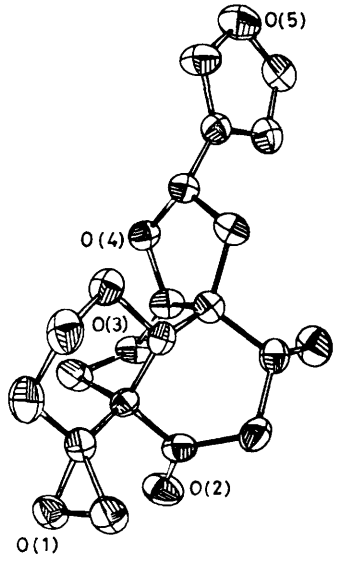

Figure 2. Crystal structure of form (B) of teucrin P1.

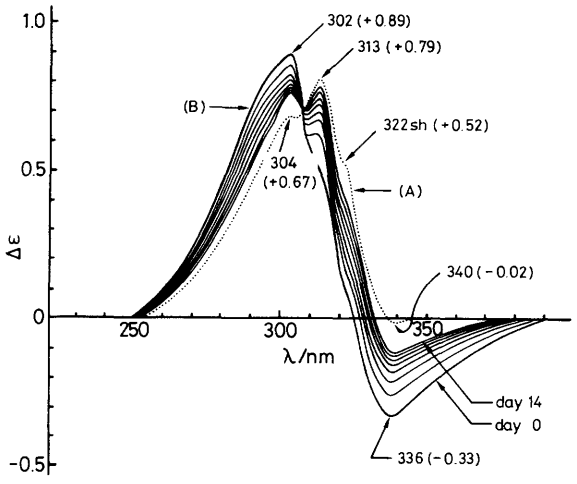

Figure 3. Solid line (——): change in c.d. of teucrin P1 (B) with time. Form (B) (2.24×10^{-2} mol) in $CHCl_3$ was sealed in a cuvette at 25.0 ± 0.1 °C, and the spectra were recorded every 2 days during 14 days. Dotted line (· · · ·): c.d. of form (A) (2.06×10^{-2} mol) in $CHCl_3$, 25.0 ± 0.1 °C; no changes are observed with time.

in B) signals;‡ similarly, irradiation of the 8-Me signal at δ 1.06 caused 9 and 14.2% enhancements, respectively, of the δ 5.10 20-H signals of (A) and (B).‡ In view of this unexpected transformation of (A) into (B), an *X*-ray crystallographic study on (B) was performed,[4] the results (Figure 2) of which showed that ring E adopts a chair conformation in contrast to the boat conformation in (A) (Figure 1).§

Although the c.d. spectra of (A) in EtOH [Δε (296sh nm) +0.89, Δε (303) +0.96 Δε (312sh) + 0.83, and Δε (340) −0.08] and in $CHCl_3$¶ (Figure 3) remained virtually unchanged when left at 20 °C for 30 days, those of (B) in EtOH [Δε (300 nm) +1.11 and Δε (336) −0.32] and in $CHCl_3$¶ (Figure 3) underwent changes during 14 days with an isosbestic point at 307 nm. After 14 days, the solution of (B) gave in 95% yield a *ca.* 1 : 2 mixture of (B) and (A) (separable by repeated t.l.c.); gradual decomposition of the sample occurred when it was left longer at this temperature.

‡ For this irradiation, C14-H and C15,16-H showed enhancements of 3.3 and 4.0%, respectively, for (A) and 3.4 and 3.9% for (B). Furthermore, irradiation of C20-H induced a 2.0% enhancement of C8-Me in both conformers. These n.O.e. values were regarded as references for enhancements of C18-H and C20-H in (B) to (A).

§ Suitable crystals for *X*-ray analysis of teucrin P1 'form (B)' were obtained by repeated recrystallization from ether–acetone, however they converted into disordered crystals containing 74% (A) and 26% (B). The constitution [(A), (B)] of the crystals was consistent with the change [Δε, (A) : (B) *ca.* 7 : 3] of the negative maximum (336 nm) in the c.d. spectrum. *Crystal data*: $C_{20}H_{24}O_5$, M = 344.39, orthorhombic, space group $P2_12_12_1$, T = 24 °C, a = 13.849(4), b = 15.545(3), c = 7.896(2) Å, U = 1699.9(8) Å^3, Z = 4, D_c = 1.34 g cm^{-3}, μ(Cu-$K_{\bar{\alpha}}$) = 7.41 cm^{-1}, F(000) = 736. 1247 Reflections with $F_0 > 2\sigma F_0$ out of 1367 collected were recorded on a Rigaku four-circle diffractometer (2θ ≤115°; θ–2θ scan). The structure was determined by MULTAN. Block-diagonal least-squares refinement led to R and R_w values of 0.048 and 0.064, respectively. O(3) and O(4) are disordered over two sites. Full details will be published in ref. 4. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, issue No. 1, 1986.

¶ The c.d. spectra were recorded in $CHCl_3$ in order to minimize solvent effects in comparisons of c.d. with ^{1}H n.m.r. data. The recorded c.d. value of teucrin P1 (A) was Δε (303 nm) +0.93 in EtOH (ref. 1).

Thus treatment of form (A) with LDA converts it into (B) which when left in $CHCl_3$ or EtOH slowly changes into an equilibrium mixture of (B) and (A); however, (A) remains stable in solution at room temperature. Form (B), produced from (A) with LDA, can be recrystallized from ether–acetone (9 : 1), but when recrystallized from boiling EtOAc or EtOH only crystals of conformer (A) are obtained. These results show that conformer A is the more stable form of teucrin P1, the rationale for which is not clear at this stage.**

Although isolation of two forms of the same compound has been reported for large cyclic tetrapeptide[5] and unsaturated seven-membered ring compounds,[6] we believe teucrin P1 is the first example of a cage-structured polycyclic molecule which can be isolated in two different conformational forms at room temperature.

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** Preliminary attempts with molecular mechanics calculations led to the following slight differences in stability (which differ from the observed): rings B/E = b/b 61.62; c/b 61.32; b/c 61.04; c/c 60.33 kcal mol^{-1} (1 cal = 4.184 J).

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