# Absolute Stereochemistry of Cynaropicrin and Related Guaianolides

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*Summary* The absolute stereochemistry of cynaropicrin (**1**), dehydrocynaropicrin (**2**), grosheimin (**3**), and isoamberboin (**4**) has been determined by relating them to α-santonin.

Cynaropicrin (**1**) occurs with dehydrocynaropicrin (**2**) or with grosheimin (**3**) in fresh *Cynara scolymus* L., depending on the place of gathering.[1] Extraction of a putrid batch of this plant of Italian origin six days after harvesting, gave no cynaropicrin, but a different guaianolide, m.p. 183°, $[\alpha]^{20}_{D}$ +138° ($CHCl_3$), $\nu_{max}$ (Nujol) 3500, 3080, 1750, 1740, and 1650 cm$^{-1}$, identical with isoamberboin (**4**)[2] according to its physical and spectral properties. We now outline results which define the absolute stereochemistry of these sesquiterpenic lactones.

The crystalline dihydroxy-lactone (**5**), obtained by mild alkaline hydrolysis of cynaropicrin,[1] was converted into the αβ-unsaturated hydroxy-ketone (**6**), m.p. 168°, $[\alpha]^{20}_{D}$ +177° ($CHCl_3$), $\lambda_{max}$ (MeOH) 230 nm (ε 7500), $\nu_{max}$ (Nujol) 3480, 3080, 1760, 1720, and 1635 cm$^{-1}$, by stereoselective reduction of the conjugated double bond with sodium borohydride[3] followed by selective oxidation of the allylic hydroxy-group with Jones reagent at −30°. Reduction of compound (**6**) in benzene–ethanol with hydrogen and *pre*reduced Wilkinson catalyst[4] and treatment of the crude hydrogenated product in chloroform with alumina to ensure that the C-4 methyl group had the α-configuration,[5] yielded the saturated ketone (**7**), m.p. 154°, $[\alpha]^{20}_{D}$ +13·7° ($CHCl_3$), $\nu_{max}$ (Nujol) 3520, 1760, and 1740 cm$^{-1}$; the configuration at C-10 of the latter has not yet been determined, but only one epimer was obtained by the described procedure.

Treatment of isoamberboin (**4**) in benzene–ethanol solution with hydrogen and *pre*reduced Wilkinson catalyst[4] afforded the same epimer (**7**), thus establishing the identity of the configurations at the corresponding asymmetric centres in (**4**) and (**5**). Analogous conclusions were drawn for the stereostructures of grosheimin (**3**) and dehydrocynaropicrin (**2**) since the same dihydroxy-lactone (**8**),[6] isolipidiol,[2] m.p. 170°, $[\alpha]_D^{20}$ $+32{\cdot}1°$ ($CHCl_3$), $\nu_{max}$ (Nujol) 3420, 3380, 1750, and 1645 $cm^{-1}$, was obtained on reduction of (**3**) and (**4**) with sodium borohydride and since oxidation of cynaropicrin in acetic acid with chromium trioxide at 0° gave *inter alia* dehydrocynaropicrin (**2**).

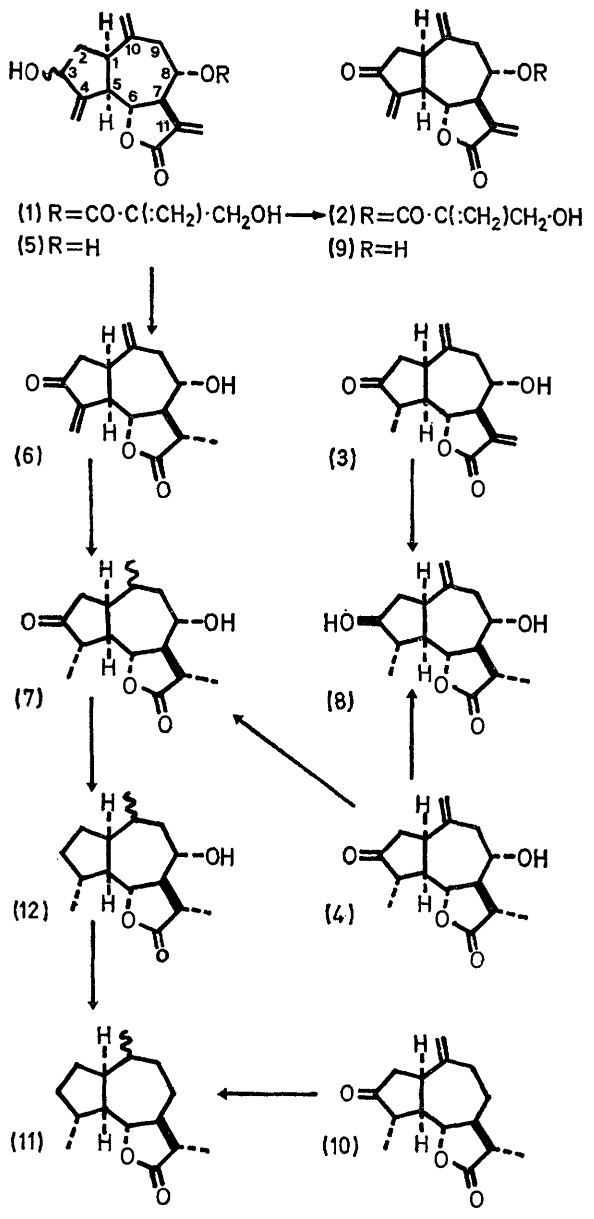
The stable epimer at C-4 of dihydro-isophoto-α-santonic lactone[7] of known absolute stereochemistry[8] was converted, by treatment with thionyl chloride in pyridine solution at $-10°$, into the anhydrolactone (**10**),[9] m.p. 83°, $[\alpha]_D^{20}$ $+140°$ ($CHCl_3$); hydrogenation of (**10**) in benzene solution with Wilkinson catalyst and treatment of the reduced compound with ethanedithiol and boron trifluoride etherate followed by desulphurization of the thioacetal with Raney nickel afforded only one epimer at C-10 of the guaianolide (**11**), m.p. 93°, $[\alpha]_D^{20}$ $-27°$ ($CHCl_3$), $\nu_{max}$ ($CCl_4$) 1780 $cm^{-1}$.

Conversion of the saturated ketone (**7**) into the corresponding ethylene thioacetal followed by reduction with Raney nickel in ethanol solution gave the hydroxy-lactone (**12**), m.p. 118°, $[\alpha]_D^{20}$ $-5{\cdot}2°$ ($CHCl_3$), $\nu_{max}$ (Nujol) 3570, 3490, 1765, and 1750 $cm^{-1}$. Oxidation of (**12**) with Jones reagent and reduction of the carbonyl group *via* the ethylene thioacetal afforded the same epimer (at C-10) of the guaianolide (**11**) obtained from α-santonin.

The correlation between α-santonin and the guaianolides from *Cynara scolymus* established the absolute configurations at C-1, C-5, C-6, and C-7 of cynaropicrin (**1**) and related sesquiterpenes (**2**), (**3**), and (**4**), as well as the configurations at C-4 of grosheimin and at C-11 of isoamberboin.

The c.d. and n.m.r. spectra of the compounds described confirmed the foregoing conclusions and in addition, according to the method of Samek *et al.*[10,11] the n.m.r. spectra indicated an α-configuration of the C-8 hydroxy-group in (**1**), (**2**), and (**3**). Bretón *et al.* obtained an analogous result for the configuration at C-8 in grosheimin and proposed a β-configuration for the hydroxy-group at C-3 in 8-*O*-acetyl-isolipidiol,[2] using the Horeau method.

Although the structures of a large number of guaianolides have been determined, the stereochemistry at C-1 of many members of this class of sesquiterpenes was uncertain owing to the difficulties of interpretation of c.d. and n.m.r. data in relation to the flexibility of these systems; the foregoing correlation represents one of the first resolutions of the problem by chemical methods.[9,12]



(1) $R=CO{\cdot}C(:CH_2){\cdot}CH_2OH$ → (2) $R=CO{\cdot}C(:CH_2)CH_2{\cdot}OH$

(5) $R=H$ (9) $R=H$

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