The Absolute Configuration of Colchicine by Correct Application of the *CIP* Rules

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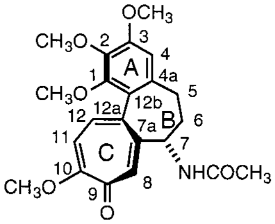
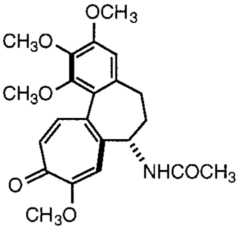
Dedicated to the memory of Prof. *Vladimir Prelog*

The absolute configuration of natural (−)-colchicine is (*aR*,7*S*)

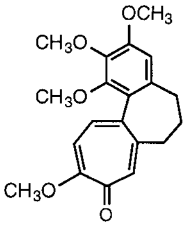
Colchicine, **1**, the principal alkaloid from *Colchicum autumnale*, is a well-known antimitotic drug, which has been extensively studied for many years. The molecular structure of colchicine was first suggested by *Dewar* [1]. The structure was firmly established a few years later by chemical degradation [2], X-ray analysis [3], and confirmed by several total syntheses, first by *Eschenmoser* and co-workers in 1959 [4].



(−)-(7*S*)-Colchicine (**1**)



Isocolchicine (**2**)



Deacetamidocolchicine (**3**)

Natural (−)-colchicine has a stereogenic atom C(7) and an axis of chirality, as the benzenoid A-ring and the troponoidic C-ring are twisted 53° with respect to each other as shown above in **1**. Both chemical and X-ray crystallographic methods agree on the absolute configuration at C(7) as well as about the phenyl-tropone axial configurations. The importance of the helicity has been clearly demonstrated. Thus, for deacetamidocolchicine **3**, which can be resolved into enantiomers, only the enantiomer with the same helicity as natural colchicine binds to tubulin [5]. Consequently, the helicity is of major importance for the understanding of the biological properties of colchicine and its analogues. So, what's the fuss? As will be seen below, the axial configuration has been erroneously assigned as (*aS*) for a long time in the literature.

The relative configuration was determined by the first X-ray crystallographic work [3], followed by numerous crystallographic studies on various colchicinoids (see, *e.g.*, [6]). These studies agree on the relative helicity of the biaryl moiety; the substituent at C(7) prefers an equatorial orientation, which induces preference in the A- and C-ring backbone conformation. The atropisomer with reversed helicity has never been observed for colchicine, but is often present as a minor conformer in solutions of isocolchicine **2** and its derivatives. The assignment of the absolute configuration was never given any attention in these crystallographic papers. A conclusive determination of the absolute configuration was achieved with the X-ray analysis of thiocolchicoside, a β-D-glucoside derivative of known configuration, however, without mention of its stereochemical implications [7]. Hence, the absolute configuration of colchicine is as in **1**, also shown in a stereoview in *Fig. 1.*

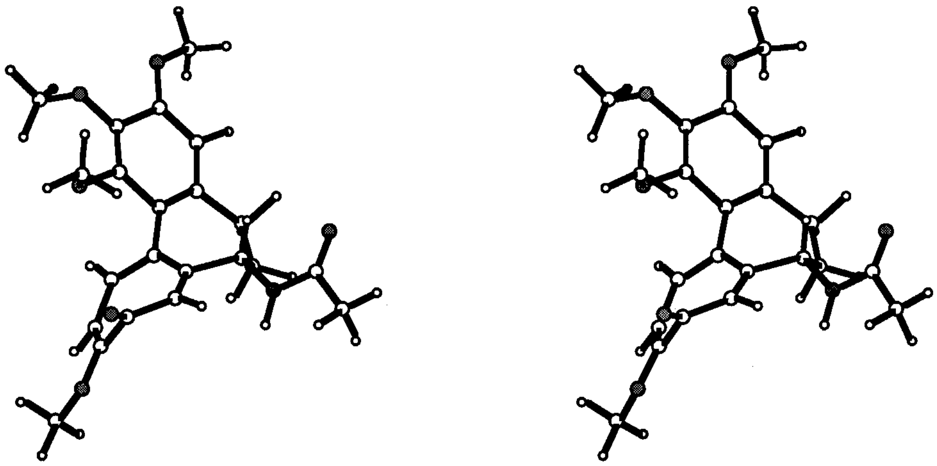


Fig. 1. *Stereoview of (7S)-colchicine* (**1**) *as calculated by the MM2 force field*

The first assignment of the helical configuration of colchicine was reported by *Detrich et al.* [8] as (*R*) without further comment. In 1988, *Brossi* and co-workers treated the helicity of colchicine and analogues and its importance for tubulin-binding and antimitotic effect [9]. By reference to the *IUPAC* rules [10], they assigned the configuration (*aS*,7*S*) to natural (−)-colchicine. This assignment has since been used throughout the literature, including our own publications [5][6i,h]. As will be shown below, this assignment was wrong.

Application of the rules of *Prelog* and *Helmchen* [10] (adopted by *IUPAC*) to colchicine is shown in *Fig. 2.* Accordingly, the configuration of colchicine is (*aR*,7*S*).

Fig. 2. *Schematic representation of the chirality rule to colchicine using the atom numbering from* **1**

Every chemist knows how easy it is to allocate an incorrect assignment to a stereocenter of known absolute configuration by plain mistake. A misinterpretation, however, seems to be responsible for the erroneous nomenclature in the assignment of the axial chirality of colchicine. Using the chirality rule, all four ligands were considered tetrahedrally arranged and treated as a stereogenic atom, neglecting the first paragraph of the sequence rule: nearer end of axis or side of plane precedes further. Without this rule, the configurational assignment of C_2-symmetrical biphenyls and analogous compounds would not be possible.

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