

ON THE ABSOLUTE CONFIGURATIONS OF SOME SYNTHETIC
SIDE CHAIN DERIVATIVES OF 18 β -OLEAN-11-ON-12-ENES

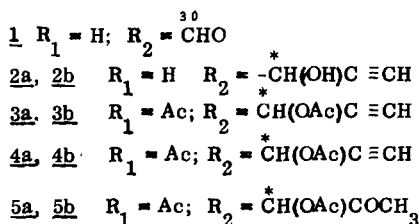
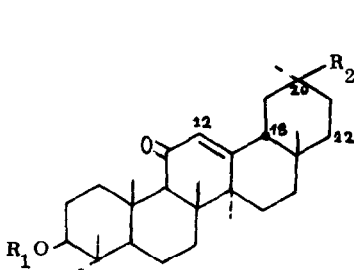
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(Received in UK 29 August 1973; accepted for publication 8 October 1973)

In a previous study¹⁾ the preparation of derivatives 2, 3, 4, 5 from glycyrrhetaldehyde (1) has been described. These contain a C₃ side-chain and are formed in pairs of epimers with respect to C-30,-a new asymmetric center.

There are several reports in the literature in which the absolute configuration of the side-chain C-20 was established by observing various nmr shifts of the near C-19 methyl group.²⁾ We wish to report an attempt to elucidate the absolute configurations of our epimers, mainly by observing changes in nmr shifts³⁾ of the far vinylic hydrogen at C-12.



The compounds 2 and 5 (each of which is an epimeric mixture) were separated by preparative tic into their constituents a and b (a with the higher R_f value). The nmr absorptions of the two epimers of 3 and 4 were measured without previous separation. The relevant absorptions of the four couples 2-5 are shown in Table 1.

Table 1

	H-12	H-30	acetylenic proton		H-12	H-30	acetylenic proton
<u>2a</u>	5.62	4.64 ^a	2.47 ^a	<u>3a</u>	5.62	4.65 ^a	2.47 ^a
<u>2b</u>	5.65	4.61 ^a	2.45 ^a	<u>3b</u>	5.67	4.62 ^a	2.45 ^a
<u>5a</u>	5.44	5.21	-	<u>4a</u>	5.49	5.73 ^a	2.48 ^a
<u>5b</u>	5.76	5.18	-	<u>4b</u>	5.63	5.71 ^a	2.46 ^a

a:d, J = 2Hz

One sees immediately that the most significant differences affect the vinyl proton at C-12. These differences are small (0.03 ppm) for 2a, 2b and 3a, 3b, but acetylation of the C-30 hydroxy group (4) increases them to 0.14 ppm and transformation of the acetylenic bond to the methyl ketone group (5a, 5b) even to 0.32 ppm.

Dreiding models of these compounds show that the C-30 hydroxy group can not be near enough to the C-12 hydrogen to have any effect on its nmr absorption. On the other hand the acetylenic hydrogen can easily reach the distance of only 1.2 Å from H-12 which is sufficient to influence the vinylic proton (Van der Waal effects or long range shielding by carbon-carbon or carbon-hydrogen single bonds)⁴.

While obviously in all our compounds free rotation around the C₂₀-C₃₀ bond exists, we assume that 2b has at least one spatial conformation which allows the acetylenic group to be for prolonged periods, closer to the vinylic C-12 proton, than in the case of 2a (fig. 1).

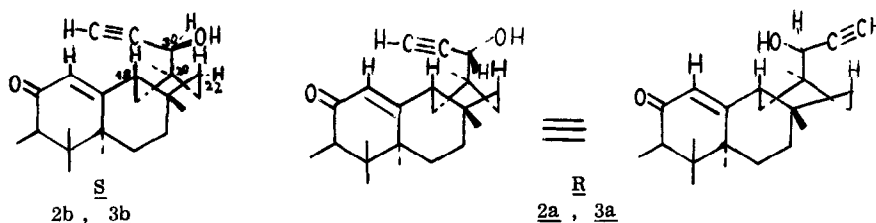
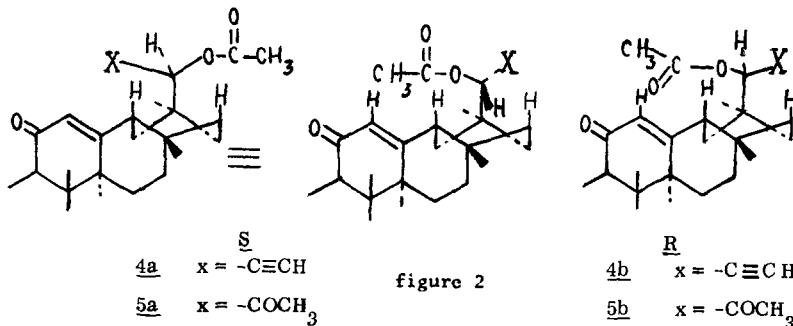


figure 1

In the configuration R the hydrogen at C-30 is hindered to some degree by the axial hydrogen atoms at C-22 and C-18. This should restrict the free rotation about the C₂₀-C₃₀ bond and so prevent the acetylenic group from approaching the C-12 vinylic proton. In the S configuration, on the other hand, there is no such steric interference and no restraint on the acetylenic group from approaching the C-12 hydrogen. Therefore, we assume that 2b has configuration S and 2a-R. The fact that the acetylenic hydrogen itself resonates at higher field in 2b than in 2a can be explained by long range effects of the axial C-18 and C-22 hydrogens on it.

Quite analogous effects are observed in compound 3. Much greater shifts are found in 4; they are caused most probably by the acetoxy group. Dreiding models show that the C-30 acetoxy group can approach the C-12 proton much closer than does the acetylenic group. Figure 2 shows, that this time the C-30 hydrogen in 4b does not interact with the axial hydrogen atoms at C-18 and C-22, when the acetoxy group approaches the C-12 vinylic hydrogen. The opposite is true for 4a. Therefore it follows that 4a has the configuration S and 4b configuration R.

When the acetylenic group in 4 is transformed into the bulkier methyl ketone group (5), Dreiding models show that free rotation round the C₂₀-C₃₀ bond becomes difficult. We can assume therefore that the acetoxy group in the R configuration and only in this one, is present for a considerable part of time near the C-12 vinylic proton. Consequently the differences in the chemical shifts of the C-12 vinylic hydrogen become now very large.



A further insight into the fine structure of 5a and 5b is provided by the CD spectra of the two epimers. (Table 2).

Table 2

<u>5a</u> (c, 0.22; dioxane) 25 ^o	<u>5b</u> (c, 0.20, dioxane) 25 ^o
$\Delta\epsilon_{400} = 0$; $\Delta\epsilon_{385} = 0.039$; $\Delta\epsilon_{378} = 0$	$\Delta\epsilon_{400} = 0$; $\Delta\epsilon_{387.5} = 0.025$
$\Delta\epsilon_{372.5} = -0.052$; $\Delta\epsilon_{365} = -0.0098$	$\Delta\epsilon_{373} = -0.107$; $\Delta\epsilon_{367} = -0.078$
$\Delta\epsilon_{355} = -0.192$; $\Delta\epsilon_{349} = -0.091$	$\Delta\epsilon_{356} = -0.29$; $\Delta\epsilon_{348} = -0.191$
$\Delta\epsilon_{340} = -0.198$; $\Delta\epsilon_{332.5} = -0.077$	$\Delta\epsilon_{341} = -0.308$; $\Delta\epsilon_{334} = -0.205$
$\Delta\epsilon_{305} = -0.405$; $\Delta\epsilon_{300} = -0.366$	$\Delta\epsilon_{295} = -1.56$; $\Delta\epsilon_{225} = +9.4$
$\Delta\epsilon_{296} = -0.405$; $\Delta\epsilon_{288} = -0.098$	
$\Delta\epsilon_{230} = +9.7$	

Like other 18 β -11-keto-12-en-oleans⁵⁾ 5 has several negative cotton effects, due to the enone system in the area of the R band, of which the most important is found around 300 nm. The additional carbonyls of the free rotating side-chain at C-20, which are far away from the main asymmetric center, should add very little to the CD values⁶⁾. Inspection of these values (table 2) shows very considerable differences between 5a and 5b which cannot be explained by the additional contribution of the side chain carbonyls. In the configuration R (5b) the carbonyl of the acetoxy group can reach the distance of only 0.7Å from H-12 without causing any strain on the molecule. At such short distances, a hydrogen bond type of interaction can occur between the hydrogen atom and the acetoxy carbonyl. This interaction is likely to cause an increase in the δ angle (deviation from coplanarity of the enone system) and consequently in the $\Delta\epsilon$ values^{5a)}.

The great differences in the nmr and the CD spectra of 5a and 5b apparently reflect considerable differences between the configurations 5a and 5b. This may also be the reason why this pair is much easier to separate than the pairs 2, 3, and 4.

References

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