Stereochemistry of Theaspirone and the Blumenols

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Summary The stereochemistry of theaspirone (**9**), blumenol A (**5**), and blumenol B (**8**) has been established; a stereospecific preparation of theaspirones is also described.

In connection with studies[1] on (+)-abscisic acid (ABA), the plant growth regulator, to which the absolute configuration (**7**) has been assigned,[1,2] we have carried out experiments which elucidate the full stereochemistry of blumenol A (**5**)[3] and blumenol B (**8**).[3] The absolute configuration of (−)-theaspirone,[4–6] an important component of tea aroma, has also been established as (**9**). In addition the effect of γ-substituents on the c.d. of conjugated enones is discussed.

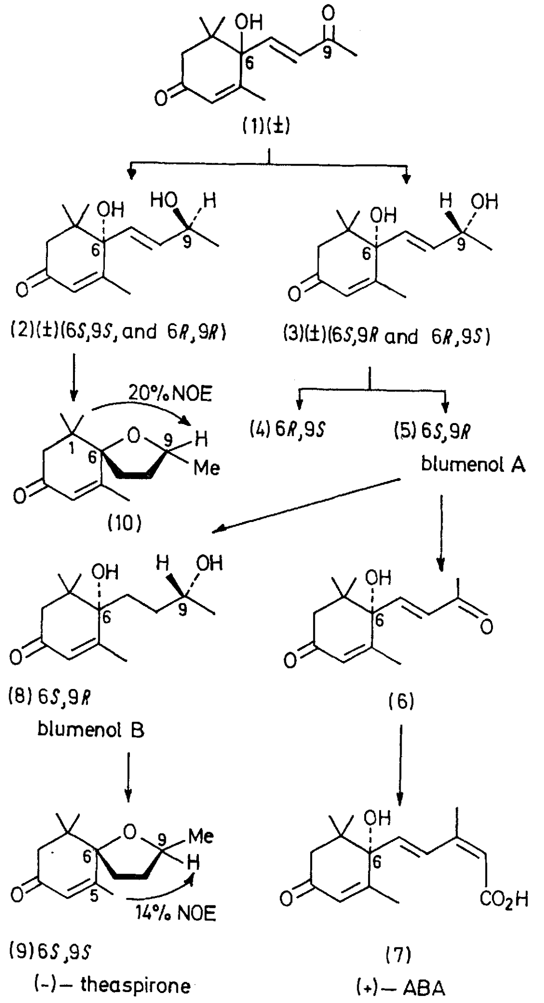
The racemic bis-enone (**1**) [prepared by t-butyl chromate oxidation[7] of (±)-α-ionone] was reduced with sodium borohydride in ethanol at 0° (quantitative yield), and the resulting diastereoisomeric mixture of 6,9-diols was separated into (**2**) and (**3**) by high speed liquid chromatography (l.c.).

Comparisons of i.r. spectra (KBr) of the two diastereoisomers, (±)-(**2**) (m.p. 116—118°) and (±)-(**3**) (m.p. 112—114°) with that of blumenol A† clearly showed that the less polar (by l.c.) (**3**) corresponded in relative configurations at C-6 and C-9 to the natural product.

The racemic diol (**3**) was resolved by preparation of the diastereoisomeric (+)-α-methoxy-α-trifluoromethylphenylacetyl (MTPA) esters[8] followed by l.c. Basic hydrolysis (quantitative yield) of the separated MTPA esters thus gave the two enantiomers diol (**4**) [(enantiomer of structure (**3**)], c.d. (MeOH) $\Delta\epsilon_{241}$ − 8·7, $\Delta\epsilon_{317}$ + 0·39, and diol (**5**) [(same as structure (**3**)], c.d. (MeOH) $\Delta\epsilon_{242}$ +9·6, $\Delta\epsilon_{317}$ −0·44. The c.d. data of (**5**) corresponded to those of blumenol A, and hence the two are identical.†

Diol (**5**) was oxidized with Jones reagent to the bis-enone (**6**), the optical properties of which corresponded to the bis-enone [$\Delta\epsilon_{208}$ −30·2/$\Delta\epsilon_{242}$ +38·4 (exciton-splitting), $\Delta\epsilon_{320}$ −2·28 (in methanol)] that had earlier[1] been converted into natural (+)–ABA (**7**). This defines the C(6) configuration of diol (**5**) (blumenol A) as *S*.[9]

Blumenol B (**8**) was obtained by hydrogenation[3] of blumenol A with platinum oxide–ethyl acetate (90%). Interestingly the sign of the main π,π^* c.d. Cotton effect (CE) of blumenol B (**8**), $\Delta\epsilon_{217}$ +11·4, $\Delta\epsilon_{250}$ −8·2, and $\Delta\epsilon_{325}$ +1·01, was opposite to that of blumenol A (**5**). It has been



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shown[10] that the helicity between an enone moiety and a γ-hydroxy-group is in agreement with the sign of the longest π,π^* enone CE. This indeed is the case with the 250 nm CE of blumenol B (**8**). However, the fact that it is reversed in blumenol A (**5**) (242 nm) suggests that the effect of the homoconjugated 7-ene outweighs that of the γ-hydroxy-group.‡

Mesylation of (**8**) at C(9) followed by refluxing in pyridine–benzene gave the spiro-ether (**9**) [75% yield from (**8**); stereospecific inversion at C-9], c.d. (MeOH) $\Delta\epsilon_{221}$ +7·0, $\Delta\epsilon_{252}$ −7·0, and $\Delta\epsilon_{317}$ +0·90. Irradiation (n.m.r.) of the 5-Me group in (**9**) exhibited a 14% intramolecular nuclear Overhauser effect (NOE) on 9(H). As the C(6) configuration is known (6*S*), this establishes the configuration at C(9) in (**9**) (9*S*), and also that at C(9) in blumenol B (**8**) (9*R*) and blumenol A (**5**) (9*R*). Since natural (−)-theaspirone shows NOE (10%)[5] and optical properties[6] essentially the same as those of (**9**), (−)-theaspirone can be fully represented by structure (**9**).

In a similar reaction sequence (±)-(**2**) was converted into "*trans*-theaspirone"[5] (**10**), which showed a 20% NOE at 9(H) upon irradiation of the 1-Me group and thus corroborated the C(9) configuration in theaspirone (**9**). The fact that the C(6) configurations of natural products, (+)-ABA (**7**), blumenol A (**5**), blumenol B (**8**), and (−)-theaspirone (**9**), are identical is of biogenetic significance.§

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‡ Molecular models show that the helicity is independent of the configuration of the cyclohexenone ring.

§ The same configuration at C(6) for blumenols A and B has been established by Galbraith and Horn. We thank Dr. Horn for this information prior to publication.

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