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^{13}C NMR STUDY OF GINSENG SAPOGENINS AND THEIR RELATED DAMMARANE TYPE TRITERPENES

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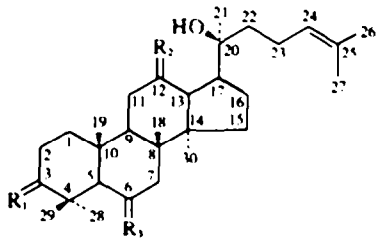
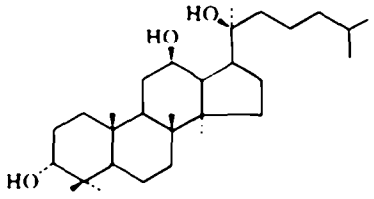
Abstract—In connection with structure studies on dammarane type triterpenes and their glycosides, assignments of ^{13}C NMR signals of fifteen 20-hydroxy-dammarane derivatives including Ginseng sapogenins have been achieved by the aid of shift reagents and deuterated compounds. It has been found that the differences of the 17 C, 21 C and 22 C chemical shifts between pairs of C-20 epimers are remarkable especially in the case of 12β-hydroxy derivatives, being significant for the study of the C-20 stereochemistry.

In continuation of the studies on chemical constituents of Ginseng and its related medicinal plants,[1] ^{13}C NMR was expected to offer excellent advantage over all other spectroscopic and chemical procedures for structural determination and identification of saponins which consist of the acid unstable dammarane-type sapogenins,[2] e.g. 20(*S*)-protopanaxadiol(**1**)[3] and 20(*S*)-protopanaxatriol(**2**).[4] In this connection, the present authors have explored the assignments of carbon signals of **1**, **2**, and their related triterpenes.



1: R_1 = 20(*S*)-OH, R_2 = 20(*S*)-OH, R_3 = H$_2$
2: R_1 = 20(*R*)-OH, R_2 = 20(*S*)-OH, R_3 = 20(*R*)-OH
3: R_1 = 20(*R*)-OH, R_2 = 20(*S*)-OH, R_3 = H$_2$
4: R_1 = O, R_2 = 20(*S*)-OH, R_3 = H$_2$
6: R_1 = 20(*S*)-OH, R_2 = H$_2$, R_3 = H$_2$
7: R_1 = O, R_2 = H$_2$, R_3 = H$_2$
11: R_1 = 20(*R*)-OH, R_2 = 20(*R*)-OH, R_3 = H$_2$



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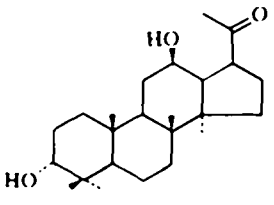

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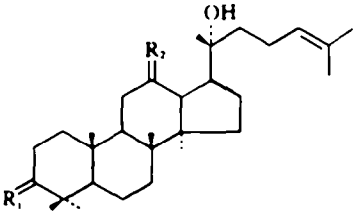
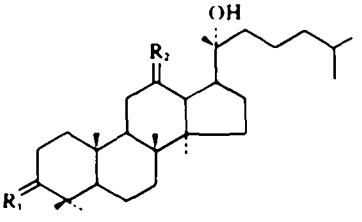
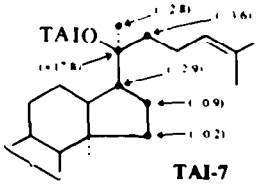


8: R_1 = 20(*S*)-OH, R_2 = 20(*S*)-OH
9: R_1 = 20(*S*)-OH, R_2 = H$_2$
10: R_1 = O, R_2 = H$_2$



12: R_1 = 20(*R*)-OH, R_2 = 20(*S*)-OH
14: R_1 = 20(*S*)-OH, R_2 = 20(*S*)-OH



( ): Δδ ppm [(TAI-7)–(7)]

Chart 1.

Besides the general techniques for ^{13}C NMR spectroscopy, application of chemical shift rules for alicyclic compounds,[5-7] and the reported data for some other type of triterpenes (oleanane, ursane,[8] euphane and lanostane[9]) were useful for determination of the shift allocation. The spectra recorded in $CDCl_3$ solution were assigned as follows.

Carbinyl carbons. A singlet peak in the range of signals δ 65–80, must be due to 20C because of its multiplicity. In comparison with spectra of 12β-hydroxy derivatives (**1**, **2**) betulafolienetriol (**3**),[10] betulafolienediolone (**4**),[10] and betulafolianetriol (**5**)[10] with those of dammarenediol—II (**6**)[11] and hydroxydammarenone—II (**7**),[11] the strong intramolecular H-bonding between 12β- and 20-t-OH groups exerts *ca.* 1.4–1.7 ppm upfield shift in the position of the 20C resonance.

Referring to the data for oleanane and other triterpenes,[8,9] a peak (doublet) near δ 79 in the spectra of **1**, **2**, **6**, 20(*R*)-protopanaxadiol (**8**),[1] and dammarenediol—I (**9**)[11] is obviously attributable to 3C, which is absent in the spectra of **4**, **7** and **10** and is displaced by *ca.* 2.8 ppm upfield on going to the 3α-OH derivatives, **3**, **5**, **11**[12] and **12**.[2]

It follows that a remaining carbinyl carbon signal (doublet) of **1**–**5**, **8** and **12** near δ 70.7 can be assigned to 12C, which is absent in the spectra of **6**, **7**, **9** and **10** and is shifted by 2.4 ppm upfield on conversion into the 12α-hydroxy-derivative (**11**). In the spectrum of **2**, an additional signal (doublet) at δ 68.4 was thus unequivocally designated as 6C.

Olefinic carbons in the side chain and carbonyl carbons. Signals due to the side chain double bond were identified unambiguously on the basis of their chemical shifts and multiplicities.

Carbonyl carbon signals of **4**, **7** and **10** were also readily characterized from their chemical shifts.

Quaternary carbons (singlets). Assignments of quaternary carbon signals which can be easily observed as singlets even in the noise off-resonance decoupled spectra, were straightforward by analysis of the spectrum of 20-ξ-dammaran-3β-ol (**13**)[11] with the aid of the shift reagent. Figure 1 demonstrates the relationship between the magnitude of an induced shift for each quaternary carbon signal of **13** and the amount of added $Eu(fod)_3$. From the result of this experiment, the four quatenary carbon signals of **13** can be designated to 4C (nearest to the 3β-OH group), 10C, 8C and 14C (most remote from the 3β-OH group), respectively in the order of decreasing the rate of the induced shift. A comparison with this assignment under the consideration of the substituent effects[5-7] led to the assignments of quaternary carbon resonances of all of other compounds.

Methine carbons (doublet). A methine peak which is shifted by *ca.* 6 ppm upfield on going from the 3β-OH derivatives to their 3α-OH counterparts, can be assigned to 5C.[8] This assignment is in good agreement with the reported data for α- and β-amyrins[9] and is further substantiated by the remarkable downfield shift caused by the introduction of the 6α-OH group in the spectrum of **2**.

A methine signal of **1** which disappears in the spectrum of 20(*S*)-protopanaxadiol-2,2,11,11,13-$^2H_5$ (**1-d$_5$**) must be attributable to 13C, being consistently observed at the almost same position in the spectra of **2**, **3** and **5**. The 13C signal of **8** and **12** (20(*R*)-series) was also identified by the inspection of the spectrum of 20(*R*)-dihydroprotopanaxadiol-2,2,11,11,13-$^2H_5$(**14-d$_5$**).

The identification of the other two methine signals of **1** was permitted by the comparison of the spectrum of **1** with that of its 20-epimer, **8**. A signal which appears in the significantly different position between the spectra of this C-20 epimeric pair should be due to 17C (β to the epimeric center) and not to 9C (remote from the epimeric center). The resonance of 9C of **1** thus assigned was found to be more shielded on going from **1** to **11**, the latter of which has an axial OH group at C-12.

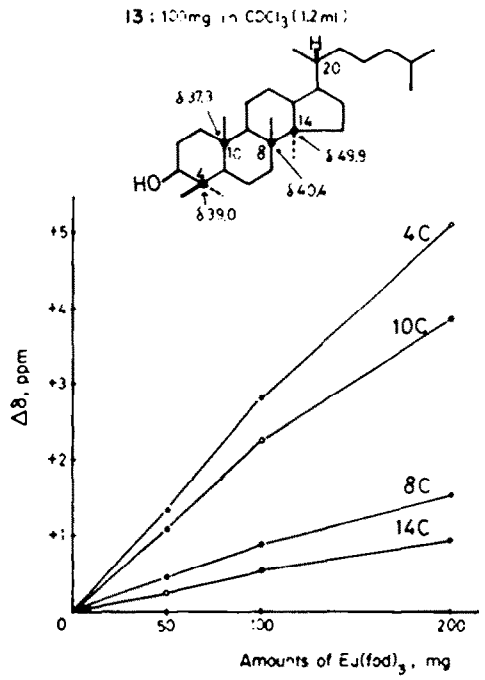


Fig. 1. Lanthanide induced shifts for quaternary carbons.

In the case of the compounds having no OH function at C-12, differentiation of 17C from 13C was performed by the examination of the trichloroacetyl isocyanate (TAI) derivative.[11] A doublet which is deshielded by 2.9 ppm on conversion of **7** into its TAI derivative should be assigned to 17C, while a resonance which appears unchanged must be due to 13C, (being more remote from the C-20-TAI group than 17C). The distinction between the signals of 9C and 17C of **6** and **9** were also established by comparison of the spectrum of **9** with that of its 3, 20-di-TAI-derivative.

On going from **6** to its 12β-OH derivative (**1**), the 17C resonance is expected to be displaced upfield by the γ-effect of the 12β-OH group. However, it appears at remarkably lower field in the spectrum of **1** than that of **6**. This anomalous shift can be rationalized in terms of the conformational change around the C-17–20 linkage due to the intramolecular H-bonding between the 12β- and 20-OH groups.

The characterization of the 25C resonance of the dihydro-derivative (**5**) was established by comparison with the spectrum of the parent compound (**3**).

Methylene carbons (triplet). The assignment data reported for α- and β-amyrins[8] and 4,4,10-trimethyl-trans-decalol[14] permitted the assignments of 1C, 2C and 6C signals of 3β-OH derivatives. The 2C signal was further substantiated by comparison of the spectrum of **1** with that of its 2,2-$^2H_2$ derivative (**1-d$_2$**). Conversion of the 3β-OH group into its epimer, caused the peaks due to 1C and 2C to be displaced upfield by a change of the magnitude of the β- and γ-effects of the OH substitution. Downfield shift of the 2C resonance also took place on

Table 1a. ^{13}C chemical shifts in $CDCl_3$

	1	2	3	4	5	6	7	8	9	10	11	12	14	15
1	39.0	39.1	33.8	39.6	33.7	39.0	39.8	39.0	39.0	39.8	33.5	33.7	39.0	33.7
2	27.4	26.7	25.2	34.0	25.2	27.4	34.0	27.4	27.3	34.0	25.3	25.5	27.4	25.4
3	78.8	78.4	76.0	217.7	75.8	78.9	217.6	78.9	78.8	217.7	76.1	75.9	78.9	75.8
4	39.0	39.1[B]	37.6	47.3	37.5	39.0	47.3	39.0	39.0	47.3	37.6	37.6	39.0	37.5
5	56.3	61.0	49.4	55.2	49.4	55.9	55.3	55.9	55.8	55.3	49.5	49.5	55.9	49.4
6	18.3	68.4	18.2	19.6	18.2	18.3	19.6	18.3	18.3	19.6	18.2	18.2	18.3	18.1
7	34.8	46.8	34.7	34.0	34.7	35.3	34.5	34.8	35.3	34.6	35.1	34.7	34.8	34.9
8	39.8	40.8	39.9	39.6	39.8	40.4	40.2	39.8	40.4	40.2	40.5	39.9	39.8	40.0
9	50.2	49.5	49.9	49.3	49.9	50.7	49.9	50.1[D]	50.6	49.9	45.3[D]	49.9	50.0	50.4[D]
10	37.1	39.2[B]	37.2	36.7	37.1	37.1	36.7	37.1	37.1	36.7	36.9	37.2	37.1	37.3
11	31.2	30.9	31.2[C]	30.9	31.0	21.6	22.0	31.2[C]	21.4	21.9	29.0	31.3[C]	31.3	32.0[C]
12	70.8	70.5	70.7	70.4	70.7	25.4	25.4	70.7	25.3	25.2	68.4	70.7	70.8	71.6
13	47.7	47.2	47.4	47.8	47.4	42.3	42.3	48.5	42.2	42.2	45.3[D]	48.4	48.5	51.0[D]
14	51.6	51.3	51.6	51.5	51.6	50.3	50.2	51.6	50.0	49.9	48.8	51.7	51.6	51.2
15	31.1	30.9	31.0[C]	31.5	31.0	31.2	31.1	31.1[C]	31.1	31.0	31.3	31.1[C]	31.0	32.2[C]
16	26.6	26.4	26.6	26.4	26.5	27.6	27.5	26.4	27.5	27.4	24.1	26.3	26.3	26.8
17	53.6	53.5	53.6	53.5	53.6	49.9	49.7	49.9[D]	49.5	49.4	46.9[D]	49.9	50.0	52.9[D]
18	16.2[A]	17.2[A]	16.0[A]	15.8[A]	15.9[A]	16.2[A]	15.9[A]	16.2[A]	16.2[A]	15.9[A]	15.9[A]	16.1[A]	16.2[A]	17.3[A]
19	15.7[A]	17.2[A]	15.7[A]	15.4[A]	15.6[A]	15.5[A]	15.2[A]	15.7[A]	15.5[A]	15.4[A]	15.2[A]	15.7[A]	15.7[A]	15.7[A]
20	74.0	73.9	73.7	73.8	73.5	75.4	75.1	74.5	75.8	75.6	75.3	73.6	74.5	214.8
21	26.8	26.7	26.6	26.6	26.7	24.9	24.7	27.8	23.5	23.5	26.9	22.0[E]	21.9	29.5
22	34.8	34.6	34.7	34.7	35.3	40.5	40.5	42.3	41.8	41.8	36.3	42.9	42.9	----
23	22.4	22.3	22.3	22.3	21.4	22.6	22.5	21.8	22.3	22.2	22.4	20.8	20.7	----
24	125.2	125.0	125.3	125.0	39.8	124.8	124.7	124.6	124.7	124.6	124.7	39.8	39.9	----
25	131.4	131.4	131.2	131.2	28.2	131.5	131.3	131.9	131.4	131.3	131.9	28.0	28.0	----
26	25.8	25.7	25.7	25.7	22.7	25.7	25.7	25.8	25.7	25.7	25.7	22.7	22.7	----
27	17.8	17.7	17.7	17.7	22.7	17.7	17.6	17.8	17.7	17.6	17.7	22.7	22.7	----
28	28.1	30.9	28.3	28.6	28.3	28.0	28.6	28.1	28.0	28.6	28.3	28.5	28.0	28.3
29	15.6[A]	15.5[A]	22.1	21.0	22.1	15.4[A]	21.0	15.4[A]	15.4[A]	21.0	22.2	22.1[E]	15.4[A]	22.1
30	16.9	16.9	16.9	16.7	16.9	16.5	16.2	17.2	16.4	16.2	19.4	17.3	17.2	16.1

Table 1b. ^{13}C chemical shifts in C_5D_5N

	1	2	3	4	5	6	7	8	9	10	11	12	14	15
1	39.5	39.3	34.1	39.8	34.0	39.5	39.8	39.5	39.5	39.9	34.2	34.0	39.4	34.3
2	28.2	28.0	26.3	34.2	26.3	28.3	34.2	28.2	28.1	34.2	26.4	26.3	28.3	26.5
3	77.9	78.3	75.2	216.0	75.1	78.0	216.2	78.0	78.0	216.2	75.3	75.1	78.0	75.2
4	39.5	40.2	38.0	47.3	38.0	39.5	47.3	39.5	39.5	47.3	38.1	38.0	39.5	38.1
5	56.3	61.7	49.6	55.2	49.6	56.5	55.3	56.4	56.5	55.5	50.0	49.6	56.4	49.9
6	18.7	67.6	18.6	19.9	18.5	18.8	19.8	18.8	18.8	19.9	18.7	18.6	18.8	18.6
7	35.2	47.4	35.1	34.2	35.1	35.7	34.8	35.3	35.7	34.9	35.8	35.1	35.3	35.7
8	40.0	41.1	40.1	39.8	40.1	40.7	40.5	40.1	40.8	40.5	41.0	40.1	40.1	40.4
9	50.4	50.1	50.2	49.6	50.2	51.1	50.2	50.6	51.2	50.2[B]	45.8[B]	50.2	50.5	51.0[B]
10	37.3	39.3	37.5	36.9	37.5	37.4	35.8	37.4	37.4	36.9	37.4	37.5	37.4	37.7
11	31.0	31.9	31.8	32.3	31.8	21.9	22.2	32.2	21.9	22.3	30.6	31.9	32.2	32.9
12	70.9	70.9	70.9	70.7	70.8	25.8	25.8	70.8	25.8	25.6	68.3	70.7	70.8	71.3
13	48.6	48.1	48.3	48.7	48.3	42.6	42.6	49.2	42.6	42.6	46.2[B]	49.0	49.2	52.8[B]
14	51.6	51.6	51.6	51.6	51.6	50.6	50.5	51.7	50.4	50.2	49.9	51.7	51.8	51.6
15	31.3	31.3	31.2	31.3	31.2	31.7	31.5	31.5	31.5	31.5	32.3	31.3	31.5	32.9
16	26.8	26.8	26.9	26.8	26.7	28.1	28.0	26.6	28.1	28.0	24.8	26.3	26.6	27.7
17	54.7	54.6	54.5	54.6	54.4	50.3	50.2	50.6	49.9	49.8[B]	46.4[B]	50.6	50.8	54.7[B]
18	16.2[A]	17.5[A]	16.3[A]	15.9[A]	16.3[A]	16.5[A]	16.0[A]	16.3[A]	16.5[A]	16.1[A]	16.5[A]	16.3[A]	16.5[A]	16.5[A]
19	15.8[A]	17.4[A]	15.8[A]	15.6[A]	15.8[A]	16.3[A]	15.2[A]	15.9[A]	15.9[A]	15.4[A]	15.5[A]	15.9[A]	15.9[A]	15.9[A]
20	72.9	72.9	72.9	72.9	73.0	74.0	73.9	72.9	74.4	74.2	74.2	73.0	73.2	213.3
21	26.9	26.9	26.9	26.8	27.0	25.5	25.2	22.7	24.5	24.6	25.4	22.6	22.8	30.6
22	35.8	35.7	35.7	35.8	35.9	41.9	41.7	43.2	42.9	42.9	40.3	43.3	43.4	----
23	22.9	22.9	22.8	22.9	21.9	23.3	23.2	22.7	23.0	23.0	23.2	21.2	21.4	----
24	126.2	126.2	126.2	126.2	40.1	126.0	126.0	126.0	126.0	126.0	126.1	40.1	40.1	-
25	130.6	130.6	130.5	130.7	28.3	130.6	130.5	130.6	130.6	130.6	130.6	28.1	28.3	-
26	25.8	25.8	25.8	25.7	22.8	26.1	26.1	25.9	25.8	25.8	25.8	22.6	22.8	----
27	17.6	17.7	17.6	17.6	22.8	17.7	17.7	17.7	17.7	17.7	17.7	22.6	22.8	- -
28	28.6	31.9	29.3	25.8	29.2	28.7	26.7	28.7	28.7	26.8	29.3	29.2	28.7	29.4
29	15.4[A]	15.4[A]	22.4	22.1	22.4	15.8[A]	21.0	15.9[A]	15.8[A]	21.1	22.6	22.6	16.5[A]	22.4
30	17.0	17.0	16.9	16.9	16.9	16.9	16.6	17.3	16.8	16.5	20.1	17.2	17.4	17.0

A, B, C, D, E: Values in any vertical column may be reversed although those given here are preferred.

oxidation of the 3β-OH group to the ketone. The 6C signal was observed at the same position for all compounds except for the 6α-hydroxy derivative (**2**).

The signal which appears consistently in the spectra of the compounds having the side chain double bond and is displaced by *ca.* 1 ppm upfield on hydrogenation, was identified as 23C.

The inspection of the α-carbon deuterium isotope effect of betulafolianetriol-22,22-$^2H_2$ (**5-d$_2$**) and 20-epi-betulafolianetriol-22,22-$^2H_2$ (**12-d$_2$**, 20 (*R*-series) provided the assignment of 22C signals of 20(*S*)- and 20(*R*)-12β-OH derivatives. In the case of the compounds having no OH function at C-12, characterization of the 22C resonance was achieved by comparison of the spectrum of **7** with that of its TAI derivative (**TAI-7**). Of all of the methylene signals, a peak which is displaced mostly upfield (by 3.6 ppm) on conversion into **TAI-7**). Of all of the methylene signals, a peak which is displaced mostly upfield (by 3.6 ppm) on conversion into **TAI-7** must be due to 22C (adjacent to the C-20-TAI group). It should be noted that the intramolecular H-bonding gives rise to a remarkable upfield shift of the 22C resonance as in the case of 20C and 17C (*vide supra*).

The 11C signal of the 12β-OH derivatives was unambiguously designated by the α-carbon deuterium isotope effect of **1-d$_2$** and **14-d$_2$**. This signal was displaced upfield by 2 ppm on conversion into the 12α-OH derivative (**11**) and by 9 ppm on going to compounds having no 12β-OH group.

A signal which appears consistently near δ 31 in the spectra of all compounds except for 20-oxo-hexakisnordammarane-3α,12β-diol (**15**) was identified as 15C. This peak is displaced upfield by only 0.2 ppm on conversion of **7** into its TAI derivative (**TAI-7**). A peak near δ 27.4 of **7** and **10** which is displaced upfield by 0.9 ppm in the spectrum of **TAI-7** and by *ca.* 1 ppm on going to the 12β-OH derivatives, must be assigned to 16C. The characterization of the 7C resonance was established by the β-effect of the 6β-OH group, i.e. comparison of the spectrum of **1** with that of **2**. The 12C resonances of **6**, **7**, **9** and **10** were assigned by comparison with the spectra of their corresponding 12β-OH derivatives. The identification of the 24C resonance of the dihydroderivative (**5**) was furnished by comparison with the spectrum of the parent dehydro-compound (**3**).

Methyl carbons (quartet). Since ^1H NMR signals due to the 21-methyl and methyls on the side chain double bond have been known to appear at lower field than those of other methyl proton signals, the proton selective decoupling technique revealed the characterization of the signals due to 21C, 26C and 27C. The effect associated with the intramolecular H-bonding was also observed as a remarkable downfield shift of the 21C resonance on going from **8** and **12** to **1** and **5**, respectively. Distinction of 26C and 27C signals was achieved on the basis of the general rule for allylic methyl carbon shift of an isopropylidene type double bond.[5]

The literature data for oleanane and ursane type triterpenes[4] permitted the designation of the signals due to the 4,4-gem-dimethyl carbons, i.e. 28C and 29C. The introduction of the 6α-OH group (in case of **2**) gave rise to a downfield shift of the 28C resonance by peri-diequatorial Me-OH interaction,[6,7] while the conversion of 3β-OH group into its epimer caused *ca.* 6 ppm downfield shift in the position of the 29C resonance. Comparison of the spectra of the 12β-OH derivatives with that of the 12α-OH counterpart (**11**) (1,3-diaxial Me-OH interaction[6,7]) allowed the assignment of the 30C signal.

The remaining two methyl carbon resonances which appeared in the range of δ 15–16 must be due to 18C or 19C, and needed to be distinguished from each other.

^{13}C NMR and stereochemistry of C-20 chirality. The chemical shift differences of the carbons around C-20 between each pair of the C-20-epimers are shown in Table 2. In the case of the compounds having no 12-OH function, the 21C resonance of the 20(*S*)-series was found to be more deshielded than that of the corresponding compound of the 20(*R*)-series, while 22C of the 20(*S*)-series is more shielded than that of its counterpart.

As mentioned, the introduction of the 12β-OH group results in the anomalous displacement of the 16C, 17C, 20C, 21C and 22C resonances owing to the formation of the intramolecular H-bonding. Similarly, differences of the 17C, 21C and 22C chemical shifts between both the series (20(*S*) and 20(*R*)) were found to be more remarkable in the case of the 12β-OH derivatives than that of the compounds lacking this OH function. This can be explained in terms of the difference of the non-bonded interaction between both series associated with the conformation around C-17–20 linkage which is fixed by the strong H-bonding (Chart 2).

Since each of the C-20 epimeric pairs of the dammarane type triterpenes exhibits similar R_f values of TLC, optical rotation, IR, mass and ^1H NMR spectra, they were extremely difficult to distinguish from each other. The present finding in the ^{13}C NMR which is structurally

Table 2. ^{13}C chemical shifts differences between the pair of 20-epimers (in $CDCl_3$)

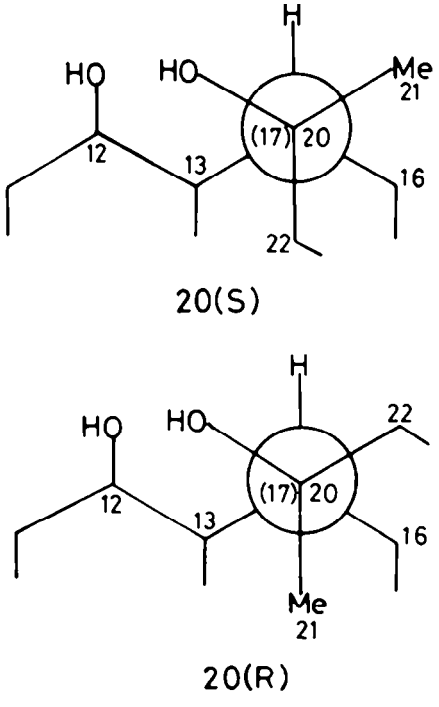


Chart 2.

diagnostic, must be promising for the study of the stereochemistry of triterpenes of this type, especially the saponins and sapogenins of Ginseng and its related plants.

In order to identify the dammarane-type saponins, the ^{13}C NMR spectra of the present compounds in C_5D_5N solution in which most of plants glycosides are readily soluble, were determined. The assignments of the signals recorded in this solvent were performed by comparison with the results in $CDCl_3$ solution under the consideration of the solvent effects (see the values in Table 1b).

EXPERIMENTAL

The ^{13}C NMR spectra were taken in $CDCl_3$ and C_5D_5N soln (0.2–0.5M) on JEOL-PFT-100 spectrometer (25.15 MHz).

Measurement conditions. Temp. 25°; pulse width 12 μsec (*ca.* 45°); repetition time 1.2–3.6 sec; accumulation time 1000–2000; spectral width 4 KHz, 5 KHz, and 6.25 KHz, acquisition time 0.5, 0.4, and 0.3 sec, respectively; data points 4096. A 10 mmϕ sample tube was used. The chemical shifts are expressed as δ ppm from an internal reference, TMS.

Compounds **1**–**15** which were used for recording the spectra in the present work, were prepared previously.[1,4,10,12]

TAI derivatives.[11] To a $CDCl_3$ soln of a sample in an NMR sample tube was added TAI reagent drop by drop until there was no more effervescence under ice cooling. The mixture was subjected directly to recording a spectrum.

20(S)-*Protopanaxadiol*-2,2-$^2H_2$ (**1-d$_2$**). Na (100 mg) was dissolved in MeOD (2 ml) and to this soln was added D_2O (1 ml), and then a soln of **4** (100 mg) in MeOD (4 ml) and the mixture was refluxed for 24 hr. After cooling, the mixture was diluted with D_2O (*ca.* 5 ml) and the deposited crystals were collected by filtration, washed with D_2O and dried. To a soln of betulafolienediolone-2,2-$^2H_2$ thus obtained in dioxane (6 ml) was added a 1 M soln of $NaBH_4$ (6 ml) in dioxane: D_2O (1:1) and the mixture was allowed to stand at room temp. overnight. After decomposing the excess reagent with acetone, the mixture was extracted with Et_2O, and the resulting Et_2O soln was washed with H_2O, dried, and concentrated to dryness, affording **1-d$_2$** for spectrum analysis. The ^2H content in **1-d$_2$** was substantiated by mass spectrometry.[13]

20(S)-*Protopanaxadiol*-2,2,11,11,13-$^2H_5$ (**1-d$_5$**). To a soln of **4** (100 mg) in C_5H_5N (1 ml) was added 3% CrO_3-C_5H_5N soln (10 ml) and the mixture was allowed to stand at room temp. overnight. Working up in the usual way gave dammaren-20(S)-ol-3,12-dione (80 mg), which was deuterated by refluxing with MeONa in MeOD–D_2O (*vide supra*) for 94 hr. The deuterated product was reduced with $NaBH_4$ in the same way as **1-d$_2$** to yield **1-d$_5$**. The content of ^2H in the product was confirmed by mass spectrometry.[13]

20(R)-*Dihydroprotopanaxadiol*-2,2,11,11,13-$^2H_5$ (**14-d$_5$**). Dammaran-20(*R*)-ol-3,12-dione[2] which was prepared from **14**, was subjected to deuteration followed by reduction with $NaBH_4$ in the same way as **1-d$_2$** yielding **14-d$_5$**. The content of ^2H in **14-d$_5$** was substantiated by mass spectrometry.[13]

Betulafolianetriol-22,22-$^2H_2$ (**5-d$_2$**) and 20-*epibetulafolianetriol*-22,22-$^2H_2$ (**12-d$_2$**). To a suspension of $LiAlD_4$ (1 g) in Et_2O (50 ml) was added a soln of methyl isocapronate (6 ml) in Et_2O (50 ml) and the mixture was stirred at room temp. for 1 hr. After addition of H_2O and then 2N H_2SO_4 under ice-cooling, the Et_2O layer was separated. The H_2O layer was extracted with Et_2O and the extracts combined. After washing with H_2O, the Et_2O soln was dried and concentrated to dryness affording **16** (6 ml), the structure of which was secured by ^1H NMR and mass spectroscopy. To a soln of **16** (5 ml) in CCl_4 (40 ml) was added dropwise a soln of PBr_3 (1 ml) in CCl_4 (10 ml) at −15° under stirring. Then the mixture was stirred at room temp. overnight and finally refluxed for 1 hr. After cooling, the supernatant of the mixture was poured into excess ice water. The CCl_4 layer was separated and the aqueous layer was extracted with CCl_4. The CCl_4 layer and the extracts were combined, washed with 5% $NaHCO_3$, dried, and concentrated to dryness. The oily residue was purified by distillation under reduced pressure yielding **17** (4 ml). The purity and content of ^2H of **17** were confirmed by ^1H NMR and mass spectroscopy.

To a suspension of Li-metal (1 g) in THF (50 ml) was added a soln of **15** (450 mg)[12] and **17** (3 ml) in THF (100 ml) and the mixture was stirred at room temp. for 2 hr. The excess Li was removed by filtration and to the filtrate was added a saturated soln of NH_4Cl. The organic layer was separated and the H_2O layer was extracted with Et_2O. The Et_2O extract was combined with the organic layer and the mixture was washed with H_2O, dried, and concentrated to dryness. The residue was subjected to column chromatography on silica gel (eluted with C_6H_6: acetone (10:2)). The separation of **5-d$_2$** and **12-d$_2$** was followed by TLC on silica gel (solvent C_6H_6: acetone (10:2)) under comparison with authentic samples of **5** and **12**[2], yield: **12-d$_2$** 40 mg and **5-d$_2$** 10 mg. The structures and ^2H contents of both compounds were confirmed by mass spectroscopy.[13]

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