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Lupulin structures revisited

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The crystal structures of lupulin A, $C_{30}H_{46}O_{11}$, and lupulin D, $C_{25}H_{38}O_8$, should both display the neoclerodane skeleton, but the deposited atomic coordinates of lupulin D correspond to the inverted enantiomer.

Comment

The X-ray analysis reports for the isolates from *Ajuga lupulina*, *viz.* lupulin A (Chen *et al.*, 1997) and lupulin D (Chen, Tan, Liu, Liu & Chen, 1996) (also called clerodinin B; Lin *et al.*, 1989), show contradictory graphical information. The simpler structure of lupulin D, as shown in Chen, Tan, Liu, Liu & Chen (1996) (Fig. 1 of the paper = Fig. 1*a* here), could be described as 15α-methoxydihydroclerodin (but is named 3-deoxy-14,15-dihydro-15-methoxycaryoptinol). The formula shows the corresponding neoclerodane skeleton with a few stereochemistries undisclosed. The 15α-methoxy substitution (discussed as C17 in the *Comment*, according to the atom-numbering scheme in Fig. 1 of the paper) was 'in agreement with the structural elucidation of Lin *et al.* (1989)'. However, this Fig. 1 displays the view with displacement ellipsoids of an *ent*-neoclerodane structure with a 15α-methoxy substitution. Thus, the deposited atomic coordinates must correspond to the inverted enantiomer of lupulin D [Cambridge Structural Database (Allen, 2002) refcode TEHZOV, Fig. 1*b*] and, further, the correct stereoformulae should be revised to 15β-methoxydihydroclerodin [see revised lupulin D in Fig. 1*c*]. As a consequence, the early C-15 stereochemical assignments for clerodinins A and B (Lin *et al.*, 1989) must also be reversed. The reversal of the previously assigned stereochemistries at position C-15 for both clerodinins A and B (change from β to α and from α to β, respectively), was already proposed by Ben Jannet *et al.* (1999) from the results of NMR NOESY experiments reported for hativenes A–C.

The structures of lupulin A and lupulin B were first elucidated by spectroscopic means (Chen, Tan, Liu, Zhang & Yang, 1996) and reported as 15β-methoxy (Fig. 2*a*) and 2-deoxy-15α-methoxydihydroajugapitin, respectively, by comparison with NMR data of clerodinin A and clerodinin B. Lupulin A

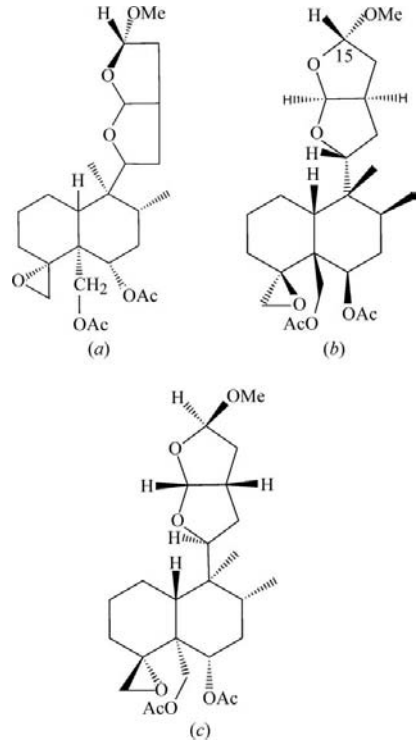

Figure 1
Lupulin D in Chen, Tan, Liu, Liu & Chen (1996), showing (*a*) the formula shown in the original paper, (*b*) the structure according to deposited data (TEHZOV) showing an *ent*-neoclerodane skeleton, and (*c*) lupulin D/clerodinin B (revised) showing the neoclerodane skeleton and the 15β-methoxy substitution.

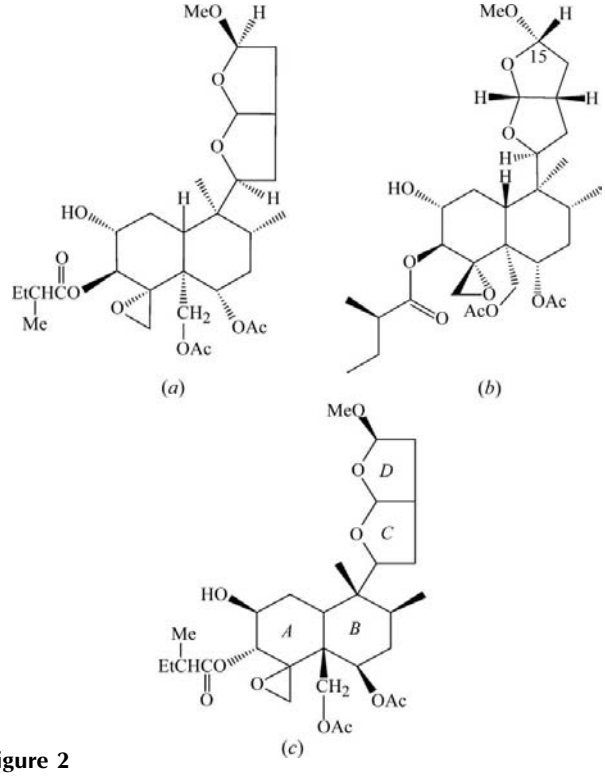

Figure 2
Lupulin A according to (*a*) Chen, Tan, Liu, Zhang & Yang (1996) and to deposited data RAVWUG, (*b*) (revised) showing the neoclerodane skeleton and the C-15 α-substituent, and (*c*) the stereoformula shown in Chen *et al.* (1997).

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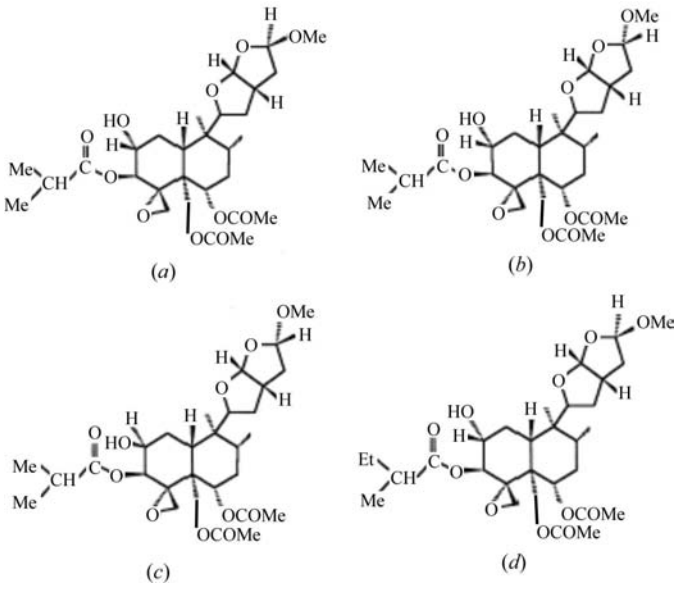

Figure 3
Structures of (*a*) hativene A, (*b*) hativene B, (*c*) hativene C and (*d*) uncorrected lupulin A in Ben Jannet *et al.* (2000).

showed strong antibacterial activity, and accordingly, it should be the compound studied by means of X-ray crystallographic analysis (Chen *et al.*, 1997) (confirmed by melting point and empirical formula). This X-ray report shows the neoclerodane structure of 15α-methoxydihydroajugapitin (Fig. 2*b*) in the view with displacement ellipsoids. In this instance, quite unexpectedly, opposite graphical displays were again shown. There, the stereoformula displayed was the inverted enantiomer *ent*-neoclerodane 15β-methoxydihydroajugapitin (Fig. 2*c*).

Furthermore, this X-ray structure already points out the reversal of the previously assigned stereochemistries at position C-15 for lupulins A and B (change from β to α and from α to β, respectively), based on NMR data. As already mentioned for clerodinins A and B, the reversal of the stereochemistries at C-15 for lupulins A and B had been already proposed from the results of NMR NOESY experiments (Ben Jannet *et al.*, 1999, 2000). Unfortunately, the structure depicted in both papers for lupulin A (as shown in Fig. 3) was yet the uncorrected 15β-methoxydihydroajugapitin analogous to hativene A, rather than the revised proposal analogous to hativene B.

In summary, lupulin A should display a revised 15α-methoxyneoclerodane structure (Fig. 2*b*), whereas lupulin B and lupulin D (Fig. 1*c*) display a 15β-methoxy neoclerodane structure.

Note added in proof. The authors acknowledge Professor Hichem Ben Jannet for kindly providing a reprint (Ben Jannet *et al.*, 2002) reporting the 'Structure of a new neoclerodane diterpenoid from *Ajuga pseudoiva*'. The compound was named hativene D, being in fact elucidated as the 15-epimer (15α-MeO) of the uncorrected structure reported for lupulin A (Fig. 3*d*, 15β-MeO). However, the reported NMR data (an extended set showing a few corrections and assignment changes likely based on HMQC or HMBC spectroscopic data) match, not unexpectedly, quite well those of lupulin A, since the proposed structure revision points out the identical nature of hativene D and lupulin A.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG9000). Services for accessing these data are described at the back of the journal.

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