# 50. 3-Phenyl-$D_3$-Trishomocuban-4-ol: Structure and Configuration

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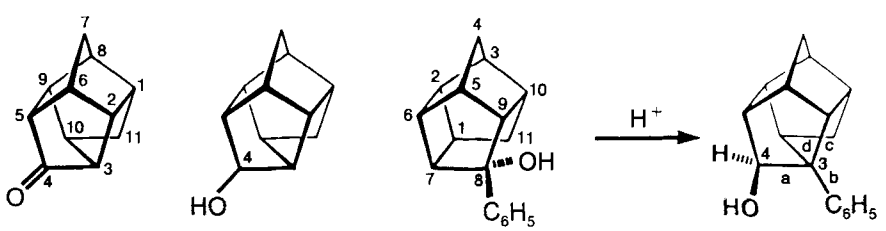
The crystal structure of 3-phenyl-$D_3$-trishomocuban-4-ol (**4**) was determined by X-ray crystallography (*Fig. 1*). Compound **4** was prepared from 8-phenylpentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecan-8-ol in acidic medium. This is a facile method to prepare substituted trishomocubanes with a specific configuration at C(4).

**Introduction.** – Trishomocuban-4-one ( = pentacyclo[6.3.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecan-4-one; = decahydro-1,3,5-methenocyclopenta[*cd*]pentalen-2-one; **1**), trishomocuban-4-ol (**2**), and their substituted derivatives were implicated as likely key substrates for the synthesis of trishomocuban-4-amine with potential biological activity [1–4]. The synthesis of the $D_3$-trishomocubyl system from pentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecane and its derivatives of type **3** involves, for the most reported routes, cationic rearrangement reactions [1] [2] [5]. Several geometrical isomers are subsequently possible depending on the substitution pattern of the pentacyclic skeleton, *e.g.*, four geometrical isomers are possible for disubstituted trishomocubanes of type **4** (3*R*,4*R*), (3*S*,4*S*), (3*R*,4*S*), and (3*S*,4*R*) [6]. We previously reported the acid-catalyzed rearrangement of secondary and tertiary alcohols of type **3** [1] [2]. *Naemura* and coworkers subsequently reported the synthesis of 3-methyl-trishomocuban-4-ol utilizing the optically active methyl-substituted tertiary alcohol corresponding to compound **3** [7]. X-Ray crystallographic data recently provided evidence for a stereospecific rearrangement of the tertiary alcohols using the *Ritter* reaction [8] to yield $D_3$-trishomocubyl system, with a specific configuration at C(4). In continuation of our interest in the synthesis and stereoismerism of the




**1** **2** **3** **4**

$D_3$-trishomocubyl system, we wish to report the structure of phenyl-$D_3$-trishomocubane-4-ol (**4**), prepared from 8-phenylpentacyclo[5.4.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecan-8-ol [9] (**3**), and the determination of the configuration at C(4).

**Experimental.** – Colourless single crystals were obtained by slow evaporation from a $CHCl_3$ soln. of (3*S*,4*S*)-3-phenylpentacyclo[6.3.0.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$]undecan-4-ol (**4**). The crystallographic data are the following: $C_{17}H_{18}O$, $M_r$ 238.3, monoclinic symmetry; space group $P2_1/c$, with $a = 13.371(6)$, $b = 25.447(12)$, $c = 15.355(8)$ Å, $\beta = 106.27(4)°$, $V = 5015.47$ Å$^3$, $Z = 16$ (4 independent molecules), $D_x = 1.26$ g·cm$^{-3}$, $F(000) = 2048$, Cu$K_\alpha$, $\lambda = 1.54184$ Å, $\mu = 5.5$ cm$^{-1}$, $T$ 300 K. This unusual $Z$ value in the monoclinic system, leading to 4 independent molecules, prompted us to check carefully the *Niggli*-matrix values to be sure of the crystal lattice. There is no relationship between the $S_{ii}$ values ($S_{11} = 179.1021$, $S_{22} = 652.8317$, $S_{33} = 235.8714$) and the $S_{ij}$ values ($S_{32} = -0.6774$, $S_{31} = -57.5132$, $S_{21} = 0.4321$). There is a pseudo-relationship between the cell parameters with $a \cdot \sin\beta \neq b/2$ suggesting a tetragonal symmetry with $a' = b' \neq a \cdot \sin\beta$ or $2a.\sin\beta$, and $c' = c$. However, it is impossible to transform a monoclinic cell into a tetragonal cell. Nevertheless, this pseudo-4-fold symmetry was observed between the 4 independent molecules. The selected crystal was a block of dimensions 0.27 × 0.25 × 0.20 mm. The unit cell dimensions were determined using the least-squares fit from 25 reflections ($\theta < 20°$). Intensities were collected with an *Enraf-Nonius-CAD4* four-circles automatic diffractometer using the Cu$K_\alpha$ radiation and a graphite-oriented monochromator up to $\theta = 65°$ (scan type $\omega/\theta$, scan width 1.5°). No intensity variation of 2 standard reflections measured every 90 min was observed. The instrument instability factor was 0.040. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Of 8520 measured unique reflections, 4853 were considered as observed ($3\sigma(I)$ criterion) and included in the refinement. The structure was determined by the direct methods using MOLEN [10]. Calculations were performed on a *MicroVAX-3100/80* computer. The scattering factors were taken from [11]. The best solution gave most atoms of the four independent molecules. C- and O-Atoms were refined anisotropically. The H-atoms were placed in theoretical positions or were located, when necessary, from difference *Fourier* maps and refined isotropically. The unweighted agreement factor was $R = 0.051$ and $R_w = 0.049$ for 937 refined parameters. The convergence largest shift was 4.61; the highest and lowest peaks in the final difference map were 0.30(4) and −0.10(4) e/Å$^3$.

The atomic coordinates, were deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, U.K.

**Results and Discussion.** – A perspective view of molecule 1 with the numbering of atoms is given in *Fig. 1*. In the text and in the supplementary material (*CCDC*), 100 has been added to these numbers in molecule 1, 200 in molecule 2, 300 in molecule 3, and 400 in molecule 4.

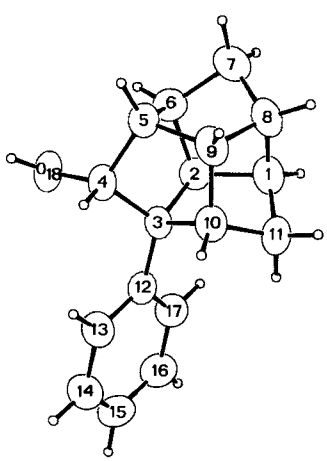



Fig. 1. *Perspective view of molecule* **4**, *with atomic numbering*

Structural features unique to the $D_3$-trishomocubane skeleton are also observed for the structure of **4** as previously described by *Marchand et al.* [12] and us [9], *i.e.* the half-chair conformations of the six cyclopentane rings and the non-eclipsed arrangement of the methine H-atoms. The X-ray structure of **4**, which has (*S*)-chirality at C(3), indicates (*S*)-configuration at C(4). Conversely, (4*R*)-configuration is implicated for 3-phenyl-trishomocuban-4-ol with (3*R*)-configuration. The identical configuration at C(3) and C(4) was also observed for the related amino-substituted biologically active derivative prepared by the *Ritter* reaction [3] [9].

These results clearly indicate that tertiary alcohols of type **3** rearrange specifically to the $D_3$-trishomocubyl system producing a preferred configuration at C(4). A similar mechanism for the rearrangements of these tertiary alcohols is implicated, *i.e.* an $S_N2$-type mechanism. *Coxon* and coworkers [13] recently reported the unusual acid-catalyzed rearrangement of a tertiary alcohol of a tetracyclic pentadecane *via* an intramolecular nucleophilic capture [14]. Similarly, the rearrangement of the deuterium-labelled secondary alcohol of type **3** (D instead of Ph) yielded a mixture of deuterium-labelled trishomocuban-4-ols, indicating multiple rearrangement mechanisms for the secondary alcohol [15]. The stereospecificity of the rearrangement of tertiary alcohols suggests a unique stabilization of the carbocation species during the acid-catalyzed rearrangement of tertiary alcohols to yield skeleton-substituted trishomocubanes with a specific configuration at C(4).

As mentioned in the *Exper. Part*, the 4 'independent' molecules derived one from another by a pseudo-4-fold axis in a general (*x*,*y*) position and about parallel to O*z*. There are four consequences: *i*) the conformations of the 4 'independent' molecules are almost identical and are similar to the conformation found for 3-methyl-trishomocuban-4-amine hydrochloride monohydrate [8] (*Fig. 2*); *ii*) the 4-molecules pattern forms a crown; *iii*) the 4 OH groups are directed towards the center of the crown and are linked together *via* H-bonds, ensuring the cohesion of this particular pattern (O(118)–O(318) = 2.766(4) Å, O(118)–O(418) = 2.740(4) Å, O(218)–O(318) = 2.746(4) Å, and O(218)–O(418) = 2.736(4) Å; *Fig. 3*); *iv*) the 4 Ph rings are located with the hydrophobic skeleton on the outside of the crown; the centers of these rings are *ca.* 5.8 Å distant and almost coplanar, the rings themselves are oriented at *ca.* 70°.

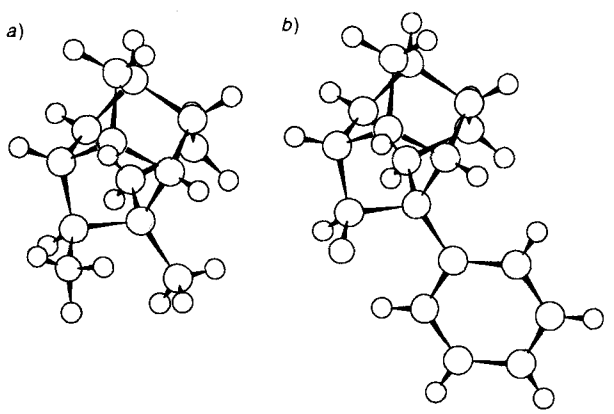



Fig. 2. *Comparison of the conformations* a) *of protonated 3-methyl-trishomocuban-4-amine and* b) *of 3-phenyl-trishomocuban-4-ol* (**4**)

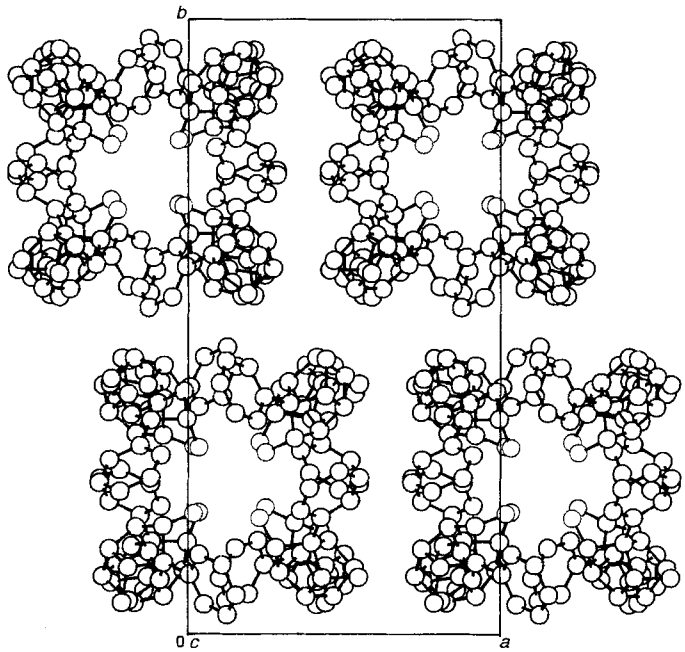



Fig. 3. *A (xy0) projection of the monoclinic cell showing the packing of the molecules* **4** *and the particular 4-fold arrangement*

**Conclusion.** – The synthetic route described in this study provides a facile method to prepare 3-substituted trishomocubanes with a specific configuration at C(4). Contrary to the 3-methyl-trishomocuban-4-amine hydrochloride monohydrate, the 3-phenyl-trishomocuban-4-ol molecules arrange themselves in the crystals to form a pseudo-4-fold pattern. The cohesion of this pattern, forming a crown, is ensured by strong intermolecular H-bonds. The cohesion of the crystals is ensured by hydrophobic interactions between the crowns. The existence of such a pseudo-4-fold axis is unusual in the monoclinic system. The absence of relationship between the monoclinic cell and a pseudo-tetragonal cell was checked carefully.

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