Proposed Conventions for Describing Germacranolide Sesquiterpenes

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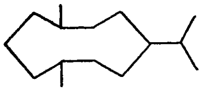
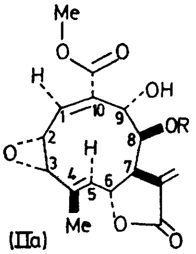
Summary An attempt is made by proposing new conventions to avoid the ambiguity and confusion implicit in the present method of representing germacranolides in two dimensions.

The representation in two dimensions of the stereochemistries and conformations of the germacranolides is a notorious problem. During our work on melampodin[1] we identified two sources of confusion; so, to resolve them, we here put forward new rules for discussion and possible adoption.

(A) *Assignment of the α and β faces and numbering of the ring.* The familiar conventions for drawing and numbering sterols, selinanes, *etc.* are unambiguous because the carbon skeleta are asymmetric. However, the skeleta of the germacranolides are symmetric† and thus incapable *by themselves* of defining the α and β faces uniquely. Kupchan, Kelsey, and Sim[2] (KKS) in 1967 proposed a convention to meet this difficulty, in which the ring is drawn with the alkyl group β at C(7), and with the ring numbering running anticlockwise. However, the numbering produced by these rules is *ambiguous until the absolute configuration is known.* Thus, until the absolute configuration (IIa) of melampodin was determined, the formulae for the two enantiomorphic alternatives required by the KKS rules were (IIa) and (IIb), and they were equally valid despite the fact that the numbering of the rings (and, therefore, the corresponding positions of the substituents) differ, and that the double bonds have apparently moved (Δ^4 *trans*, $\Delta^{1(10)}$ *cis* $\rightarrow \Delta^9$ *trans*, Δ^3 *cis*). Examples of both types of representation, (Δ^4, $\Delta^{1(10)}$) and (Δ^3, Δ^9), continue to appear in the literature for compounds before their absolute configuration is known, and this has led to considerable confusion and correspondence. We consider that this convention is unacceptable as (i) it can only be applied when C(7) is tetrahedral and (ii) it is ambiguous in numbering and ring aspect if used before the absolute configuration is known. We consider it preferable to represent enantiomorphs by formulae such as (IIa) and (IIc) [*i.e.* the rotamer of (IIb)] which retain the same aspect of the ring and numbering of its atoms. We, therefore, base the following rule on some asymmetric feature of the ring rather than on the configuration at C(7).


(I)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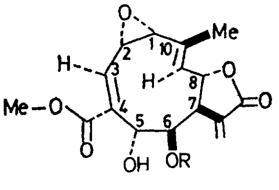
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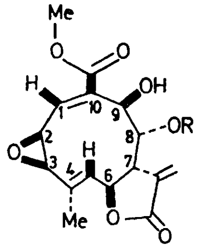
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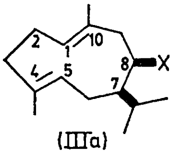
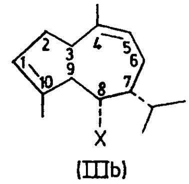

(IIIa)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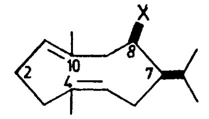
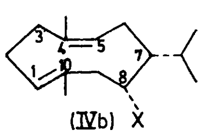
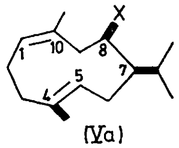
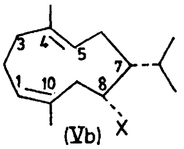
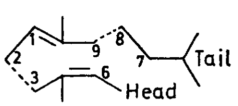

(IVa)


(IVb)


(Va)


(Vb)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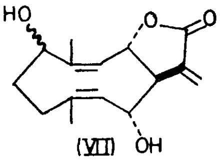
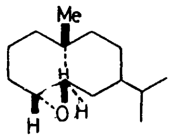
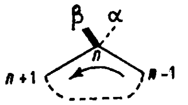
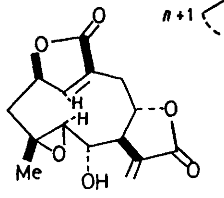

(VII)


(VIII)


(IX)


(X)

Rule 1 The distinction between the α and β faces shall be based on any evidence which can be firmly related to the asymmetry of the molecule's mode of biogenesis, *e.g.* positions of double bonds or their equivalents (*e.g.* epoxides), patterns of oxygen functions that are indicative of the former positions of the double bonds, or, in the last resort,

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† So too are the skeleta of the cembranolides. The considerations and rules presented here may have some relevance to the much discussed problems of their nomenclature.

tracer studies. The α and β faces and the atom numbering shall conform to diagrams such as (IIIa) (germacrolides), (IVa) (heliangolides), or (Va) (melampolides),[1] in which *the actual or masked double bonds are standardised in the* Δ^4, $\Delta^{1(10)}$ *positions and the numbering runs anticlockwise.* This particular choice ensures that cyclisation products conform to established conventions for the selinanes, sterols, *etc.*, and that in all cases known to us it gives the same results as the KKS rules do for compounds of known chirality. The rule implies that the head–tail sequence in the farnesyl precursor runs *clockwise* in our choice of diagram [see (VI)]. Indeed this statement could be regarded as an alternative way of defining the β face of the ring.

If ever it is necessary to flip the molecule over to view it from the α side [*cf.* (IIIa), (IVa), (Va) with (IIIb), (IVb), (Vb)], it is imperative to reverse the numbering sequence as shown and to be careful that the *cis–trans* character of the double bonds is correctly reproduced. In this respect (IVb) and (Vb) are acceptable non-standard variants, but (IIIb) is not as Δ^4 and $\Delta^{1(10)}$ have changed from *trans* to *cis*.

Rule 2 The chiralities at all the dissymmetric ring atoms if known shall be given explicitly in the *R,S* notation.[3] If only relative configurations are known, this notation can still be used (as R_a, S_a) in relation to an assumed disposition α for H(7). Herz and Bhat[4] and McClure *et al.*[5] have asserted that all germacranolides of known chirality have H(7) α, but such a statement was no more than the consequence of applying the first KKS rule, for, as shown above, any germacranolide can be drawn with H(7) either α or β if one is not bothered by the consequent change in numbering, and the KKS rules are not.

Using the new convention we found one apparent exception to this generalisation, eupatoriopicrin.[6] It was discussed by KKS, who, putting H(7) α, were willing to accept double bonds in the Δ^3 and Δ^9 positions. We prefer to keep them in the Δ^4, $\Delta^{1(10)}$ positions, and, when necessary as here, to accept H(7)β. Recently, however, the chirality of this compound has been re-examined and reversed;[7] it is, therefore, no longer an exception. So, until a proven exception is found, it seems legitimate to retain the first KKS rule as a supplementary means of distinguishing the α and β faces. However, the resulting ambiguity of the numbering rule must not be forgotten.

One can devise compounds that cannot be handled immediately by the new rules, and a few have recently been discovered. Thus tatridin [(VII); nature of the double bonds unspecified: unpublished work by Geissman] does not have its double bonds correctly related to C(7). Its reactions and congeners, however, indicate that it has come from a precursor like (IVa), so it could at least be given a tentative numbering. Liatrin and eupacunin,[8] are two other examples that can be dealt with in a similar way.

(B) *Drawing the ring.* *X*-Ray studies of germacranolides have shown (a) that the ring is often very contorted and has no standard shape, (b) that both *cis* and *trans* endocyclic double bonds can occur, and (c) that such bonds—especially the *trans* variety—usually lie with their planes nearly perpendicular to the ring and thus have substituents α or β orientated. It is difficult enough to render these features with any accuracy in a two-dimensional schematic diagram, but we have discovered that published diagrams are being interpreted in two, sometimes different, ways. Some readers treat each ring atom in isolation as if it were a member of an acyclic chain, and thus find diagrams such as (VIII) ambiguous, even incomprehensible. Others, using the analogy of the sterols, *etc.*, regard all substituents as being defined with respect to the α or β faces of the ring at the vertex concerned. We propose, therefore:

Rule 3 At tetrahedral ring atoms the conventional symbols (—, - - -) shall relate to the β, α faces of the ring and will be used exactly as in the sterols. The geometry and numbering at each vertex will be of the form (IX) and hydrogen atoms will not normally be shown explicitly. Re-entrant angles should be avoided at tetrahedral ring atoms unless they correspond to reality, and then (and only then) the substituents should be drawn inside the ring.

Rule 4 The terms *cis* and *trans* when applied to endocyclic double bonds indicate the sequence of *ring* bonds. The perimeter of the ring may be drawn in any way that clearly portrays the *cis–trans* character. If the plane of such a double bond is known to be roughly perpendicular to the macrocycle, we shall indicate which of its two possible orientations occurs by borrowing the above symbols to denote the orientation of its substituents α *or* β *to the general plane of the macrocycle.* Epoxide rings formed across *trans*-double bonds have given special trouble, but, as the epoxide ring can be regarded as an extension to the macrocycle, we suggest that they can most simply be represented as in the Figure. Elephantol (X) contains an example and shows rather well the ability of these conventions to convey a maximum of information with a minimum of drawn detail. Several other structures drawn according to these rules appear in the preceding note on melampodin.[1]

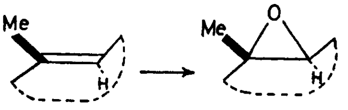

FIGURE.

These proposals owe much to correspondence with Professors Sutherland, Fischer, and Herz, and have their support. Approval has also been indicated by Messrs. Barton, Guissman, Kupchan, Mabry, Ourisson, Overton, and Sorm, who have offered useful comments for which we are grateful.

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[1] S. Neidle and D. Rogers, *Chem. Comm.*, preceding communication.
[2] S. M. Kupchan, J. E. Kelsey, and G. A. Sim, *Tetrahedron Letters*, 1967, 2863.
[3] R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Intern. Edn.*, 1966, **5**, 385.
[4] W. Herz and S. V. Bhat, *J. Org. Chem.*, 1970, **35**, 2608.
[5] R. J. McClure, G. A. Sim, P. Coggon, and A. T. McPhail, *Chem. Comm.*, 1970, 128.
[6] L. Dolejš and V. Herout, *Coll. Czech. Chem. Comm.*, 1966, **31**, 2899.
[7] R. W. Doskotch and F. S. El Feraly, *J. Org. Chem.*, 1970, **35**, 1928.
[8] (a) S. M. Kupchan, V. H. Davies, T. Fujita, M. R. Cox, and R. F. Bryan *J. Amer. Chem. Soc.*, 1971, **93**, 4916; (b) S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, T. Fujita, P. D. Cradwick, A. D. V. Hardy, and G. A. Sim, *J. Amer. Chem. Soc.*, 1971, **93**, 4914.