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^{1}H and ^{13}C NMR assignments and conformational analysis of some tetracyclic compounds with a bicyclo[4.2.0]octane ring system

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ABSTRACT: This paper reports on the assignment of the ^{1}H and ^{13}C NMR spectra of 14 bicyclo[4.2.0]octane derivatives. Resonance assignments were made on the basis of one- and two- dimensional NMR techniques which included ^{1}H, ^{13}C, DEPT, HMQC and ^{1}H–^{1}H COSY and also 1D NOE difference spectroscopy. The ratio of the different conformers in the six-membered ring of the bicyclooctane system was determined by molecular mechanics calculations, analysis of proton spin–spin coupling constants and ^{13}C chemical shifts. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ^{1}H NMR; ^{13}C NMR; conformational analysis; MMX calculations; bicyclooctane derivatives; podocarpane derivatives; spongian precursors

INTRODUCTION

In recent years, a group of novel spongian tetra- and pentacyclic terpenoids have been isolated from marine sponges[1] and nudibranches.[2] These compounds have a common tetracyclic skeleton and show different cytotoxic properties.[1]

In the course of our work on the synthesis of two spongian pentacyclic diterpenes (**11a** and **11b**), using podocarpenones (**10a** and **10b**) as starting materials, we prepared several tetracyclic intermediates (**1**–**9**) which share a common bicyclo[4.2.0]octane system (rings C and D, Scheme 1).[3]

In this paper, we show that the presence of the rigid *cis*-cyclobutene ring generally makes the six-membered ring of this moiety (ring C) have a strong preference to exist in the boat conformation. However, when no additional substituents are present, the energies of the two conformations (boat and chair) differ by only 2–3 kcal mol^{-1} (1 kcal = 4.184 kJ). Therefore, the presence of certain substituents at C-13 can reverse the conformational equilibrium. The effect of several substituents at C-13 on the ratio of the various conformers was studied using molecular mechanics calculations, ^{1}H NMR chemical shifts and coupling constants and ^{13}C NMR chemical shifts.

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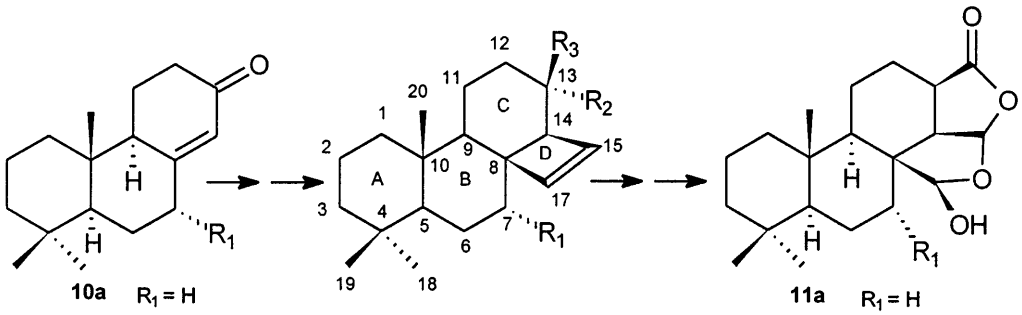


	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7	8	9
R_1	H	OH	H	OH	H	OH	H	OH	H	OH	H	H	H	H
R_2	=O	=O	H	H	CN	CN	H	H	CO_2Me	CO_2Me	OH	CO_2Me	OH	$C(SMe)_3$
R_3			CN	CN	H	H	CO_2Me	CO_2Me	H	H	CO_2Me	OH	$C(SMe)_3$	OH

Scheme 1

CCC 0749-1581/98/080579–08 $17.50

RESULTS AND DISCUSSION

Assignments

All ^{13}C NMR signals can be separated into different classes of carbon atoms using the editing technique DEPT, and according to their chemical shifts and multiplicities most signals in this study were assigned (Table 1). Complete assignment of the A–B rings signals was made by comparison with similar compounds.[4] The remaining signals (C-11, C-12, C-13, C-14, C-15, C-17) were assigned on the basis of their multiplicity, displacement and the ^{1}H–^{13}C shift correlation experiment (HMQC). The ^{1}H NMR spectrum was assigned using ^{1}H–^{1}H COSY, the ^{1}H–^{13}C HMQC shift correlation experiment and some 1D NOE difference experiments (NOED). The most relevant signals and coupling constants for the conformational analysis are shown in Table 2.

The stereochemistry of the cyclobutene ring was determined on the basis of the NOED experiments performed on **1a** and **1b**. The NOE enhancements observed between H-17 (irradiated) and H-20 in both compounds conclusively proved the β-orientation of the previously mentioned cyclobutene ring. Since the rest of the compounds were obtained by addition reactions on the carbonyl group at C-13 of **1a** and **1b**, without modifying the cyclobutene system, the stereochemistry of this moiety remains then fixed for all of them.

Additional NOED experiments were performed to determine the stereochemistry of the new asymmetric carbon (C-13) in the intermediates (**2**–**9**). The NOE effect observed in **6** between the methyl of the carbomethoxy moiety (irradiated) and the olefinic proton H-15 proved the stereochemistry assigned. In the same way, irradiation of H-15 in the isomer **7** gave a NOE enhancement to 13-OH. This fact, together with the absence of NOE enhancement to H-15 from the methyl of the carbomethoxy group, indicated the α-disposition of the methyl ester function in this compound. Since **6** and **7** are obtained from **8** and **9** by hydrolysis of the *ortho* thioester function, the stereochemistry at C-13 of these two precursors is unambiguously established. Similarly, irradiation of H-15 of **4a** gave an NOE enhancement to the methyl of the carbomethoxy moiety, whereas irradiation of the same proton of **5a** gave an NOE enhancement to H-13, supporting conclusively the assigned stereochemistries for the two isomers. The assigned stereochemistry at C-13 of the two nitriles **2a** and **3a** was achieved by comparing their spectroscopical data were those from esters **4a** and **5a**. In the same way, the stereochemistry at the mentioned C-13 was assigned for the four corresponding 7-hydroxy derivatives (**2b**, **3b**, **4b** and **5b**).

Conformational analysis

The conformational study was carried out using molecular mechanics calculations by means of the PCMODEL program. For every compound (**1**–**9**) a rotational analysis incrementing the dihedral angle C-11—C-12—C-13—C-14 in 1° steps from −70° to 70°

Table 1. ^{13}C NMR data for compounds **1–9**[a]

Carbon	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6	7	8	9
1	38.89	38.60	38.52	38.21	38.24	37.97	38.66	38.27	38.49	38.12	38.47	38.67	38.57	38.87
2	18.46	18.46	18.46	18.42	18.48	18.42	18.56	18.48	18.57	18.53	18.58	18.52	18.53	18.62
3	41.97	41.95	41.93	41.88	41.87	41.85	42.07	41.94	42.03	41.91	42.08	42.04	42.11	42.27
4	33.30	32.83	33.25	32.80	33.26	32.82	33.28	32.76	33.29	32.78	33.27	33.27	33.21	33.41
5	56.00	47.10[b]	56.20	47.39	55.85	47.34	56.34	47.43	56.19	47.05	56.12	56.36	56.25	56.45
6	20.53	27.32	20.52	27.82	20.57	27.32	20.71	27.52	20.64	26.42	20.74	20.52	20.82	20.59
7	38.49	73.12	38.38	74.00	38.53	73.96	38.66	74.50	38.93	74.03	39.27	38.67	39.52	40.22
8	53.74	57.60	50.56	54.05	50.67	54.45	51.00	54.45	50.97	54.91	51.72	52.23	53.49	53.52
9	54.72	47.81[b]	50.61	43.96	50.01	43.63	51.17	44.41	51.13	44.17	49.70	50.53	49.54	57.44
10	38.25	38.28	38.28	38.40	38.53	38.62	38.30	38.34	38.41	38.57	38.31	38.37	38.24	38.56
11	18.24	17.44	15.83	15.29	15.20	14.76	16.14	15.58	15.89	15.44	15.33	16.96	16.66	16.37
12	39.98	40.38	21.59	21.62	20.64	20.67	20.31	20.32	20.20	20.49	28.18	30.33	28.72	40.22
13	213.08	211.88	25.29	25.92	25.18	25.80	39.57	40.13	39.86	39.08	77.46	75.65	85.34	82.35
14	63.14	59.79	50.80	47.98	50.72	47.80	51.56	48.41	50.64	46.89	57.43	55.54	58.59	55.91
15	132.40	134.60	134.10	136.65	134.17	136.74	136.02	138.45	136.40	137.60	134.74	134.70	136.13	135.75
16			122.30	122.22	123.93	123.58	176.28	176.16	177.08	178.75	177.39	176.60	81.22	81.48
17	147.14	145.04	146.51	144.36	146.73	144.96	145.06	143.03	144.75	143.34	145.47	145.79	144.19	142.57
18	33.42	33.14	33.51	33.24	33.36	33.12	33.57	33.27	33.41	33.13	33.45	33.40	33.40	33.28
19	21.56	21.52	21.71	21.66	21.69	21.68	21.75	21.66	21.72	21.81	21.68	21.64	21.54	21.30
20	15.12	14.51	14.72	13.94	14.78	14.03	14.77	13.96	14.80	14.15	14.75	14.77	14.87	16.22
SCH_3													16.30	16.09
OCH_3							51.41	51.48	51.61	52.32	52.66	52.46		

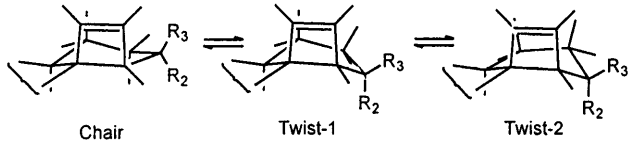
[a] Spectra measured in $CDCl_3$ at 298 K and referenced relative to TMS (δ, ppm).
[b] Assignments interchangeable.

Table 2. Selected ^{1}H NMR chemical shifts (ppm) and coupling constants (Hz) of compounds **1–9**[a]

Compound	H-9	H-12α	H-12β	H-13	H-14	H-15	H-17
1a	1.13[b]	2.15(dddd, 19.0, 11.0, 8.1, 2.0)	2.61(dddd, 19.0, 5.9, 1.7, 0.7)		2.88(bs)	5.99(dd, 2.7, 1.2)	6.35(d, 2.7)
1b	1.65[b]	2.21(dddd, 19.1, 10.9, 7.8, 1.7)	2.62(dddd, 19.1, 5.3, 2.0, 1.0)		3.18(m)	6.11(dd, 2.8, 1.3)	6.38(d, 2.8)
2a	1.23(dd, 12.6, 6.0)	1.8–2.0(m)	1.8–2.0(m)	2.85(ddd, 11.5, 7.2, 3.8)	2.59(ddd, 3.8, 0.9, 0.7)	6.19(dd, 2.9, 0.7)	6.44(d, 2.9)
2b	1.71(dd, 13.0, 5.9)	1.85–1.95(m)	1.85–1.95(m)	2.92(ddd, 10.1, 8.8, 3.8)	2.99(bd, 3.8)	6.30(dd, 3.0, 0.9)	6.27(d, 3.0)
3a	1.87(dd, 13.0, 5.7)	1.8–2.0(m)	1.8–2.0(m)	2.82(ddd, 6.4, 2.2, 2.2)	2.65(ddd), 2.2, 1.4, 0.9)	5.93(dd, 2.9, 0.9)	6.42(d, 2.9)
3b	2.19(dd, 13.2, 5.9)	1.88(ddddd, 14.5, 10.8, 3.9, 2.4, 1.6)	1.98(dddd, 14.5, 10.5, 6.4, 5.3)	2.89(ddd, 6.4, 2.4, 2.4)	3.01(ddd, 2.4, 1.6, 0.9)	6.05(dd, 2.9, 0.9)	6.29(d, 2.9)
4a	1.28(dd, 12.4, 5.5)	1.71(ddddd, 13.9, 10.2, 5.7, 5.7, 1.7)	1.86(dddd, 13.9, 12.9, 10.9, 5.3)	2.73(ddd, 12.9, 5.7, 3.7)	2.56(ddd, 3.7, 1.7, 0.9)	6.11(dd, 2.9, 0.9)	6.36(d, 2.9)
4b	1.75(dd, 12.7, 5.7)	1.75(m)	1.84(dddd, 13.5, 12.7, 10.7, 4.9)	2.81(ddd, 12.7, 6.1, 3.7)	2.92(ddd, 3.7, 1.0, 1.0)	6.23(dd, 2.9, 1.0)	6.19(d, 2.9)
5a	1.23[b]	1.8–2.0(m)	1.8–2.0(m)	2.62(ddd, 6.9, 3.0, 2.5)	2.79(bs)	6.00(dd, 2.9, 0.9)	6.31(d, 2.9)
5b	1.64(dd, 12.5, 5.3)	1.9–2.1(m)	1.9–2.1(m)	2.70(ddd, 7.8, 2.4, 2.4)	2.98(bs)	6.12(dd, 2.9, 1.0)	6.21(d, 2.9)
6	1.88(dd, 12.8, 5.1)	1.64(dddd, 13.9, 11.0, 5.2, 2.2)	2.21(ddd, 13.9, 11.5, 4.0)		2.31(dd, 2.2, 0.9)	6.01(dd, 2.8, 0.9)	6.42(d, 2.8)
7	1.29(dd, 12.2, 5.6)	2.03(dddd, 14.1, 10.3, 6.0, 1.7)	1.87(ddd, 14.1, 9.8, 5.6)		2.71(dd, 1.7, 0.9)	6.18(dd, 2.9, 0.9)	6.44(d, 2.9)
8	1.90(dd, 11.9, 5.2)	1.83(dddd, 14.4, 10.0, 6.5, 2.7)	2.16(dddd, 14.4, 9.6, 4.0, 1.0)		2.66(d, 0.7)	6.29(dd, 3.0, 0.7)	6.31(d, 3.0)
9	1.05(dd, 11.3, 2.8)	2.02(ddd, 14.4, 13.0, 4.5)	1.94(ddd, 14.4, 4.3, 3.2)		2.99(d, 1.0)	6.17(dd, 2.9, 1.0)	6.25(d, 2.9)

[a] Spectra measured in $CDCl_3$ at 298 K and referenced relative to TMS.
[b] Not resolved.

using the option D-DRV was performed. In most cases, three minimum energy conformations were found. These were chair (dihedral angle $>0°$), twist-1 (dihedral angle between 0° and $-45°$) and twist-2 (dihedral angle $<-45°$) (Scheme 2), the rotational barrier among them being low (3–5 kcal mol^{-1}) or even zero.



Scheme 2

Every conformer of every compound was independently minimized. In the case of unstable conformers, with a low rotational barrier, the dihedral angle was fixed with the FXTOR option. For **1b**, **2b**, **3b** and **4a**–**9**, which have groups such as OH and CO_2Me that can occur in different non-equivalent spatial orientations, an independent rotational study for each group was carried out in order to find the most stable conformation. In the case of compounds having a hydroxyl group able to form hydrogen bonds, the option H-BND activated was used.

Results obtained from these calculations are shown in Table 3, together with the conformer population (n_C, n_{T_1}, n_{T_2}) expressed in a molar fraction and calculated using the relation between the Gibbs free energy (ΔG) and the equilibrium constant (K):[5]

$$\Delta G_{\text{Chair}-\text{Twist-1}} = -RT \ln(K_{\text{Chair}-\text{Twist-1}})$$

$$\Delta G_{\text{Twist-2}-\text{Twist-1}} = -RT \ln(K_{\text{Twist-2}-\text{Twist-1}})$$

where $R = 1.988 \times 10^{-3}$ kcal K^{-1} mol^{-1} and $T = 298$ K. Considering $K_{\text{Chair}-\text{Twist-1}} = n_{T_1}/n_C$, $K_{\text{Twist-2}-\text{Twist-1}} = n_{T_1}/n_{T2}$ and $n_C + n_{T_1} + n_{T_2} = 1$, and also considering $\Delta S \approx 0$, so that $\Delta G \approx \Delta H \approx \Delta E_{MMX}$, then

$$n_{T_1} = 1/\{\exp[(E_{T_1} - E_C)/RT] + \exp[(E_{T_1} - E_{T_2})/RT] + 1\} \quad (1)$$

$$n_{T_2} = n_{T_1} \exp[(E_{T_1} - E_{T_2})/RT] + 1\} \quad (2)$$

and

$$n_C = 1 - n_{T_1} - b_{T_2} \quad (3)$$

(see Table 3).

From the above results, it can be seen that when a substituent different from H is present at C-13β (**2a**, **2b**, **4a**, **4b**), conformers twist-1 and twist-2 have similar energies, around 3 kcal mol^{-1} lower than that of the chair conformer. Also, owing to the small barrier between them, these compounds exist at room temperature in a rapid conformational equilibrium between the two twist conformations. If these substituents occur at C-13α (**3a**, **3b**, **5a** and **5b**), their axial orientation makes the twist conformations slightly less stable than before. Then, the difference in energy decreases to reach 1–2 kcal mol^{-1}, thereby increasing the population of molecules in the chair conformation until it reaches 2–8%. When two substituents are present at C-13 (**6**–**9**) the energy difference between the twist and the chair conformations is smaller. In the case of **7**, where the largest group is at C-13α, the population of the chair conformer is 17%. In the case of **9**, with a very bulky group [—$C(SMe)_3$] at the α-face, the chair conformation is 4–5 kcal mol^{-1} more stable than any of the twist conformations, which means that this compound only occurs in the chair conformation at room temperature.

Finally, when a carbonyl group exists at C-13 (**1a** and **1b**), the sp^2 hybridization of this carbon makes the chair

Table 3. Molecular geometry and distribution of the different conformations of compounds 1–9

	Chair			Twist-1			Twist-2		
Compound	E_{Chair}[a]	n_c[b]	Dihedral[c]	$E_{Twist-1}$[a]	n_{T_1}[b]	Dihedral[c]	$E_{Twist-2}$[a]	n_{T_2}[b]	Dihedral[c]
1a	65.94	0.70	5	66.46[d]	0.29	−21	68.40[d]	0.01	−57
1b	67.21	0.76	9	67.91[d]	0.23	−21	70.03[d]	0.01	−57
2a	70.95[d]	0.00	41	67.90[d]	0.46	−37	67.80	0.54	−48
2b	71.50[d]	0.00	27	68.75	0.49	−36	68.72	0.51	−48
3a	70.10	0.02	42	68.07	0.53	−42	68.17	0.45	−53
3b	71.24	0.03	38	69.54	0.49	−42	69.56	0.48	−47
4a	73.31	0.00	29	70.15	0.61	−44	70.41	0.39	−57
4b	74.56	0.00	27	71.44	0.58	−41	71.64	0.42	−54
5a	72.53	0.08	49	71.61	0.40	−37	71.45	0.52	−53
5b	73.74	0.03	44	71.93	0.53	−36	72.04	0.44	−50
6	71.99	0.01	16	69.85	0.53	−33	69.94	0.46	−54
7	71.70	0.17	33	70.88	0.68	−6	71.79	0.15	−57
8	82.17[d]	0.03	18	80.41	0.65	−18	80.84	0.32	−61
9	79.88	1.00	18	83.12[d]	0.00	−20	83.99	0.00	−57

[a] Steric energy in kcal mol^{-1} obtained from MMX calculations.
[b] Molar fraction calculated from Eqns (1), (2) and (3).
[c] Dihedral angle C-11—C-12—C-13—C-14.
[d] Unstable conformations obtained using the option FXTOR of the PCMODEL program.

conformation more stable (70–76% of the population). However, owing to the small dihedral angle C-11—C-12—C-13—C-14 (5° and 9°), carbons C-11, C-12, C-13, C-14 and C-8 are almost in the same plane, and it would be more correct to term this conformation an envelope conformer.

^{1}H NMR and coupling constants analysis

There are some signals in the ^{1}H NMR of **1–9** that are useful for studying the favourite conformations adopted by those compounds, specifically the chemical shift of the H-9 signal and the coupling constants between H-13 and H-12/H-11 when H-13 exists or between H-12 and H-11 when H-13 does not exist.

From Scheme 2, it can be seen that the dihedral angle between H-9 and the two H-11s is very similar in the three possible conformations, so the value of the coupling constants of H-9 does not help in studying the preferred conformation. Nevertheless, the chemical shift of proton H-9 is very sensitive to the 1,4-interactions with substituents at C-13, specifically to R_2 since this is at the same face of the molecule as H-9. In the chair conformation, the above-mentioned substituent R_2 adopts an equatorial disposition, far from H-9, so the effect on the mentioned proton is very small. However, in the twist-1 and twist-2 conformations R_2 is axially oriented so it can have an important effect on H-9. This 1,4-diaxial interaction usually induces a deshielding effect, except for the cases were R_2 is an ester group (—CO_2Me) because its magnetic currents can make H-9 shift upfield.

From Table 2, it can be seen that the signal corresponding to proton H-9 when $R_1 = H$ and $R_2 = H$ appears between 1.2 and 1.3 ppm (**2a**, **4a**). However, the chemical shift of proton H-9 changes when R_2 is different from H. For instance, in **3a**, **6** and **8** (with R_2 = CN, OH), H-9 resonates 0.5–0.7 ppm at lower field compared with **2a** and **4a**, which is consistent with the twist conformations predicted. When $R_2 = CO_2Me$ (in **5a** and **7**), the chemical shift of H-9 does not change or changes upfield because H-9 is in the diamagnetic zone of the carbonyl. Finally, for **9** [with $R_2 = C(SMe)_3$], H-9 shifts to 1.05 ppm, considerably upfield compared with compounds in which $R_2 = H$ (**2a**, **4a**), which is consistent with a chair conformation at room temperature. Further support for this conformational assignment was derived from the comparison with the chemical shift of H-9 in some analogues in which ring C can only adopt a chair conformation.[6]

The chemical shift of proton H-9 in **2b**, **3b**, **4b** and **5b** is also consistent with the twist conformations. However, the presence of an additional hydroxyl group at C-7 induces a shielding effect of *ca.* 0.5 ppm in H-9, due to the 1,3-diaxial interaction.

A more accurate conformational analysis can be inferred from the study of the coupling constants. As can be seen in Scheme 2, the dihedral angles between H-13 and H-12/H-14 or between H-12 and H-11 are different enough in the three conformations to permit not only a qualitative but also a quantitative study.

Coupling constant data [^3J(HH)] between H-13 and H-12/H-14 (**2–5**) and between H-12 and H-11 (**1a**, **1b** and **6–9**) are shown in Table 4. The [^3J(HH)] (J_{Chair}, $J_{Twist\text{-}1}$, $J_{Twist\text{-}2}$) were obtained using the PMR option of the PCMODEL program for every calculated conformation (Table 3). This option makes use of a generalization of the Karplus equation.[7] The average ^3J(HH) was calculated by including the mole fractions of every conformation from the equation $n_C J_{Chair} + n_{T_1} J_{Twist\text{-}1} + n_{T_2} J_{Twist\text{-}2}$,[8] where n_C, n_{T_1} and n_{T_2} are calculated using Eqns (1–3).

Agreement can be seen between the experimental values and the calculated averages. Differences (last column in Table 4) can be explained by the fact that the calculations were performed using only the most stable conformations without considering the small vibrational variations, the use of angular constraints in certain conformers and the possibility of similar energy rotamers in the cases of groups: CO_2Me, OH and $C(SMe)_3$. It can be concluded that the mole fractions calculated using molecular mechanics are very similar to the real values, and the study of the ^{1}H coupling constants in general confirms the results of the previous MM-based conformational analysis. In the case of **7** the experimental values could accommodate a higher population for twist-2.

It is worth noting the unusual long-distance coupling constant in **8** between the proton of the hydroxyl group at C-13 and the protons H-12 (dd, J 2.7 and 1.0 Hz).

^{13}C NMR analysis

The ^{13}C NMR data (Table 1) show that C-9 and C-12 chemical shifts are very dependent on the conformational changes in all the compounds (**1–9**). The signal corresponding to C-9 is independent of the substituents R_2 and R_3, which are δ to the carbon in question. However, it is strongly dependent on the orientation of C-13 because this carbon is in the γ-position with respect to C-9. In the case of the twist conformations, the relative orientation between C-13 and C-9 is nearly γ-eclipsed, since the dihedral angle C-9—C-11—C-12—C-13 varies between 30° and $-30°$. This is a strong γ-interaction which produces a shielding effect on C-9. However, in the chair conformation the relative disposition between C-9 and C-13 is γ-*gauche*, resulting in a smaller γ-effect. The C-9 resonance in a chair conformation is shift to a higher frequency relative to the twist conformers.

Table 1 shows that the signal due to C-9 appears at around 50 ppm in **2a**, **3a**, **4a**, **5a**, **6**, **7** and **8**, and the same signal appears at around 44 ppm in **2b**, **3b**, **4b** and **5b** (because of the γ-effect exerted by the additional hydroxyl group at C-7). Therefore, it can be concluded that all prefer the same conformation. In the compounds with a carbonyl group at C-13 (**1a** and **1b**) the signal corresponding to C-9 appears at 54.7 and 47.8

Table 4. Coupling constants $^3J_{HH}$ (Hz) of some important protons of 1–9

Compound	Vicinal protons	J_{Chair} [a]	$J_{Twist\text{-}1}$ [a]	$J_{Twist\text{-}2}$ [a]	Average[b]	Exper	Diff.[c]
1a	12α–11α	5.2	8.5	11.9	6.2	8.1	1.9
	12α–11β	12.7	9.9	1.6	11.8	11.0	−0.8
	12β–11α	1.6	0.3	4.8	1.3	1.7	0.4
	12β–11β	5.7	9.1	11.7	6.8	5.9	−0.9
1b	12α–11α	4.8	8.5	11.9	5.7	7.8	2.1
	12α–11β	12.9	9.9	1.6	12.1	10.9	−1.2
	12β–11α	1.9	0.3	4.8	1.5	2.0	0.5
	12β–11β	5.3	9.0	11.7	6.2	5.3	−0.9
2a	13–12α	6.0	6.2	4.6	5.3	7.2	1.9
	13–12β	1.4	10.7	11.8	11.3	11.5	0.2
	13–14	10.3	3.0	2.7	2.9	3.8	0.9
2b	13–12α	9.1	6.3	4.6	5.4	8.1	2.7
	13–12β	1.1	10.6	11.8	11.2	11.2	0.0
	13–14	9.7	2.8	2.5	2.7	3.8	1.1
3a	13–12α	6.0	1.6	2.6	2.1	2.2	0.1
	13–12β	11.1	6.0	4.3	5.3	6.4	1.1
	13–14	3.3	2.9	2.8	2.9	2.2	−0.7
3b	13–12α	10.6	1.5	1.9	1.9	2.4	0.5
	13–12β	6.6	6.1	5.3	5.7	6.4	0.7
	13–14	2.2	3.0	3.1	3.0	2.4	−0.6
4a	13–12α	8.4	4.9	3.0	4.2	5.7	1.5
	13–12β	1.0	11.6	12.3	11.8	12.9	1.1
	13–14	9.6	2.4	2.5	2.5	3.7	1.2
4b	13–12α	8.5	5.3	3.4	4.5	6.1	1.6
	13–12β	1.0	11.3	12.2	11.6	12.7	1.1
	13–14	9.3	2.3	2.2	2.3	3.7	1.4
5a	13–12α	11.9	1.0	2.4	2.6	2.5	−0.1
	13–12β	4.7	7.6	4.7	5.9	6.9	1.0
	13–14	5.6	2.4	2.7	2.8	3.0	0.2
5b	13–12α	11.4	1.0	2.0	1.7	2.4	0.7
	13–12β	5.4	7.7	5.3	6.6	7.8	1.2
	13–14	3.9	2.5	2.9	2.7	2.4	−0.3
6	12α–11α	3.8	11.0	11.2	11.0	11.0	0.0
	12α–11β	13.5	6.6	0.5	3.9	5.2	1.3
	12β–11α	3.7	0.4	6.2	3.1	4.0	0.9
	12β–11β	3.1	10.8	11.1	10.8	11.5	0.7
7	12α–11α	2.7	6.9	9.4	6.5	6.0	−0.5
	12α–11β	13.7	11.5	0.3	10.2	10.3	0.1
	12β–11α	4.5	1.3	8.8	2.9	5.6	2.7
	12β–11β	2.3	6.4	9.3	6.1	9.8	3.7
8	12α–11α	3.9	8.3	8.9	8.3	10.0	1.7
	12α–11β	13.4	10.3	0.4	7.3	6.5	−0.8
	12β–11α	4.0	0.7	9.0	3.4	4.0	0.6
	12β–11β	2.7	7.5	9.2	7.9	9.6	1.7
9	12α–11α	3.9	8.6	6.0	3.9	4.5	0.6
	12α–11β	13.4	9.8	1.8	13.4	13.0	−0.4
	12β–11α	3.8	0.7	11.3	3.8	4.3	0.5
	12β–11β	3.0	7.9	6.7	3.0	3.2	0.2

[a] Coupling constants for the chair, twist-1 and twist-2 conformations calculated with the option PMR of the PCMODEL program based on Karplus generalized equation.[7]
[b] Calculated from the equation $n_C J_{Chair} + n_{T_1} J_{Twist\text{-}1} + n_{T_2} J_{Twist\text{-}2}$[8] ($n_C$, n_{T_1} and n_{T_2}, see Table 3).
[c] Difference = Experimental − Average.

ppm, *ca.* 4 ppm to higher frequency. The deshielding implies that whereas the former compounds exist predominantly in the twist conformations, the latter have a higher population of molecules in the chair conformation. Finally, for **9** the C-9 carbon resonates at 57.4 ppm, an appreciably higher frequency confirming that the chair conformation is favoured.

Also of interest in the conformational analysis are the C-12 resonances since the C-12 carbon has a *γ-gauche* interaction with C-15 (see Scheme 2). This effect is transmitted through proton H-12β, so the distance between this proton and carbon C-15 will determine the intensity of the effect. These distances are *ca.* 4.3, 3.4 and 2.6 Å for the chair, twist-1 and twist-2 conformations, respectively. Therefore, in the cases of twist-2 conformations with the shortest distance, the effect will be the highest, so the signal due to C-12 will be upfield with respect to the chair conformation (with the lowest effect) and to the twist-1 conformation (with an intermediate effect).

Table 1 shows an enormous range of values owing to the different kind of substituents at C-13, which makes it very difficult to draw any obvious conclusion. Nevertheless, it is possible to compare the signal due to C-12 between epimers at C13 (**2a**–**3a**, **2b**–**3b**, etc).

It should be noted that, in the case of epimers, the presence of a substituent in the axial disposition shifts the α-carbon about 1–2 ppm to lower frequency compared with the equatorial isomer.[9] In some cases the variation of the γ effect between C-12 and C-15 is not large enough to compensate this effect.

As has been concluded previously (theoretical calculations and ^{1}H NMR analysis), in compounds in which R_3 is more voluminous than R_2 (**2a**, **2b**, **4a**, **4b**, **6** and **8**), twist will be the favourite conformation, whereas for the corresponding epimers in which R_2 is mor bulky (**3a**, **3b**, **5a**, **5b**, **7** and **9**), the number of molecules in the chair conformation will increase. The difference in the chemical shift of C-12 in the two partners of every pair of epimers will be indicative of the tendency towards a chair conformation. The smallest difference in the shift of C-12 is -1 ppm (see the previous paragraph) in the epimers **2a**–**3a**, whereas the highest difference ($+11.5$ ppm) corresponds to the pair **8**–**9**, with the rest showing intermediate values (e.g. -0.1 ppm for **4a**–**5a** and $+2.1$ ppm for **6**–**7**). In conclusion, a deshielding effect in the chemical shift due to carbon C-12 is observed as the volume of the substituent in the α face (R_2) increases and therefore the ratio of molecules in the chair conformation increases.

CONCLUSIONS

Some tetracyclic intermediates in the synthesis of spongain diterpenes share a common bicyclo[4.2.0]octane system in which the conformation of the six-membered ring is dependent on the substituents at C-13. From a detailed study of the ^{1}H and ^{13}C NMR spectra, together with molecular mechanics calculations, the ratios of the different conformers (chair, twist-1 and twist-2) of those systems have been calculated. It can be concluded that both twist conformations with a similar energy are generally preferred to the chair conformation, so those compounds exist, at room temperature, in a rapid conformational equilibrium between the conformers twist-1 and twist-2.

However, when more voluminous substituents at C-13α are present, the population in the chair conformation increases to the detriment of the twist conformers, and in the case of the substituent being $R_2 = C(SMe)_3$ (**9**), the chair conformation is the major one. Also, when a carbonyl group exists at C-13 the sp^2 hybridization of this carbon makes the chair conformation more stable (*ca.* 75% of the population).

EXPERIMENTAL

Molecular mechanics calculations[10] were performed using the MMX force field, which is a derived version of the MM2 program, developed by Allinger and implemented in the PCMODEL (4.0) program (Serena Software, Bloomington, IN, USA).

^{1}H, ^{13}C NMR and DEPT spectra were measured on a Varian XL-300 spectrometer (299.95 MHz for ^{1}H and 75.43 MHz for ^{13}C) operating at a probe temperature of 298 K using a dual ^{1}H/^{13}C 5 mm probe. The ^{1}H measurement conditions were spectral width 4000 Hz, 90° pulse with 18 μs, acquisition time 3.7 s, number of transients 16–64 and 0.1 Hz digital resolution.

^{1}H–^{1}H COSY, ^{1}H–^{13}C HMQC and NOED spectra were measured on a Varian 400 spectrometer (399.95 MHz for ^{1}H and 100 MHz for ^{13}C) equipped with a 5 mm indirect detection probe operating at 298 K. The signal of the deuterated solvent $CDCl_3$ was taken as the reference (the singlet at δ 7.24 ppm for ^{1}H and the triplet centered at δ_C 77.00 for ^{13}C NMR). Sample concentrations were typically in the range 5–20 mg per 0.5 ml of $CDCl_3$. All these experiments were performed using either standard pulse sequences supplied by the spectrometer manufacturer or slightly modified pulse sequences. NOED experiments were typically acquired with 8K data points covering a spectral width of 3200 Hz and with a 1.5 s presaturation time. Spectra at each presaturation position were interleaved in groups of four scans to minimize artefacts due to instrument inconsistencies and processed with a 1 Hz exponential line broadening to reduce subtraction artefacts. The HMQC spectrum was obtained using a spectral width of 3200 Hz in F_1 and 16 000 Hz in F_2. A total of 256 increments were collected with eight transients per increment and an acquisition time of 0.1 s.

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