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Palytoxin-related C-Glycosides: a Conformational Study using Molecular Mechanics and an Analysis of Coupling Constants

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Abstract: The conformational behaviour of ten D-gluco- or 2-deoxy-D-gluco-C-glycosides related to Palytoxin were studied. Theoretical coupling constants were derived by applying Altona's empirical generalization of Karplus equation to the torsional angles and conformational populations. The global rms (root-mean-square) deviation of the calculated coupling constants from experimental values was 0.873 Hz.

INTRODUCTION

It has been said[1] that, "If there is a Mount Everest of chemistry, it has to be Palytoxin". Each stage of its study was a monumental undertaking that required much planning and strenuous team-work. Long and arduous was the labour to isolate it. Exceptional perseverance by many in the face of much adversity was required to determine its complex structure. The struggle to achieve complete synthesis was particularly enormous and difficult; it required close enthusiastic collaboration and the mutual support of many scientists thinking and working hard in many centres of investigation in many countries.

The summit of this figurative mountain has finally been conquered by Professor Yoshito Kishi and his collegues in the Department of Organic Chemistry of Harvard University with their epic total synthesis of Palytoxin carboxylic acid.[2]

As part of their preparatory studies to determine the structure of the natural marine compound Palytoxin before attempting its synthesis, Y. Kishi et al. carried out a comparative study using ^{1}H-NMR to determine the preferred conformation of a number of C-glycosides and O-glycosides,[3] because they had recognised that large parts of the structure of Palytoxin structure could be viewed as C-oligosaccharides. This important observation oriented the Harvard chemists in the right direction as they approached the enormous task of complete synthesis of the large and complex Palytoxin molecule.[2]

For their studies of molecular conformation, Y. Kishi et al. had to prepare a series of previously monodeuterated target products by replacing diastereoselectively one of the diastereotopic methylene protons on the α-carbon by a deuterium atom. However, we suggest that this enormous and lengthy task of synthesis could be avoided if the methods of theoretical calculation could be made more reliable.

We use C-glycosides as Chiral Synthons to synthesize C-nucleosides and other potential useful products[4] and also to use them as tools in conformational and configurational studies. We used NMR for the structural analysis of the C-glycofuranosyl-glycosides and -nucleosides.[5]

The empirical force-field calculations of Molecular Mechanics are frequently used to calculate the geometries and energies of hydrocarbons and other molecules that might contain several different heteroatoms.[6] The precision and reliability of these types of calculation has stimulated their application to the stereochemical problems of carbohydrate chemistry[7] and U. Burkert[8] has published molecular mechanics calculations for cyclic acetals of pentofuranoses and related pentitols, and C-glycosides. A. A. Ovchinnikov[9] carried out a conformational analysis of cardiac glycosides and E. Osawa[10] has described similar studies of alditol peracetates as one approach designed to resolve the conformation of Palytoxin in solution. Recently, in this laboratory, we successfully employed a molecular-mechanic technique (Allinger's MM2) to determine the structure of several glycofuranosyl-C-glycosides and -C-nucleosides in preparative work for a new synthesis of showdomycin.[11] The technique appears to have much potential for this type of study.

A combination of molecular mechanics with the Karplus equation is being used at present time to analyse coupling constants.[12] One method, developed by E. Osawa[13], uses molecular mechanics calculations (MM2') to determine all the possible conformers of the target molecule and then calculates the weighted coupling constants from the previously-calculated geometries. S. Masamune and E. Osawa used this method to analyse the coupling constants of alditols peracetates[10]; it was also used by C. Jaime[14] in a similar study of di- and trisubstituted γ-lactones and other compounds.

RESULTS AND DISCUSSION

Computational Technique. The program MM2[15] modified by E. Osawa[13b] (MM2') was used throughout this present work. Osawa's modification includes the "tree" option for depicting the torsional potential energy surface, and the "vicinal proton-proton NMR coupling constant calculation" option 2(the same as 3JHH program[13b]). Up to six bonds may be rotated every 120 degrees, twice, so that all three staggered rotamers can be minimized. Using these two programs, all the vicinal proton-proton NMR coupling constants, except the conformers that contain at least one "forbidden"[16] *Gauche(+)-Gauche(−)* sequence, can be calculated by Haasnoot's empirical generalization of the Karplus equation, for all the MM2-calculated geometries, these are then weighted from the population of the preferred conformations.

Conformational Analysis. Compounds **(1)** to **(10)** are all derivatives of D-glucopyranosyl- or 2-deoxy-D-glucopyranosyl-C-glycosides, and consequently, only the $^4C_1$-chair conformation was considered. One limitation of MM2 method is that it is not appropiate for the study of hydrogen bonds. The hydrogen bonds calculated for alcohols and amines do not agree very well with those derived from experiments. In general, the MM2 hydrogen bonds are not sufficiently strong and are usually too long.

In addition, the calculation considers the molecule in the gas phase or in a non polar solvent. However, we need to correlate the calculated coupling constants with a set of experimental values determined in D_2O or CD_3OD, and fortunately, solvatation by these good hydrogen-bond acceptors minimises the contribution of intramolecular hydrogen bonds. Because of this, we only calculate one rotamer of each hydroxyl group, the same one in each case.

The corresponding conformational population of compounds **(1)** to **(10)**, were determined minimizing all possible conformations[16] of alkyl side-chains using the "tree" option of MM2' of Osawa. This enabled us to obtain the prefered conformations, geometries, energies and relative populations of each compound. The results are included in Tables I to X, and also show the populations and relative energies of the principal conformations[17] for all the products. The conformers are then denoted by the rotamers involved: **A** for Anti, **+** for Gauche(+) and **-** for Gauche(−). Our results agree with those previously reported.[3] Thus, all compounds reveal strong preference for the Anti conformation of the C2-C1-C7-C8 torsional angle. Other significative contributions (higher that 5%) are: one Gauche(−) conformation (10.8%) for compound **(5)**; a Gauche(−) conformation (7.9%) for compound **(6)**; and two Gauche(+) conformations (17.9% and 12.3%) for compound **(10)**.

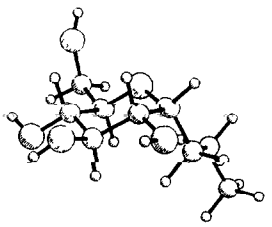
More complete and definitive information may be obtained from the data in Tables I to X. These give the mean values (M.V.) for the principal torsional angles: C1-C7-C8-C9, C2-C1-C7-C8, and C4-C5-C6-O6, and in addition, for compounds **(2)** to **(5)** and **(7)** to **(10)**, the torsional angle C7-C8-C9-O9. To ilustrate 3-dimensional relationships, we include for each compound, a stereo-view of what we term the Conformational Gravity Center, this structure depicts the mean torsional angle values (a). We also include a numbered projection (b) together with a superposed image of the more stable conformer (the darker lines) and the conformational gravity center (the lighter lines). The (c) figures show that structures **(5)** and **(10)** have the largest deviations as Y. Kishi previously reported.

α-C-Glicosydes. In compound **1**, the **AA+** conformer is revealed as the most stable (50.57%). Conformer **AA-** resulted in 1.211 Kcal/mol less stable, showing a greater dipolar interaction (-1.7714 for **AA-** and -2.524 for **AA+**). The corresponding mean values showed a small deviation (180° - 164° = 16°) for torsional angle C1-C7-C8-C9, from a higher contribution of G(+) conformers. A Gauche(−) conformation for this torsional angle showed a 1,3-diaxial like interaction between C1-O(ring) and C8-C9. For compound **2**, conformer **AA-A** appears to be the most stable (42.9%). The mean values are very similar as figure 2c shows. Unlike compound **1**, conformer **AA-A** is 0.454 Kcal/mol more stable than **AA+A**. In compound **3**, conformer **AA-A** is the most stable (39.4%) and as **1**, it reveals its preference for a Gauche(+) conformation of the C4-C5-C6-O6 torsional angle. The last two compounds, **4** and **5**, are clearly different because they both reveal only small preference for the more stable **+A-A** conformer (26.3 and 22.1% respectively). In both these cases, the **AA-A** conformer has a 1,3-diaxial-like interaction between the C1-O(ring) and the C8-O8 bonds, which destabilizes them. The next most stable conformers are the **+A+A**. Thus, as figure 4c shows, the mean torsional angle values for compound **4** show considerable deviations from the Anti conformation of C1-C7-C8-C9 (180° - 106° = 74°).

Main geometrical features of conformers for Compounds (1) and (2)

TABLE I Compound (1)

Conf.	(a)	(b)	(c)	E(REL) KCAL	POPUL %
AAA	176.38	178.70	-179.39	0.676	11.522
AA+	176.38	178.81	54.08	0.000	50.571
AA-	175.65	177.74	-74.77	1.211	6.542
A-A	-178.27	-83.67	-179.54	2.452	0.804
A-+	-177.88	-83.88	53.84	1.469	4.230
A--	-177.68	-83.07	-73.15	2.682	0.545
+AA	59.52	174.47	-179.62	1.575	3.533
+A+	59.95	174.98	53.79	0.702	15.454
+A-	59.74	173.77	-75.50	1.941	1.905
+-+	65.53	-108.16	53.69	3.574	0.121
-AA	-72.95	-167.97	-178.56	2.566	0.662
-A+	-74.62	-169.62	54.06	1.707	2.829
-A-	-81.19	-173.85	-75.74	2.878	0.391
--A	-70.01	-83.93	-179.55	3.584	0.119
--+	-68.96	-83.42	53.75	2.596	0.630
M.V.	163.95	-177.71	59.91		



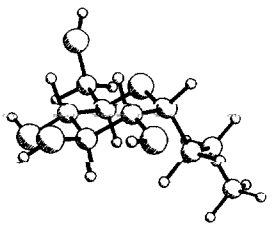


Figure 1a. Conformational Gravity Center *Stereo View* of Compound (1)

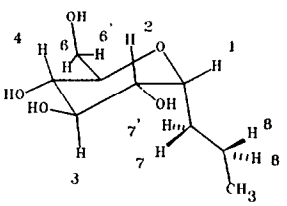


Figure 1b

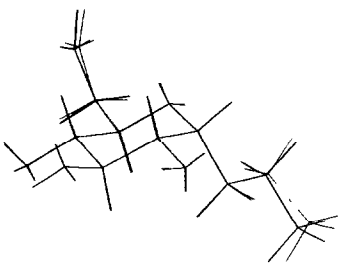
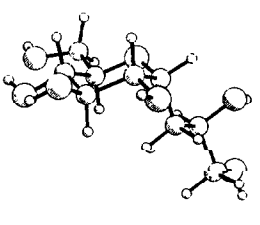


Figure 1c

TABLE II Compound (2)

Confor.	(a)	(b)	(c)	(d)	E(REL) KCAL	POPUL %
AAAA	178.16	176.03	-179.05	176.05	1.416	3.923
AAA+	177.68	176.15	-178.69	63.06	3.013	0.264
AA+A	178.87	176.24	59.09	176.32	0.454	19.937
AA++	177.92	176.43	58.50	62.98	2.158	1.120
AA+-	-179.84	177.07	58.58	-60.36	3.469	0.122
AA-A	177.64	174.95	-71.16	175.37	0.000	42.920
AA-+	177.13	175.82	-70.98	62.62	1.871	1.820
AA--	179.39	176.86	-70.92	-60.78	2.950	0.294
+AAA	51.60	179.51	-179.19	171.16	3.217	0.187
+AA-	54.50	178.98	-178.50	-75.26	2.758	0.407
+A+A	52.55	179.47	59.10	171.10	1.046	7.339
+A++	51.96	-179.69	58.61	55.83	3.218	0.187
+A+-	55.34	178.76	58.61	-75.23	2.041	1.364
+A-A	51.17	178.72	-70.99	171.11	0.967	8.379
+A-+	51.03	179.69	-70.88	55.90	3.088	0.233
+A--	54.49	178.51	-70.66	-75.31	1.957	1.572
+-+A	63.66	-108.31	58.81	172.94	3.282	0.168
+--A	63.63	-106.65	-70.92	172.52	2.990	0.275
-AAA	-77.36	-168.22	-177.90	-176.15	2.155	1.126
-A+A	-76.69	-169.16	60.38	-176.39	1.941	1.617
-A+-	-73.79	-166.94	58.92	-55.64	2.553	0.575
-A-A	-83.67	-172.58	-71.46	-178.50	1.474	3.559
--AA	-74.14	-86.67	-179.26	178.35	3.515	0.113
---+A	-73.27	-85.93	58.48	178.76	2.323	0.848
---A	-73.94	-87.55	-71.09	178.63	2.147	1.141
M.V.	170.57	178.81	-43.23	175.81		



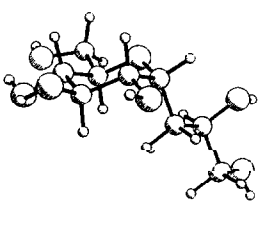


Figure 2a: Conformational Gravity Center *Stereo View* of Compound (2)

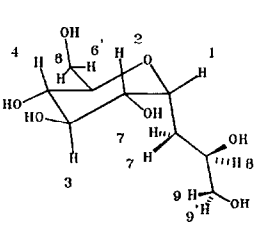


Figure 2b

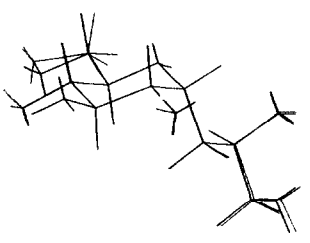


Figure 2c

(a) Bond 1-7-8-9; (b) Bond 2-1-7-8; (c) Bond 4-5-6-06; (d) Bond 7-8-9-09

Main geometrical features of conformers for Compounds (3) and (4)

TABLE III Compound (3)

Conf.	(a)	(b)	(c)	(d)	E(REL) KCAL	POPUL %
AAAA	-178.75	-179.61	-174.74	177.85	1.286	4.550
AAA+	-178.40	178.81	-175.17	65.36	2.854	0.322
AA+A	179.21	179.95	48.36	177.14	0.000	17.005
AA++	-178.83	-179.82	47.97	65.88	2.136	1.083
AA+-	-178.45	-179.56	47.83	-60.48	3.168	0.189
AA-A	179.07	178.60	-64.43	176.75	0.000	39.960
AA-A	-177.97	-85.12	-64.32	176.80	1.484	3.256
AA-+	-179.18	-179.66	-63.86	65.48	1.805	1.893
AA--	-178.73	179.86	-64.47	-61.14	2.620	0.478
A-AA	-176.86	-83.98	-175.19	177.30	2.666	0.442
A-+A	-177.24	-84.21	48.87	177.16	1.882	1.662
+AAA	45.89	178.70	-177.39	172.14	3.332	0.144
+AA+	46.94	179.84	-177.30	55.76	2.543	0.545
+AA-	54.71	-179.71	-175.88	-73.44	2.803	0.351
+A+A	48.36	178.45	48.21	172.23	1.370	3.949
+A++	50.66	-178.93	49.25	55.08	2.645	0.459
+A+-	57.29	-179.45	48.02	-74.30	2.271	0.862
+A-A	48.30	178.66	-63.29	172.33	1.260	4.756
+A-+	50.20	-177.63	-63.50	54.64	2.655	0.450
+A--	56.55	-178.19	-63.27	-74.64	2.144	1.068
+-+A	60.75	-89.22	47.59	171.11	3.108	0.210
+--A	62.19	-86.88	-64.13	169.78	2.779	0.365
-AAA	-73.14	-167.12	-174.05	-175.16	1.712	2.218
-AA+	-65.36	-162.33	-176.42	86.41	3.196	0.181
-AA-	-69.94	-166.71	-174.52	-54.79	3.118	0.206
-A+A	-79.31	-169.17	49.07	-177.58	1.648	2.467
-A+A	-81.44	-170.37	-64.45	-178.26	1.183	5.413
-A--	-80.51	-170.60	-64.55	-57.47	3.510	0.106
--AA	-65.61	-66.17	-175.92	-178.61	2.916	0.290
--+A	-65.46	-66.06	49.13	-178.61	1.887	1.648
---A	-67.00	-67.34	-63.62	-178.79	1.573	2.803
M.V.	-174.70	-172.01	30.33	-171.92		

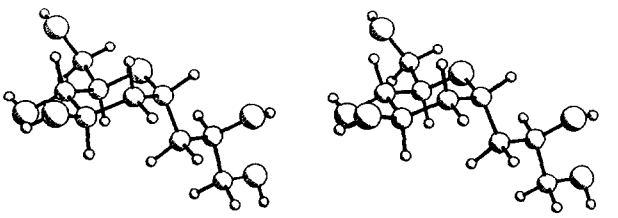


Figure 3a: Conformational Gravity Center *Stereo View* of Compound (3)

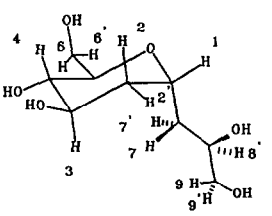


Figure 3b

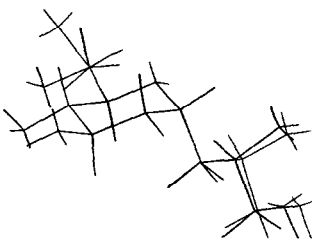


Figure 3c

TABLE IV Compound (4)

AAAA	160.55	179.94	-176.26	-178.1	2.500	0.385
AAA+	160.81	-178.20	-177.76	54.3	1.635	1.661
AAA-	162.16	-177.65	-177.06	-68.0	1.247	3.197
AA+A	161.52	179.65	50.16	-178.5	0.409	13.170
AA++	161.61	179.96	47.76	59.1	2.909	0.193
AA+-	161.87	-179.64	47.66	-69.1	2.671	0.289
AA-A	163.33	179.73	63.86	178.3	0.212	18.361
AA-A	172.95	-86.74	-63.96	-178.9	1.161	3.699
AA-+	163.44	-178.45	-62.66	60.1	2.759	0.249
AA--	164.33	-177.44	-62.76	-68.6	2.501	0.384
A-AA	173.73	-85.77	-174.46	-178.6	2.749	0.253
A---	174.77	-83.59	-63.96	-66.2	3.093	0.142
+AAA	59.72	172.90	-175.76	177.6	1.182	3.572
+A+A	60.13	173.46	49.16	178.6	0.156	20.204
+A++	59.21	174.45	48.56	56.3	2.913	0.192
+A+-	64.06	174.79	47.36	-79.4	3.214	0.115
+A-A	58.75	172.95	-63.86	178.8	0.000	26.288
+A-+	57.99	173.92	-63.96	55.9	2.705	0.272
+A--	62.69	174.98	-63.96	-79.8	2.836	0.218
+-+A	64.63	-108.10	48.76	178.5	2.626	0.311
+--A	64.98	-106.32	-63.76	177.5	2.492	0.390
-AAA	-67.73	-169.59	-173.46	-168.9	2.115	0.738
-A+A	-68.11	-169.07	49.26	-169.0	1.973	0.939
-A-A	-75.51	-172.88	-64.36	-170.8	1.461	2.227
M.V.	105.72	-178.98	-26.84	-178.61		

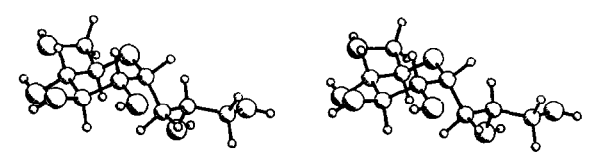


Figure 4a: Conformational Gravity Center *Stereo View* of Compound (4)

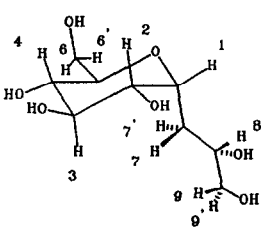


Figure 4b

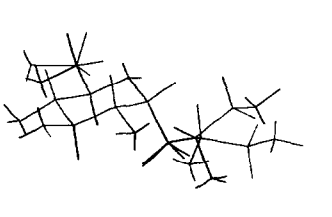


Figure 4c

(a) Bond 1-7-8-9; (b) Bond 2-1-7-8; (c) Bond 4-5-6-06; (d) Bond 7-8-9-09

Main geometrical features of conformers for Compounds (5) and (6)

TABLE V Compound (5)

Conf.	(a)	(b)	(c)	(d)	E(REL) KCAL	POPUL %
AAAA	160.04	-179.01	-176.87	-178.11	2.508	0.320
AAA+	160.97	-176.99	-177.40	54.11	1.406	2.059
AAA-	162.26	-177.18	-176.90	-67.06	0.803	5.700
AA+A	162.53	-176.84	-48.25	-178.48	0.621	7.762
AA++	160.52	-179.27	47.81	55.75	3.030	0.133
AA+-	162.10	-178.17	47.75	-67.98	2.511	0.319
AA-A	162.38	-176.62	-63.18	-178.65	0.385	11.551
AA-+	162.27	-177.42	-62.88	57.38	2.860	0.177
AA--	163.35	-176.55	-63.23	-67.79	2.296	0.458
A-AA	179.35	-69.32	-174.51	-177.73	1.878	0.928
A-+A	178.54	-69.75	48.53	-177.72	0.962	4.360
A-+-	179.25	-68.80	48.03	-65.04	2.773	0.205
A--A	178.31	-70.32	-63.99	178.19	0.426	10.778
A--+	177.24	-68.49	-63.71	59.95	3.017	0.136
A---	179.03	-68.25	-63.85	-65.76	2.321	0.439
+AAA	59.08	174.20	-176.18	177.28	1.036	3.849
+AA+	56.42	174.92	-175.14	52.26	3.017	0.136
+A+A	59.46	174.22	48.73	178.36	0.179	16.363
+A++	56.31	175.92	48.24	52.91	2.526	0.310
+A-A	58.53	173.31	-64.29	178.74	0.000	22.148
+A-+	55.53	175.76	-64.38	52.47	2.294	0.459
+A--	62.72	175.74	-64.38	-79.12	2.813	0.191
+-+A	61.91	-92.92	48.14	176.58	2.362	0.410
+--A	63.10	-91.20	-64.15	175.72	2.201	0.538
-AAA	-64.82	-166.78	-174.32	-169.45	1.476	1.831
-AA+	-60.83	-162.94	-176.73	79.71	2.633	0.259
-AA-	-65.89	-165.54	-174.55	-57.09	2.631	0.260
-A+A	-67.06	-167.54	48.55	169.40	1.523	1.691
-A-A	-71.01	-169.66	-64.35	170.44	0.998	4.103
-A--	-72.87	-167.71	-64.14	-59.28	2.877	0.172
--AA	-53.73	-69.86	-175.30	-171.06	3.146	0.109
--+A	-53.67	-70.17	49.31	-170.96	2.349	0.419
---A	-56.01	-71.44	-63.44	-171.07	1.942	0.832
M.V.	113.99	-167.64	-39.28	-176.12		

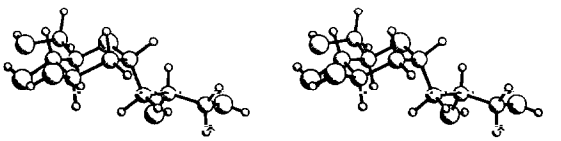


Figure 5a: Conformational Gravity Center *Stereo View* of Compound (5)

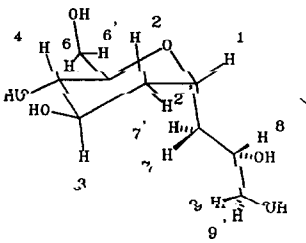


Figure 5b

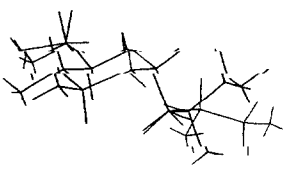


Figure 5c

TABLE VI Compound (6)

AAA	176.03	82.15	-175.24	3.171	0.154
AAA	-176.54	179.39	-175.07	1.413	3.000
AA+	-177.78	177.48	48.55	0.247	21.486
AA-	-177.91	178.16	-66.81	0.000	37.674
A++	174.54	79.48	48.23	1.964	1.183
A+-	174.28	79.55	-65.13	1.697	1.857
A-A	-174.00	-59.55	-174.84	2.315	0.653
A-+	-175.24	-61.86	48.94	1.123	4.898
A--	-175.45	-60.75	-64.54	0.837	7.931
+AA	84.37	179.11	-175.34	3.036	0.193
+A+	82.20	176.45	48.29	1.907	1.302
+A-	80.69	175.76	-64.56	1.668	1.951
+++	55.25	67.47	47.87	2.535	0.450
++-	55.25	68.22	-65.17	2.320	0.648
+-A	96.31	-60.83	-174.80	4.573	0.014
+-+	97.26	-60.78	48.97	3.388	0.107
+--	96.85	-59.63	-64.70	3.111	0.170
-AA	-59.57	-174.40	-174.87	2.040	1.040
-A+	-60.83	-176.39	48.64	0.914	6.970
-A-	-60.60	-177.71	-64.65	0.000	10.378
--A	-60.74	-50.18	-175.09	3.317	0.120
--+	-60.49	-51.44	49.15	2.081	0.970
---	-61.04	-50.34	-64.58	1.869	1.389
M.V.	-164.62	-172.86	-28.91		

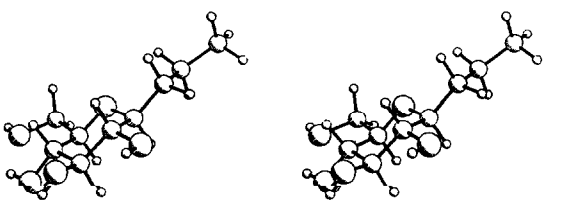


Figure 6a: Conformational Gravity Center *Stereo View* of Compound (6)

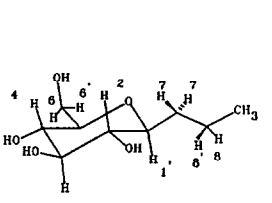


Figure 6b

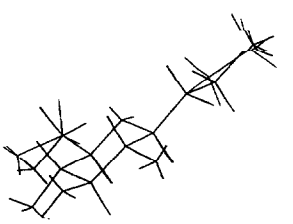


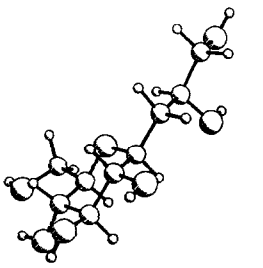
Figure 6c

(a) Bond 1-7-8-9; (b) Bond 2-1-7-8; (c) Bond 4-5-6-06; (d) Bond 7-8-9-09

Main geometrical features of conformers for Compounds (7) and (8)

TABLE VII Compound (7)

Conf.	(a)	(b)	(c)	(d)	E(REL) KCAL	POPUL %
AAAA	179.83	-179.60	-175.78	-177.08	1.513	3.594
AAA-	-179.46	-179.15	-175.39	-65.26	3.381	0.153
AA+A	179.69	179.44	63.63	177.53	0.196	33.275
AA++	178.80	179.36	48.04	62.14	3.108	0.243
AA+-	-178.86	179.86	47.40	-65.32	2.399	0.805
AA-A	-179.90	177.28	63.67	-176.79	0.000	44.322
AA-+	-179.83	-178.43	-63.74	62.98	2.936	0.325
AA--	-178.03	-178.76	-63.98	-65.00	2.090	1.356
A-AA	-176.73	-50.40	-173.77	-177.05	3.301	0.175
A-+A	-177.56	-52.04	46.60	-177.13	2.360	0.859
A--A	-177.54	-49.10	-64.17	-176.96	1.653	2.838
+AAA	84.27	177.49	-176.91	179.58	2.650	0.527
+A+A	84.10	176.41	49.57	-179.93	1.722	2.528
+A-A	87.60	-179.77	-63.79	-178.20	1.617	3.017
++AA	54.86	66.54	-175.10	177.12	3.421	0.143
+++A	55.26	64.81	47.46	177.40	2.225	1.080
++-A	54.91	67.76	-64.60	176.91	1.964	1.678
+-+A	96.18	-62.77	48.46	-177.61	3.106	0.244
+--A	94.95	-62.19	-63.51	-178.05	2.783	0.421
M.V.	174.54	-178.31	-24.88	-176.44		



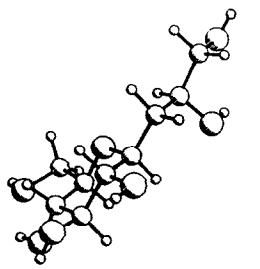


Figure 7a: Conformational Gravity Center *Stereo View* of Compund (7)

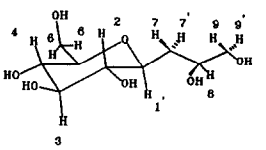


Figure 7b

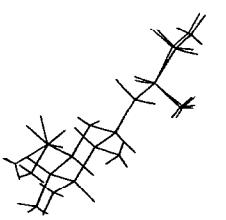
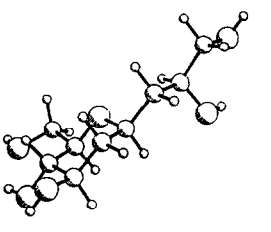


Figure 7c

TABLE VIII Compound (8)

AAAA	177.34	176.41	-176.38	-177.85	1.368	4.312
AAA-	178.55	177.84	-175.13	-65.27	3.277	0.171
AA+A	178.88	177.08	48.93	177.89	0.260	27.996
AA++	177.11	176.57	48.31	60.17	2.884	0.333
AA+-	179.81	177.61	47.86	-65.01	2.478	0.661
AA-A	179.53	88.11	-64.10	-176.46	2.045	1.373
AA-A	-179.80	179.75	63.76	-176.89	0.000	43.461
AA-+	178.20	177.76	-63.83	60.46	2.629	0.512
AA--	-179.14	179.49	-63.98	-64.39	2.080	1.295
A+AA	176.10	84.10	-175.72	-177.25	3.261	0.176
A++A	177.49	84.91	48.59	-176.86	2.369	0.794
A-+A	179.43	-56.66	46.87	-177.09	3.143	0.215
A--A	179.85	-53.77	-64.17	-177.17	2.351	0.819
+AAA	67.48	164.82	-176.26	175.08	2.137	1.175
+AA-	60.02	161.01	-176.51	-83.76	3.107	0.229
+A+A	75.35	167.65	49.65	177.38	1.741	2.295
+A-A	75.26	170.49	-63.86	176.05	1.476	3.590
++AA	59.65	58.89	-175.19	178.89	2.920	0.313
+++A	59.67	58.82	48.09	178.75	1.960	1.587
++-A	60.91	61.60	-64.37	178.68	1.579	3.017
+-+-	61.82	60.98	-64.37	-78.99	3.599	0.100
+--A	94.53	-62.40	-63.46	-177.30	3.268	0.174
-AA+	-56.13	-177.43	-176.99	72.61	3.021	0.264
-A+A	-50.12	-178.75	47.10	-171.75	2.734	0.429
-A-A	-49.20	-175.35	-64.34	-172.26	2.118	1.214
-A-+	-53.63	-177.16	-64.07	73.85	2.126	1.198
-++A	-61.51	91.49	48.71	-171.20	3.468	0.124
-+-A	-60.40	91.98	-63.44	-171.60	3.083	0.238
--+A	-50.81	-55.30	50.65	-170.81	2.791	0.390
---A	-52.18	-53.04	-63.67	-171.13	2.817	0.373
M.V.	173.10	174.41	-31.68	-177.52		



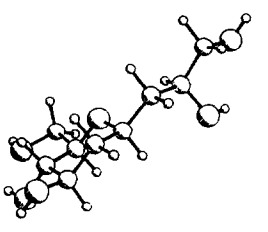


Figure 8a: Conformational Gravity Center *Stereo View* of Compound (8)

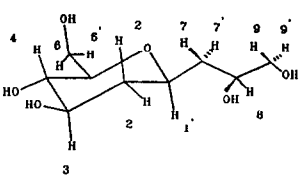


Figure 8b

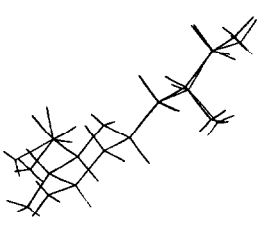


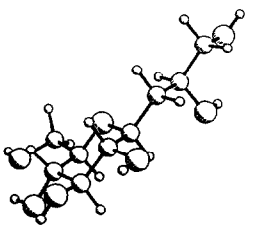
Figure 8c

(a) Bond 1-7-8-9; (b) Bond 2-1-7-8; (c) Bond 4-5-6-O6; (d) Bond 7-8-9-O9

Main geometrical features of conformers for Compounds (9) and (10)

TABLE IX Compound (9)

Conf.	(a)	(b)	(c)	(d)	E(REL) KCAL	POPUL %
AAA-	179.09	179.66	-175.34	-66.01	3.398	0.135
AAA+	178.44	177.59	48.58	176.03	0.217	29.121
AA++	177.88	178.26	47.95	61.80	3.110	0.220
AA+-	-179.55	179.30	47.39	-65.66	2.403	0.726
AA-A	179.49	179.09	46.49	177.65	0.000	42.048
AA-+	178.87	179.57	-63.93	62.08	2.933	0.297
AA--	-179.02	-179.62	-64.00	-65.52	2.089	1.234
A++-	153.59	60.53	46.45	-68.51	4.069	0.044
A-AA	177.86	-52.29	-173.17	-177.55	3.319	0.154
A-+A	-178.17	-52.94	46.65	-177.31	2.367	0.772
A--A	-178.06	-51.49	-64.86	-177.34	1.636	2.652
+AAA	63.57	164.15	-176.51	174.19	2.276	0.899
+AA+	58.20	162.88	179.37	52.60	3.563	0.102
+A+A	64.90	162.39	49.07	175.38	1.723	2.290
+A-A	65.10	162.38	-64.76	175.72	1.506	3.302
++AA	56.12	61.92	-174.83	178.66	3.447	0.125
+++A	55.92	62.52	47.57	178.15	2.238	0.959
++-A	55.55	63.81	-65.18	178.04	1.963	1.527
+-+A	61.64	-92.02	43.38	176.00	3.062	0.238
+--A	61.64	-90.76	-64.99	175.99	3.092	0.227
-AAA	-47.76	-175.77	-172.08	-171.89	3.368	0.142
-AA+	-55.94	-176.51	-177.28	73.28	2.813	0.363
-AA-	-47.85	-174.57	-178.53	-55.53	3.146	0.207
-A+A	-50.20	-177.36	46.70	-171.97	2.235	0.964
-A++	-53.78	-177.92	47.34	74.41	2.110	1.190
-A+-	-47.07	-178.30	48.93	-55.16	3.119	0.216
-A-A	-50.58	-176.56	-64.97	-172.09	1.689	2.424
-A-+	-53.75	-176.39	-64.07	74.39	1.796	2.023
-A--	-47.91	-177.77	-64.33	-55.62	2.977	0.275
-++A	-63.99	112.73	48.16	-174.49	3.339	0.149
-+-A	-63.56	114.16	-64.35	-174.69	3.011	0.260
--+A	-51.12	-56.69	50.56	-170.31	2.677	0.456
---A	-52.22	-55.48	-64.50	-170.36	2.864	0.333
M.V.	177.78	177.70	-28.30	178.80		



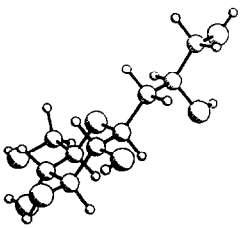


Figure 9a: Conformational Gravity Center *Stereo View* of Compound (9)

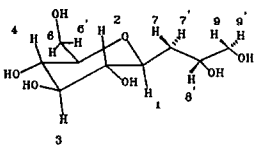


Figure 9b

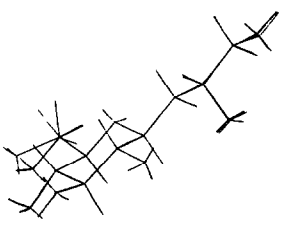
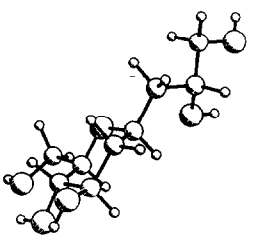


Figure 9c

TABLE X Compound (10)

AAAA	-167.71	173.31	-173.29	177.37	2.717	0.182
AAA+	-164.70	178.26	-177.52	67.03	1.137	2.621
AA+A	-169.62	172.03	47.08	177.80	1.331	1.891
AA-A	178.35	66.92	44.14	178.05	0.000	17.896
AA-A	-168.87	175.82	-63.99	178.10	0.841	4.326
AA-+	-169.70	172.09	-64.10	67.30	2.852	0.145
AA--	-168.11	174.23	-64.12	-62.07	3.377	0.060
A+AA	175.90	63.49	-175.93	177.39	1.349	1.833
A++A	176.79	64.04	48.43	177.71	0.220	12.348
A+++	175.43	61.90	47.39	64.56	2.372	0.325
A++-	177.62	63.03	47.51	-62.99	2.929	0.127
A+-+	176.72	64.22	-64.22	64.92	2.035	0.575
A+--	178.99	65.63	-64.14	-62.13	2.671	0.197
A-AA	-160.35	-61.70	-175.79	178.92	2.619	0.215
A-+A	-160.71	-61.55	49.40	178.80	1.785	0.878
A--A	-162.50	-59.83	-63.72	178.52	1.381	1.736
+AAA	60.13	164.53	-176.80	170.09	1.094	2.821
+AA-	57.21	160.78	-176.76	-77.70	2.024	0.586
+A+A	64.30	165.75	49.30	170.00	0.657	5.900
+A-A	66.17	168.05	51.78	169.16	0.435	8.292
+A-+	65.00	165.42	-64.11	56.72	2.829	0.150
++AA	50.08	64.25	-175.39	172.17	2.993	0.114
+++A	50.31	64.36	48.17	171.91	2.157	0.468
++-A	51.12	67.18	-64.52	171.69	1.788	0.873
-AAA	-59.26	-174.29	-175.50	-177.50	1.153	2.553
-A+A	-59.21	-174.42	48.80	-178.33	0.425	8.723
-A++	-61.31	-176.09	47.89	79.56	2.674	0.196
-A+-	-57.30	-176.49	48.36	-52.49	2.629	0.211
-A-A	-58.12	-171.37	-64.18	-178.66	0.032	16.943
-A-+	-60.04	-174.66	-63.85	79.63	2.289	0.374
-A--	-56.28	-174.33	-64.15	-52.91	2.225	0.417
-++A	-62.69	95.47	48.60	-176.93	2.918	0.129
-+-A	-62.82	95.42	-63.48	-176.81	2.449	0.286
--AA	-61.53	-51.43	-176.73	-175.72	2.531	0.249
--+A	-60.62	-50.83	50.15	-176.01	1.223	2.266
--+-	-57.36	-52.29	53.37	-53.58	2.809	0.156
---A	-61.84	-48.28	-63.73	-177.15	1.269	2.098
M.V.	-143.10	143.91	-34.92	175.96		

(a) Bond 1-7-8-9; (b) Bond 2-1-7-8; (c) Bond 4-5-6-Q6; (d) Bond 7-8-9-Q9



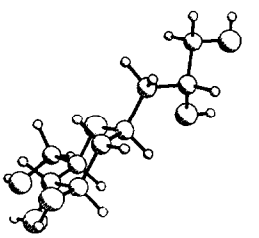


Figure 10: Conformational Gravity Center *Stereo View* of Compound (10)

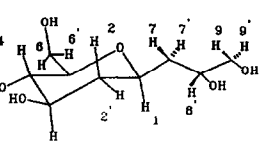


Figure 10b

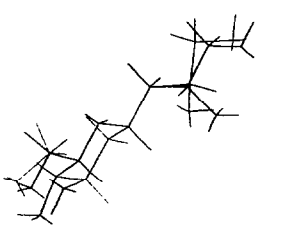


Figure 10c

Compound **5** is a similar case, it has analogous deviation of the same torsional angle (114° - 180° = -66°). Moreover, compound **5**, as previously observed by Y. Kishi, shows only small deviation from the *Anti* conformation for the C2-C1-C7-C8 torsional angle (180° - 168°) = 12°), and this is the result of the same 1,3-diaxial-like interaction. Compound **4**, cannot reduce this interaction in this way, because this would introduce another 1,3-diaxial-like interaction between the C2-O2 and C7-C8 bonds.

ß-C-Glycosides. For compound **6**, **AA−** conformer is the most stable (32.3%), this is followed as usual by the **AA+** conformer. The most significant deviation is that of C1-C7-C8-C9 (180° - 165° = 15°), which may be the result of the higher stability of the corresponding *Gauche(−)* conformers, because the 1,3-diaxial-like interactions of the C1-O(ring) and the C8-C9 bonds in the *Gauche(+)* conformers. For compounds **7**, **8** and **9**, the **AA−A** conformers are always the most stable (46.3, 43.5 and 42.0% respectively) followed by the **AA+A** conformers. As can be see in figures 7c, 8c and 9c, in all cases, the most stable **AA−A** conformer is practically superimposed on the Conformational Gravity Center. Finally, for compound **10**, the **AA−A** conformer is also the most stable (17.9%), although there are another five conformers with populations higher than 5% (**−A−A**, **A++A**, **-A+A**, **+A−A** and **+A+A**). In this way, the Conformational Gravity Center exhibits considerable deviations of the C1-C7-C8-C9 and C2-C1-C7-C8 torsional angles (180° - 143° = 37° and 180° - 144° = 36° respectively), and these reduce the 1,3-diaxial-like interaction between the C1-O(ring) and the C8-O8 bonds.

From the above results, and by applying Altona's generalization of the Karplus equation, (3JHH program), we obtained the theoretical vicinal coupling constants for compounds **(1)** to **(10)** and these are shown in Table XI. This Table gives the corresponding experimental values (from Kishi's data in CD_3OD or D_2O), together with the differences between each pair of values. The last row contains the calculated rms (root mean square) for each coupling constant type, and finally, the global rms deviation, which was only 0.873 Hz, a very acceptable value. The largest differences occur between the $J_{5,6}$ and $J_{5,6'}$ coupling constants, but the assignation of the key C7 methylene protons can be made with confidence. This effectively demostrates the usefulness of these calculations for conformational studies and coupling constants analyses and also for ^{1}H-NMR signal assignations derived from coupling constants.

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TABLE XI: Theoretical and experimental coupling constants for compounds (1) to (10)

Conformer		$J_{1,2}$	$J_{1,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{1,7}$	$J_{1,7'}$	$J_{7,8}$	$J_{7,8'}$	$J_{7',8}$	$J_{7'8'}$
1	Calculated	5.49		8.88		8.88	9.62	2.89	1.36	3.11	10.99	11.3	4.89	11.03	3.54
	Experim	5.7		9.5		8.4	9.6	2.5	5.7	3.2	11.4				
	Differences	-0.21		-0.62		0.48	0.02	0.39	-2.34	-0.09	-0.41				
2	Calculated	5.41		8.86		8.72	9.54	4.16	7.23	2.78	11.37		9.02		2.95
	Experim.	5.9		9.5		8.6	9.5	2.4	6.1	3.3	11.4		10.3		3
	Differences	-0.49		-0.64		0.12	0.04	1.78	1.13	-0.52	-0.03		-1.28		-0.05
3	Calculated	5.53	1.24	10.99	4.96	8.33	9.55	4.44	7.29	3.29	10.57		9.01		3.4
	Experim.	5.7	2.4	10.8	5.0	8.3	8.9	2.8	6 1	3.5	11.2		9.9		2.8
	Differences	-0.17	-1.16	0.19	-0.04	0.03	0.63	1.64	1.19	-0.21	-0.63		-0.89		0.6
4	Calculated	5.44		8.86		8.77	9.56	4.24	6.58	3.31	10.89	6.84		6.49	
	Experim.	5.8		9.4		8.4	9.5	2.4	6.3	4.2	10.0	6.4		6.1	
	Differences	-0.36		-0.54		0.37	0.06	1.88	0.28	-0.89	0.89	0.44		0.39	
5	Calculated	5.59	1.22	10.99	4.95	8.37	9.55	4.72	6.59	4.31	9.83	6.96		6.04	
	Experim.	5.7	2.4	10.8	4.8	8.3	8.7	2.7	6.4	6	8.7	7.7		5	
	Differences	-0.11	-1.18	0.19	0.15	0.07	0.85	2.02	0.19	-1.69	1.13	-0.74		1.04	
6	Calculated	9.28		8.87		8.86	9.59	3.69	6.97	2.68	9.61	11.05	4.97	11.03	3.64
	Experim.	9.2		8.8		8.8	9.4	2.1	5.6	2.2	8.5				
	Differences	0.08		0.07		0.06	0.19	1.59	1.37	0.48	1.11				
7	Calculated	9.29		8.9		8.84	9.58	3.97	6.88	2.36	10.94	10.68		2.81	
	Experim.	9.6		9		8.8	9.6	1.9	5.5	2.5	9.7	9.7		3	
	Differences	-0.31		-0.1		0.04	-0.02	2.07	1.38	-0.14	1.24	0.98		-0.19	
8	Calculated	11.59	2.2	11.09	4.95	8.42	9.57	4.2	7.03	2.58	10.6	10.07		3.13	
	Experim	11.4	1.8	11.4	5.1	8.3	9.6	2.2	5.8	2 8	9.5	9.5		3	
	Differences	0.19	0.4	-0.31	-0.15	0.12	-0.03	2	1.23	-0.22	1.1	0.57		0.13	
9	Calculated	9.3		8.90		8.85	9.59	3.74	6.94	1.95	7.7		6.86		6.7
	Experim.	9.3		8.8				1.8	5.9	2.8	8.9		6.9		5.3
	Differences	0.0		0.10				1.94	1.04	-0.85	-1.2		-0.04		1.4
10	Calculated	11.58	2.22	11.07	4.96	8.43	9.57	4.45	6.79	5.49	7.9		7.12		5.59
	Experim	11.4	1.8	11.4	5.1	8.4	9.6	2.3	5.8	5.1	7.6		7.6		5.1
	Differences	0.18	0.42	-0.33	-0.14	0.03	-0.03	2.15	0.99	0.39	0.3		-0.48		0.49
Parcial RMS		0.264	0.877	0.373	0.129	0.213	0.360	1.812	1.251	0.717	0.902	0.712	0.816	0.567	0.800

Total RMS = 0.873

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