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^{13}C nuclear magnetic resonance data of lanosterol derivatives—Profiling the steric topology of the steroid skeleton via substituent effects on its ^{13}C NMR

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ABSTRACT

The ^{13}C NMR spectra of over 24 tetracyclic triterpenoid derivatives have been structurally analyzed. The ^{13}C NMR chemical shifts allow one to probe the steric topology of the rigid steroid skeleton and inductive effects of its substituents.

Use of deuterium labeling in chemical shift assignment and B-ring aromatic terpenoids are also featured.

1. Introduction

Lanosterol is a key intermediate in the biosynthesis of cholesterol and bile acids [1] and related phytosterols are ingredients in traditional Chinese medicine commonly used for the treatment of a variety of diseases [2]. Lanosterol is one example of a 4α,4β,14α-trimethylsterol (a tetracyclic triterpenoidal C30 sterol). The lanostane skeleton is shown in Fig. 1. Lanosterol itself has 8,9- and 24,25-double bonds. C30 sterols are widely distributed in nature and play an important role in numerous biological processes. Several oxygenated C30 sterols isolated from the fruiting bodies of *G. lucidum* have been shown to exhibit inhibitory activity against HIV-1 protease [3]. A triterpenoidal C30 inhibitor of Farnesyl-protei transferase (FPTase) has been discovered by Jayasuriya et al. [4].

The goal of this study is to understand how structural variation on the rigid steroid skeleton affects its ^{13}C NMR chemical shifts while presenting the ^{13}C NMR data of tetracyclic triterpenoid derivatives previously synthesized in our laboratory [5]. As it will emerge it will be shown that steric effects play an important role. Thus, chemical shift comparisons allow us to probe the steric interactions within the steroid skeleton. Both the nature and orientation of substituent groups in the steroid skeleton influence their ^{13}C NMR chemical shifts.

2. Results and discussion

2.1. 17-Sidechain

The absence of substituents on C12–C17 in the steroid skeleton make the ^{13}C NMR chemical shifts of the flexible 17-sidechain the least variable. The average values from Table 1 are shown in Fig. 1 for the C_8H_{17} and $C_6H_{11}O_2$ 17-sidechains for the tetracyclic triterpenoid derivatives of this study (Fig. 2). The latter data for the $C_6H_{11}O_2$ 17-sidechain agrees with the results of our prior paper on bile acid derivatives [6].

2.2. γ-Shielding effects in bile acid derivatives

In our prior study of bile acid derivatives, we uncovered a ^{13}C NMR γ-shielding effect resulting from the interaction of a *syn* diaxial hydrogen/oxygen pair [6]. Figs. 3–5 summarize this phenomenon where the select experimental ^{13}C NMR chemical shifts for bile acid related alpha and beta hydroxyl derivatives of methyl 5β-cholanoates are given. The values within parentheses were determined by the ChemNMR ^{13}C estimation program which is part of the suite of desktop software programs included in ChemBioDraw Ultra 11.0 by CambridgeSoft. Several relevant observations can be made. First, the ChemNMR ^{13}C estimation program does not distinguish between stereochemistries of the alpha and beta orientations of the hydroxyl groups as the predicted ^{13}C NMR chemical shifts are identical for the methyl 3α- and 3β-hydroxy-5β-cholanoates, 7α- and 7β-hydroxy-5β-cholanoates, and 12α- and

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Table 1
^{13}C NMR data of terpenoid derivatives.

Carbon	**1**[7]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	35.37	35.44	33.85	33.85	33.69	33.81	33.73	34.04	34.39	34.82
2	24.23	24.26	24.14	24.18	23.87	24.14	23.95	24.03	25.77	28.41
3	80.81	80.82	80.54	80.51	79.26	80.20	79.26	80.47	78.76	79.23
4	37.58	37.61	37.42	37.46	37.65	37.42	37.73	37.46	39.01	39.09
5	49.21	49.26	50.04	50.04	50.07	50.27	50.15	50.19	50.23	49.96
6	22.79	22.85	27.06	27.06	39.52	27.09	39.59	17.24	17.39	18.17
7	119.77	119.83	67.89	67.78 t	201.43	56.01	201.77	29.81	29.93	26.36
8	142.80	142.85	161.09	160.93	150.61	159.96	150.53	164.00	164.16	138.93
9	145.54	145.60	140.71	140.79	151.70	140.98	151.70	139.31	139.55	137.18
10	37.19	37.26	38.66	38.66	36.18	38.55	36.22	37.92	37.65	37.30
11	116.60	116.64	200.68	200.88	201.88	200.60	202.16	198.94	199.28	67.08
12	37.80	37.86	51.82	51.86	51.59	51.90	51.55	51.86	51.90	43.63
13	43.67	43.71	45.84	45.88	47.43	46.07	47.47	47.24	47.24	42.70
14	50.30	50.35	47.43	47.43	48.95	47.32	48.87	51.59	51.63	49.96
15	31.46	31.52	30.04	30.04	32.14	30.01	32.14	30.94	31.01	30.86
16	27.88	27.91	28.03	28.06	27.75	27.95	27.79	27.02	27.02	27.75
17	51.00	51.08	50.93	50.93	49.03	51.01	48.99	51.59	51.63	51.01
18	15.63	15.68	17.00	17.04	16.73	17.04	16.81	16.61	16.05	17.54
19	22.77	22.84	18.01	18.01	17.47	17.16	17.55	18.44	18.44	22.44
20	36.24	36.29	35.83	35.87	36.18	36.18	35.71	36.18	36.22	36.45
21	18.48	18.52	17.20	17.24	18.55	18.40	18.17	18.98	18.98	18.79
22	36.37	36.45	31.09	31.13	36.18	36.26	31.10	36.18	36.22	36.45
23	24.10	24.14	30.94	30.94	23.95	24.03	30.98	24. 22	24.03	24.11
24	39.48	39.55	174.56	174.56	39.36	39.40	174.40	39.40	39.44	39.52
25	27.98	28.03			27.91	27.95		27.95	27.99	28.03
26	22.53	22.55			22.48	22.51		22.55	22.51	22.55
27	22.82	22.86			22.79	22.82		22.82	22.82	22.82
28(4α-Me)	28.06	28.10	28.03	27.91	27.29	27.17	27.21	28.26	28.34	28.10
29(4β-Me)	16.91	16.96	16.81	16.81	16.50	16.73	16.54	16.77	15.72	15.60
30(14α-Me)	25.52	25.58	27.37	27.37	25.85	27.17	25.89	25.77	25.77	24.49
OCH_3			51.59	51.59		51.01	51.55			
***CH*$_3$**COO(3)	21.31	21.27	21.31	21.35	21.19	21.23	21.23	21.23		
CH_3***C***OO(3)	170.96	170.83	171.18	171.18	170.79	170.68	170.79	170.71		

Carbon	**10**[9]	**10**	**11**[10]	**12**	**13**[10]	**13**	**14**	**15**[10]	**16**
1	35.50	35.83	33.70	33.50	36.20	36.10	36.10	36.10	35.98
2	23.30	23.64	23.80	23.83	24.00	23.83	23.83	23.80	23.80
3	79.60	79.81	79.30	79.92	80.50	80.39	80.39	80.30	80.31
4	37.90	38.12	38.00	38.00	37.90	37.85	37.85	38.00	37.92
5	52.10	52.44	48.30	48.13	47.70	47.67	47.59	49.00	48.95
6	38.70	39.01	36.50	36.53	31.50	31.40	31.33	27.60	27.41
7	209.00	209.22	199.80	200.57	72.30	72.24	72.24 t	73.40	73.36 t
8	52.70	52.99	142.30	139.43	47.50	47.40	47.37	44.40	44.21
9	60.00	60.28	157.60	161.87	51.50	51.39	51.39	51.00	50.93
10	36.40	36.68	39.50	39.90	36.80	36.68	36.68	36.60	36.57
11	208.40	208.60	69.60	67.04 t	210.70	210.89	210.85	210.00	210.15
12	52.10	52.33	39.30	42.47	52.30	52.21	52.21	52.30	52.25
13	48.30	48.60	43.10	43.40	59.60	59.51	59.51	59.50	59.39
14	46.20	46.43	48.90	48.99	49.00	48.87	48.87	47.20	47.20
15	32.80	33.03	32.20	32.14	35.80	35.71	35.71	34.70	34.66
16	28.30	28.61	28.80	28.72	29.00	28.96	28.96	28.80	28.80
17	48.70	48.99	50.70	50.69	49.70	49.61	49.61	49.50	49.49
18	15.70	15.95	17.00	18.44	15.60	15.57	15.57	15.60	15.64
19	13.40	13.66	19.80	20.03	14.60	14.52	14.52	14.40	14.36
20	35.50	35.63	36.30	35.98	35.80	35.87	35.87	35.80	35.87
21	18.10	18.40	18.90	17.31	18.60	18.52	18.52	18.50	18.52
22	36.00	36.26	36.30	31.17	36.40	36.29	36.29	36.30	36.26
23	23.60	23.95	24.10	29.73	24.00	23.95	23.95	23.90	23.95
24	39.10	39.40	39.50	174.60	39.50	39.40	39.40	39.50	39.40
25	27.60	27.95	28.00		28.00	27.95	27.95	28.00	28.10
26	22.20	22.51	22.50		22.60	22.51	22.51	22.50	22.55
27	22.50	22.79	22.80		22.80	22.82	22.79	22.80	22.82
28(4α-Me)	27.40	27.64	27.60	27.68	28.20	28.14	28.14	28.10	28.00
29(4β-Me)	15.80	16.11	16.40	16.50	16.80	16.65	16.65	16.60	16.61
30(14α-Me)	17.30	17.47	25.40	25.19	17.30	17.24	17.24	17.30	17.35
OCH_3				51.51					
***CH*$_3$**COO(3)	20.90	21.12	[a]	21.27	[a]	21.27	21.31	[a]	21.31
CH_3***CO*O(3)	170.60	170.48	[a]	170.95	[a]	170.95	170.95	[a]	170.87
***CH*$_3$**COO(7)								[a]	21.78
CH_3***CO*O(7)								[a]	170.29

Carbon	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
1	33.11	33.11	34.78	26.24	26.24	26.24	26.20	24.80
2	23.99	23.99	23.83	24.22	24.22	24.22	24.18	24.49
3	79.96	79.96	79.46	77.17	77.17	77.17	77.28	77.56