

## Supporting Information for

# The advanced floating chirality distance geometry approach – how anisotropic NMR parameters can support the determination of the relative configuration of natural products

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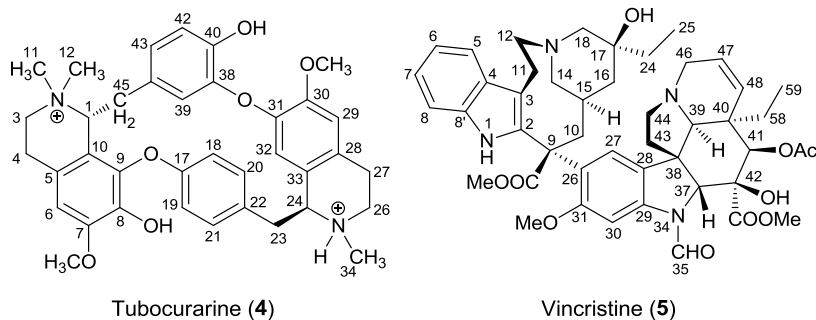
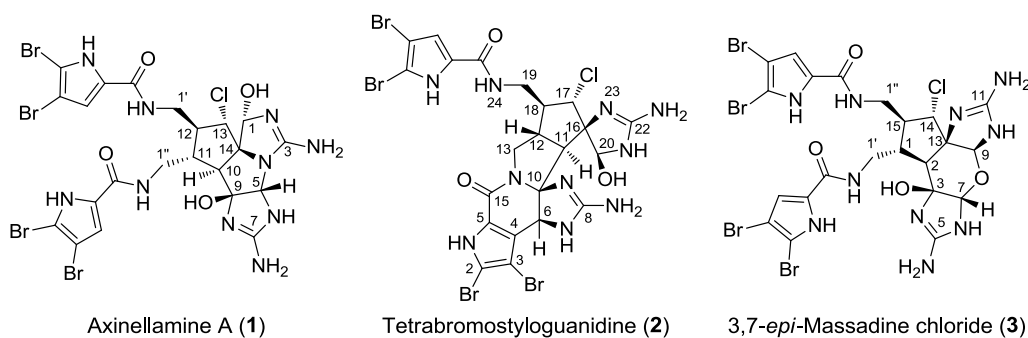
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## Formulas and Atom Numbering of Compounds (1)-(5)



## NOE and Structure Data for Axinellamine A (1)

Table S1. NOE data used for Axinellamine (1) ( $N = 37$  NOEs, the NMR-derived expectation values are denoted as  $d_{mean}$ , and the allowed lower and upper bounds – usually  $d_{mean} \pm 10\%$  – are labeled as  $d_{min} \cdots d_{max}$ ; the averaged distances back-calculated from structural data are labeled  $d_{calc}$ , and the corresponding residuals are listed only if this value falls out of range, i.e.  $d_{calc} < d_{min}$  or  $d_{calc} > d_{max}$ ; all distances are given in [Å]). The NOE labels refer to the formula shown on the right, where given as e.g. H<sup>A</sup>|H<sup>B</sup>, NOEs were recalculated from structures as  $r^{-6}$  averages over all pairs of atom-atom distances.

NOE		distances [Å]			
		$d_{mean}$	$d_{min} \cdots d_{max}$	$d_{calc}$	$\Delta d$
H1	H10	3.319	2.987-3.651	3.662	0.011
H1	H12	2.499	2.249-2.749	2.617	-
H2	H1	2.655	2.390-2.921	2.475	-
H2	H1X	3.577	3.219-3.935	3.673	-
H5	H11	3.859	3.473-4.245	4.314	0.069
H5	H13	2.768	2.491-3.044	2.472	-0.019
H5	H31	3.795	3.415-4.174	4.210	0.036
H6	H5	2.609	2.348-2.870	2.504	-
H6	H71	3.091	2.782-3.400	2.741	-0.041
H8	H10	2.837	2.554-3.121	2.651	-
H8	H11	4.014	3.612-4.415	3.681	-
H8	H71	3.300	2.970-3.630	3.644	0.014
H8	H9X	3.494	3.144-3.843	3.215	-
H10	H12	3.562	3.206-3.919	3.682	-
H10	H5	3.651	3.286-4.016	3.844	-
H13	H10	3.526	3.173-3.878	3.738	-
H13	H11	2.678	2.410-2.945	3.089	0.144
H13	H1A1	2.593	2.334-2.852	2.934	0.082
H1X	H1	2.316	2.084-2.547	2.388	-
H1X	H10	2.567	2.310-2.824	2.332	-
H9X	H10	4.149	3.734-4.564	3.888	-
H9X	H11	3.083	2.775-3.391	3.402	0.011
H9X	H13	3.373	3.036-3.711	3.048	-
H9X	H5	2.432	2.189-2.675	2.208	-
H32	H5	3.364	3.028-3.700	2.995	-0.033
H1A1	H12	2.825	2.542-3.107	2.597	-
H1A2	H11	2.648	2.383-2.913	2.760	-
H1A2	H12	2.534	2.280-2.787	2.369	-
H1A2	H1A1	1.780	1.602-1.958	1.850	-
H2A	H11	3.042	2.737-3.346	3.096	-
H2A	H12	3.660	3.294-4.026	4.002	-
H2A	H13	2.716	2.445-2.988	2.438	-0.007
H2A	H1A1	2.625	2.362-2.887	2.429	-
H2B	H10	3.148	2.833-3.463	3.798	0.335
H2B	H11	2.770	2.493-3.047	2.261	-0.232
H2B	H12	3.328	2.995-3.660	3.791	0.131
H2B	H1A2	2.804	2.524-3.085	3.189	0.104

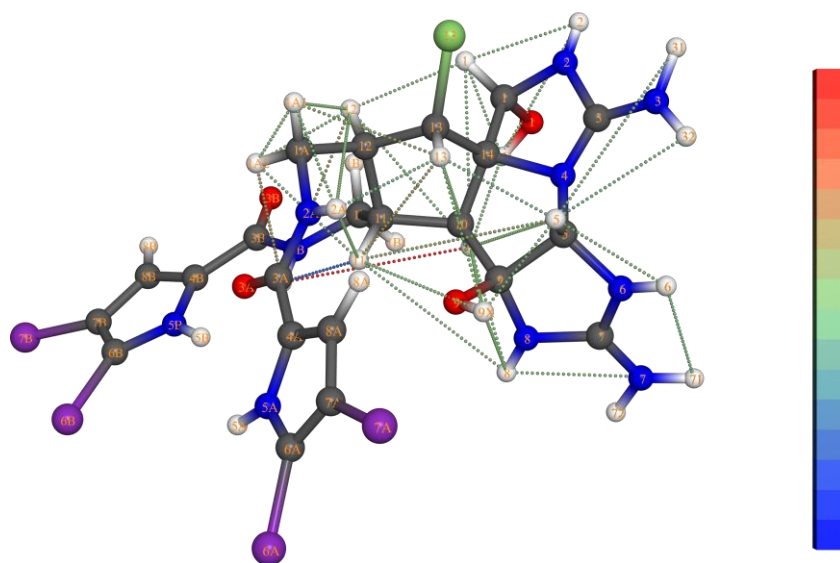
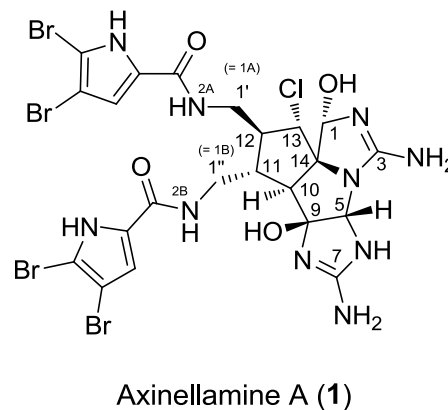


Figure S1. Plot of the best-fit (minimum pseudo energy) DG structure of Axinellamine A (1) with color-coded representation of all NOE contacts used in the configurational and conformational analysis. The color scale was adapted from calculated final NOE violations, ranging from -0.40 Å (blue) to +0.40 Å (red).

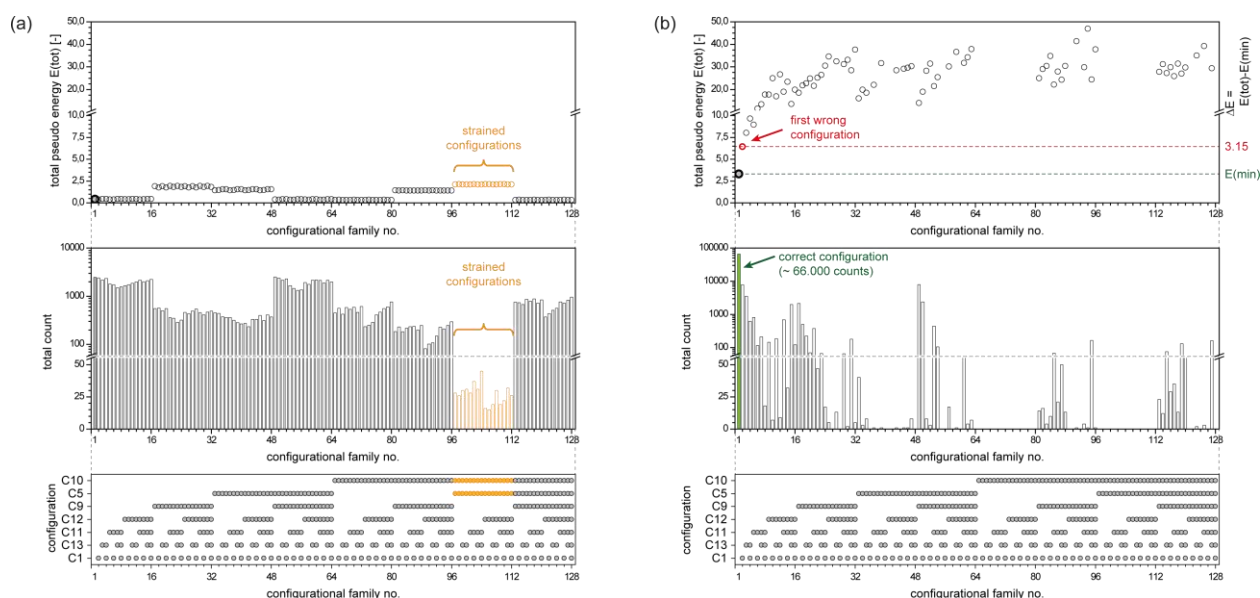


Figure S2.

(a) For Axinellamine A (**1**), an extended unrestricted floating-chirality DG calculation (100.000 structures) produces all 128 diastereomers (eight stereogenic centers,  $2^{N-1}$  configurational families, only C14 was fixed in its configuration in order to avoid enantiomeric structures). In this simulation, only holonomic distance bounds (bond lengths) were used as restraints, and no NOE information was used to restrict configurational (and conformational) space. The *top plot* shows the minimum holonomic pseudo energy of each of the 128 diastereomers, and the *center plot* provides an overview on the total number (counts as columns) of structures generated in this simulation for each configuration. The *bottom plot* identifies each configuration generated: The rows of filled circles indicate for each configurational family which stereogenic center (C1, C13, C11, C12, C9, C5, and C10) is inverted in relation to the correct configuration of Axinellamine A (**1**), the correct configuration is labeled no. #1 on the left side of the plots, a missing circle indicates retention of stereogenic centers as compared to **1**. The DG approach samples even highly strained configurations (marked in orange, configurations no. #97-112), albeit these occur with significantly lower statistical sampling rates. In all these 16 highly strained diastereomers, at least C5 and C10 feature an inverted configuration, which leads to a two-fold *trans*-anellation of two of the five-membered rings (see Figure S3 below for a superposition plot of these structures).

(b) Using NOE data for Axinellamine A (**1**) ( $N = 37$  NOEs), an extended floating-chirality DG calculations (100.000 structures) produced 74 out of the 128 possible diastereomers, the *center* and *bottom plot* and visualize the individual configurational families and their relative counts as described in (a). The left most column displays the sampling rate for the correct configuration of Axinellamine A (**1**), about 66.000 correct structures were generated in this rDG simulation, note the logarithmic scale after the axis break), whereas the sampling rate of wrong configurations significantly drops as the total pseudo energy raises. The *top plot* shows the minimum total error (= pseudo energy) for each configurational family, the correct structure (left most entry labeled no. #1, large black circle) emerges as the global pseudo energy minimum structure ( $E_{min} = 3.30$ ), the first wrong configuration (wrong configuration at C1, red circle) features a significantly higher pseudo energy ( $\Delta E = 3.15$ ), and any alternate diastereomer is characterized by even higher pseudo energies (note the break in the scale of the axis). Nevertheless, DG efficiently samples all possible configurations under the restraints of the experimental NOE data, and the correct configuration of **1** emerges as the best-fit, lowest pseudo energy structure from all rDG simulations described here.

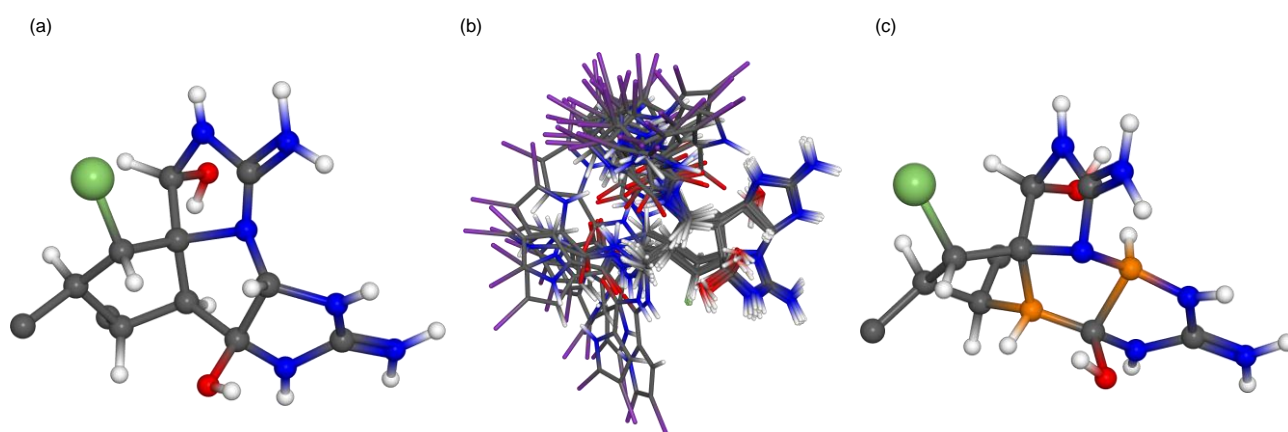


Figure S3. (a) Plot of central ring structure of Axinellamine A (**1**) with correct configuration of all stereogenic centers as identified from the rDG simulation described in Figure S2b; this structure is identical to the one shown in Figure S1. (b) Superposition of 16 highly strained diastereomers of **1**, identified from the unrestricted DG simulation as described in Figure S2a, and marked in these plots in orange. All these highly distorted structures feature a wrong configuration at C5 and C10 (atoms marked in orange in the plot on the right side (c)), and the structure shown in (c) corresponds to the configurational family labeled no. #97 in Figure S2b.

## NOE and Structure Data for Tetrabromostyloguanidine (2)

Table S2. NOE data used for Tetrabromostyloguanidine (**2**) ( $N = 27$  NOEs, the NMR-derived expectation values are denoted as  $d_{mean}$ , and the allowed lower and upper bounds – usually  $d_{mean} \pm 10\%$  – are labeled as  $d_{min} \cdots d_{max}$ ; the averaged distances back-calculated from structural data are labelled  $d_{calc}$ , and the corresponding residuals are listed only if this value falls out of range, i.e.  $d_{calc} < d_{min}$  or  $d_{calc} > d_{max}$ ; all distances are given in [Å]). The NOE labels refer to the formula shown on the right, where given as e.g.  $H^A|H^B$ , NOEs were recalculated from structures as  $r^{-6}$  averages over all pairs of atom-atom distances.

NOE		distances [Å]			
		$d_{mean}$	$d_{min} \cdots d_{max}$	$d_{calc}$	$\Delta d$
H6	H20X	2.720	2.450-2.990	2.720	-
H6	H7	2.460	2.210-2.710	2.385	-
H6	H9	4.030	3.630-4.430	4.024	-
H11	H132	2.500	2.250-2.750	2.766	0.016
H11	H17	3.270	2.940-3.600	3.625	0.025
H11	H20X	2.935	2.650-3.220	2.674	-
H11	H6	2.200	1.980-2.420	2.592	0.172
H11	H9	3.580	3.220-3.940	3.925	-
H12	H9	2.360	2.120-2.600	2.395	-
H17	H12	2.390	2.150-2.630	2.442	-
H17	H191	2.840	2.560-3.120	3.338	0.218
H17	H192	2.400	2.100-2.700	2.051	-0.049
H17	H20	3.010	2.710-3.310	3.492	0.182
H17	H23	2.320	2.090-2.550	2.612	0.062
H17	H24	3.050	2.750-3.350	3.393	0.043
H18	H11	2.330	2.100-2.560	2.415	-
H18	H132	2.600	2.340-2.860	2.600	-
H18	H17	2.780	2.500-3.060	3.035	-
H18	H20	3.110	2.800-3.420	3.427	0.007
H18	H23	4.350	3.910-4.790	4.743	-
H18	H24	2.950	2.650-3.250	2.894	-
H20	H11	2.710	2.440-2.980	3.008	0.028
H20	H20X	2.180	1.990-2.370	2.338	-
H20	H21	2.530	2.280-2.780	2.470	-
H23	H6	4.300	3.870-4.730	4.474	-
H23	H9	3.220	2.900-3.540	2.877	-0.023
H27	H24	2.340	2.110-2.570	2.191	-

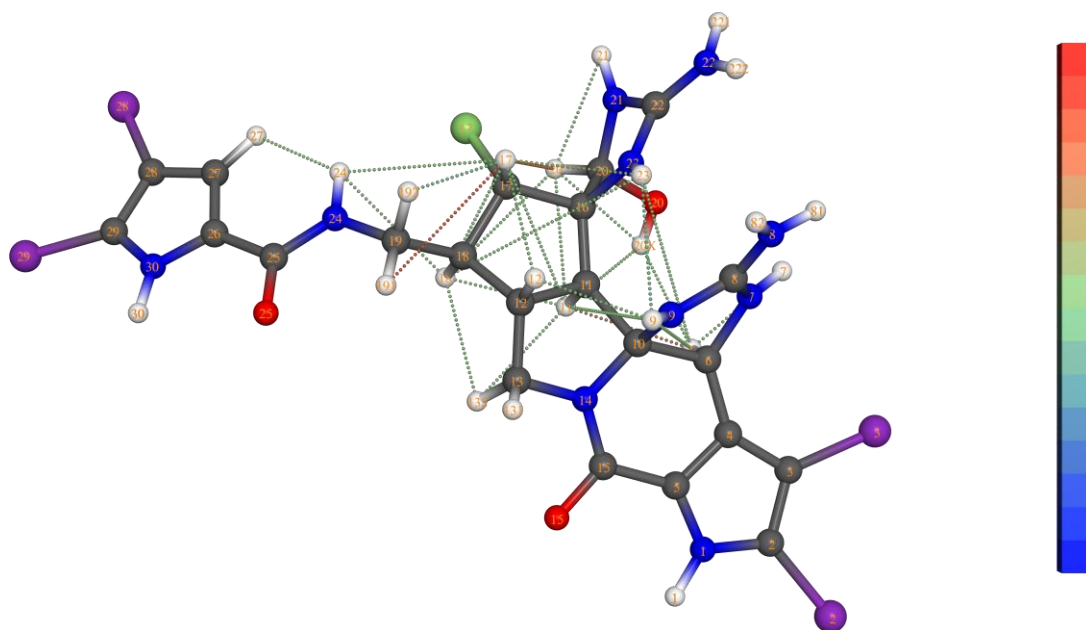
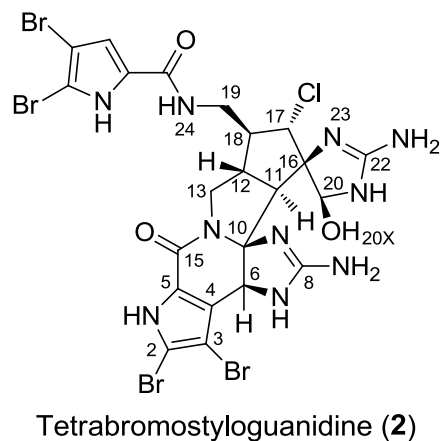


Figure S4. Plot of the best-fit (minimum pseudo energy) DG structure of Tetrabromostyloguanidine (**2**) with color-coded representation of all NOE contacts used in the configurational and conformational analysis. The color scale was adapted from calculated final NOE violations, ranging from  $-0.40$  Å (blue) to  $+0.40$  Å (red).

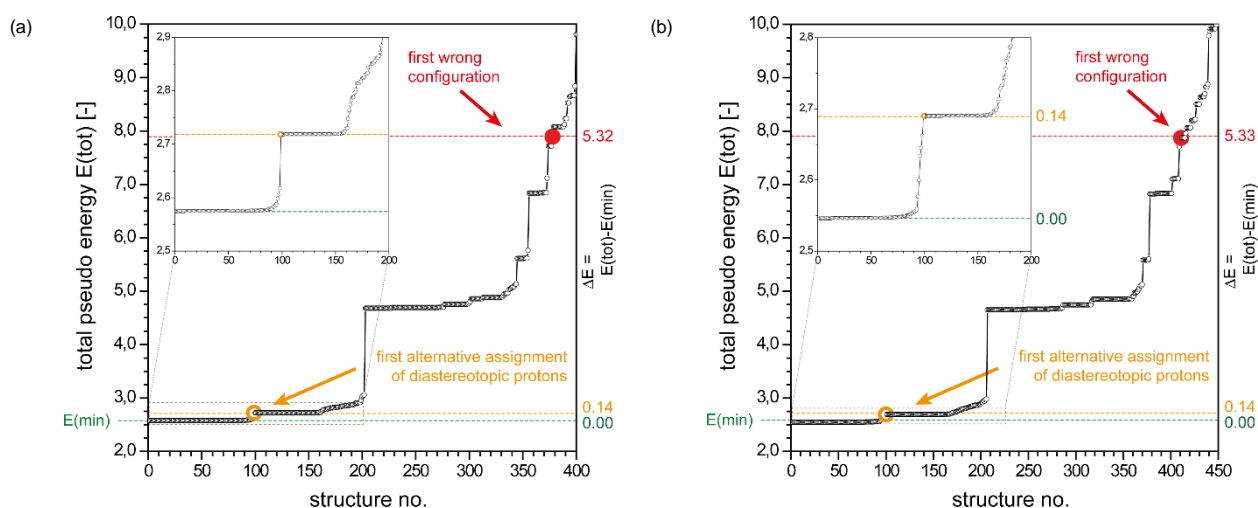


Figure S5.

(a) The *top left* plot shows pseudo energy sorted and ranked rDG structures of Tetrabromostyloguanidine (**2**) as discussed in the main paper. In this rDG simulation, a chiral volume restraint arbitrarily has been applied to a single stereogenic center (i.e. C10) in order to avoid enantiomeric structures.

(b) On the *top right*, the plot shows the corresponding pseudo energy of ranked rDG structures emerging from a simulation which did not use any chiral restraints at all, except on planar  $sp^2$ -type centers ( $V_{chir} = 0$ ). The features of this plot, and in particular the energy steps are identical to the plot shown in (a), thus indicating that the arbitrary use of a single chiral volume restraint does not affect the final results of configurational and conformational analysis. In fact, this simulation produced the enantiomeric structures as shown below (Figure S6).

(c) On the *bottom right*, single chiral volume restraints were applied in rDG simulations on Tetrabromostyloguanidine (**2**), each using one of the eight stereogenic centers as a restrained and fixed reference. Restraining either one of C6, C10, C11, C12, C16, C17, C18, or C20 produces within very narrow margins of error the same energy step characteristics that have already been manifested in plots (a) and (b). In all cases, the first small step in energy results from an alternative assignment of diastereotopic methylene protons (see inset plot), and the first wrong relative configuration of one of the eight stereogenic centers (indicated by the bold-face large symbols) is always characterized by a significantly higher error in its total pseudo energy.

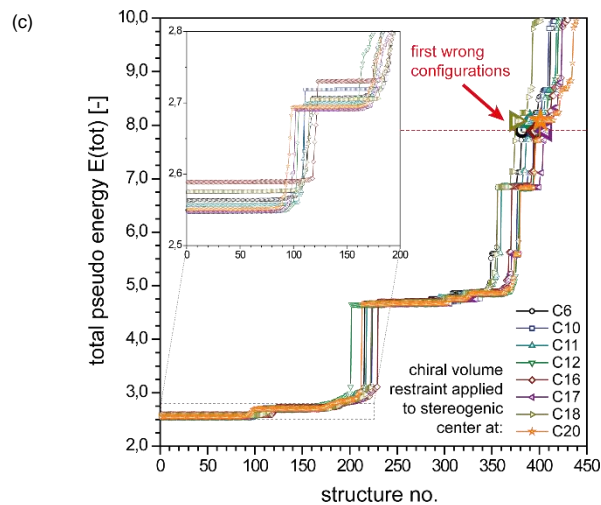
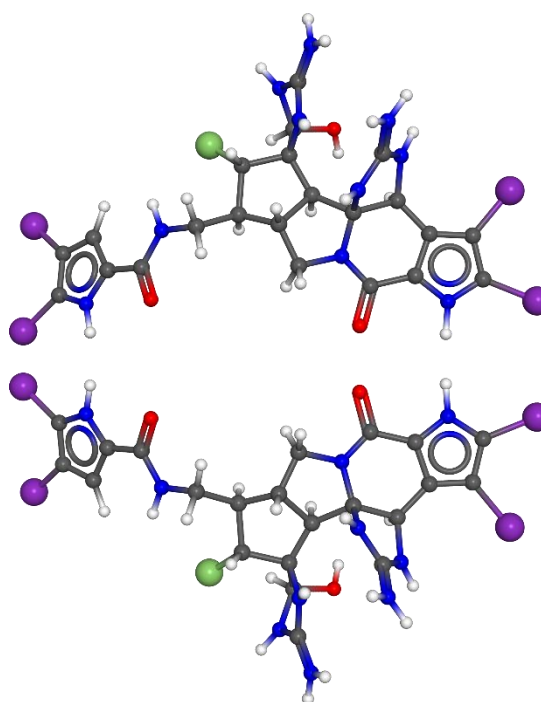
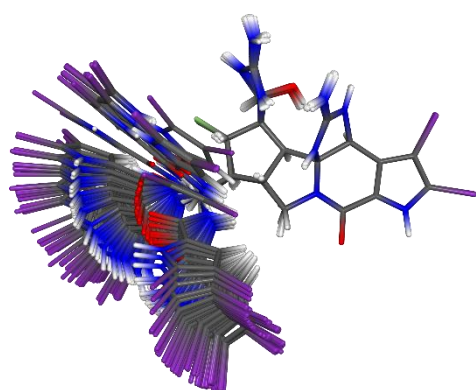
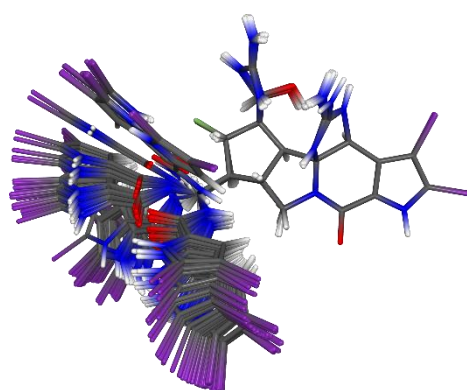


Figure S6. Ball-and-stick type representation of the first two lowest pseudo energy structures emerging from a rDG simulation on Tetrabromostyloguanidine (**2**) using no chiral restraints on any of the eight stereogenic centers, as shown in Figure S5b. These structures are actually exact enantiomers with identical pseudo energies.

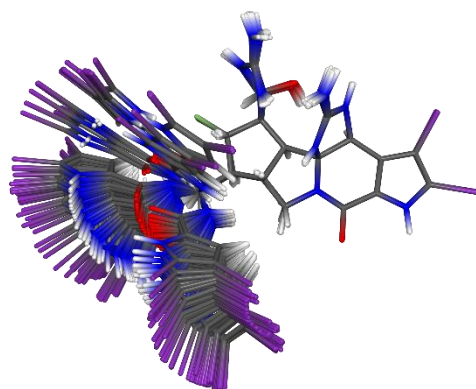




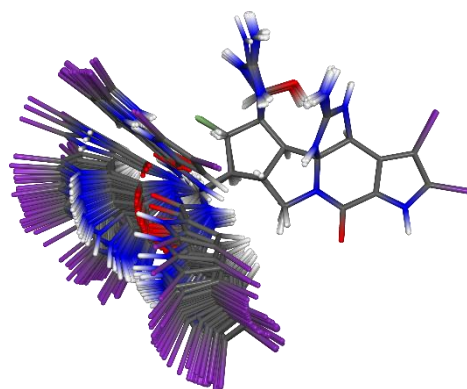
(a) chiral volume restraint applied to C6



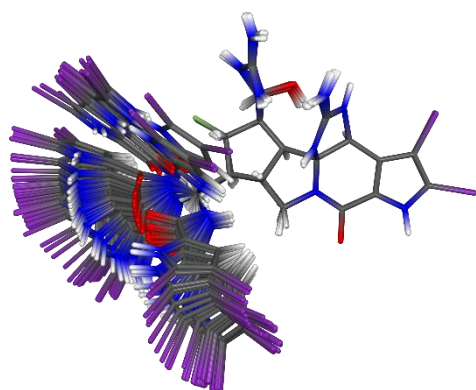
(b) chiral volume restraint applied to C10



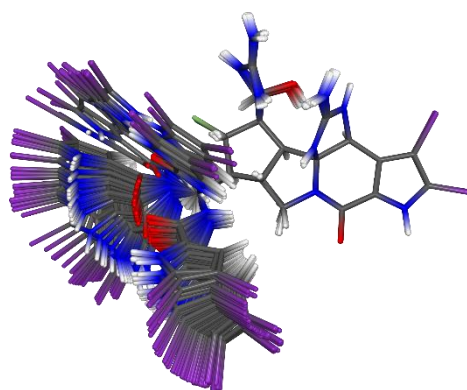
(c) chiral volume restraint applied to C11



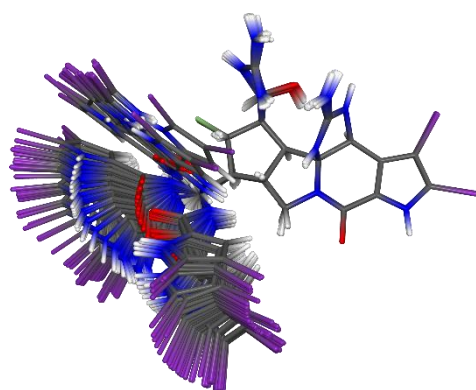
(d) chiral volume restraint applied to C12



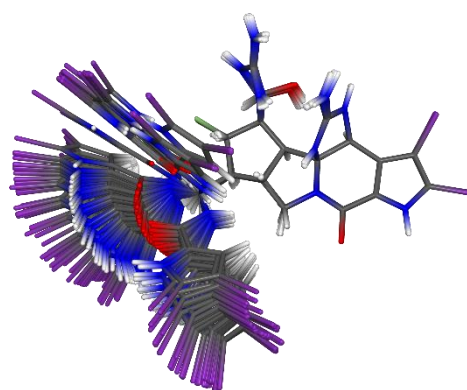
(e) chiral volume restraint applied to C16



(f) chiral volume restraint applied to C17



(g) chiral volume restraint applied to C18



(h) chiral volume restraint applied to C20

Figure S7. Ball-and-stick type representations of all low pseudo energy structures up to the first wrong configuration emerging from rDG simulations on Tetrabromostyloguanidine (**2**) using a single chiral volume restraints on one of the eight stereogenic centers, as shown in Figure S5c. All structures shown here actually feature the same configuration of all eight stereogenic centers (a: 381, b: 393, c: 389, d: 395, e: 396, f: 406, g: 374, and h: 400 structures in total).

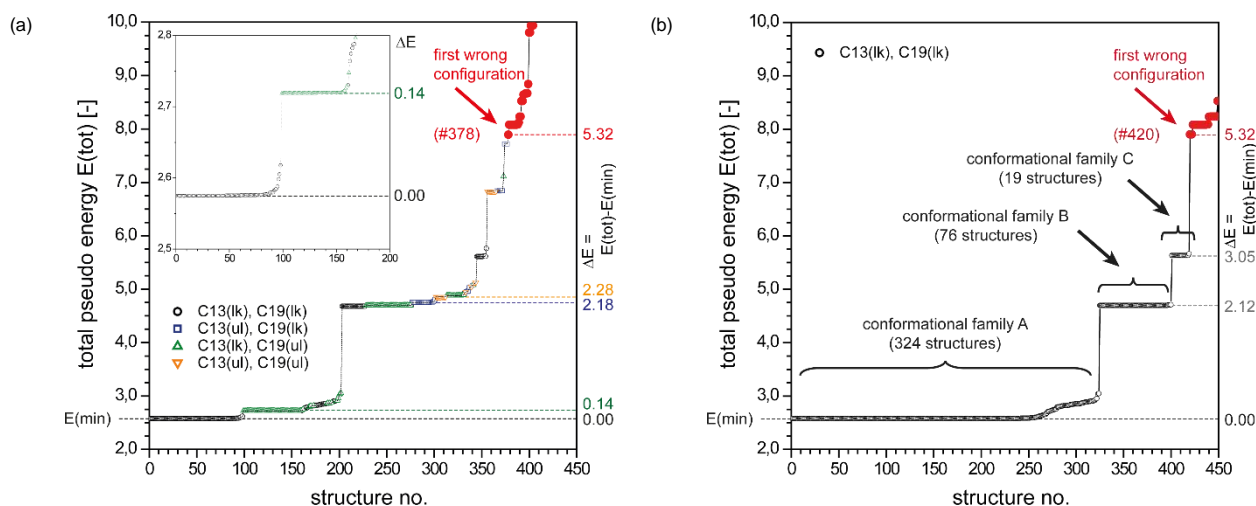


Figure S8. Detailed analysis of the assignments of diastereotopic methylene protons of Tetrabromostyloguanidine (**2**). (a) The *left plot* shows pseudo energy sorted and ranked rDG structures of **2** as discussed in the main paper. In addition, the color-coded symbols designate rankings of alternative assignments of CH<sub>2</sub>-protons (methylene groups C13 and C19), where the relative stereodescriptors “*lk*” (*like*) and “*ul*” (*unlike*) refer to the global pseudo energy minimum “*lk/lk*” assignment; the right scale gives  $\Delta E$  values relative to  $E(\min)$ . Different CH<sub>2</sub>-assignments were found (total number of structures generated: *lk/lk*: 162 (black), *ul/lk*: 44 (blue), *lk/ul*: 146 (green), and *ul/ul*: 25 (orange), with rankings of first occurrence *lk/lk*: #1 ( $\Delta E = 0.00$ ), *ul/lk*: #277 ( $\Delta E = 2.18$ ), *lk/ul*: #99 ( $\Delta E = 0.14$ ), and *ul/ul*: #302 ( $\Delta E = 2.28$ )), which were ranked below the first wrong configuration of a stereogenic center (ranked no. #378,  $\Delta E = 5.32$ ). (b) The *right plot* shows the pseudo energy of ranked rDG structures emerging from a simulation in which chiral volume restraints were used to restrict the pseudo configuration of both methylene groups in the correct low-energy configuration of plot (a). The sampling quality of correct *lk/lk* structures increases to 419 located below the occurrence of the first structure of wrong configuration ranked no. #420. The energy steps become significantly more pronounced as alternative assignments of methylene groups are discarded, and the low-energy structures cluster into three very distinct conformational families A-C. Below, superimposed structure plots of these different conformations are given (Figure S9).

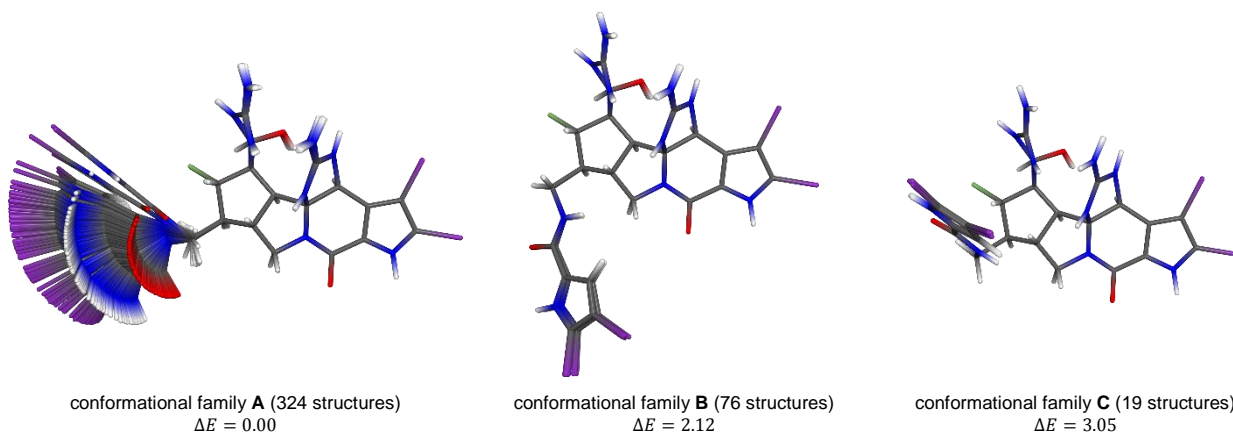


Figure S9. Superimposed structures for the conformational families A-C of Tetrabromostyloguanidine (**2**) as identified from the rDG simulation depicted in Figure S8b.

## NOE and Structure Data for 3,7-*epi*-Massadine chloride (3)

Table S3. NOE data used for 3,7-*epi*-Massadine chloride (3) ( $N = 37$  NOEs, the NMR-derived expectation values are denoted as  $d_{mean}$ , and the allowed lower and upper bonds – usually  $d_{mean} \pm 10\%$  – are labeled as  $d_{min} \dots d_{max}$ ; the averaged distances back-calculated from structural data are labelled  $d_{calc}$ , and the corresponding residuals are listed only if this value falls out of range, i.e.  $d_{calc} < d_{min}$  or  $d_{calc} > d_{max}$ ; all distance are given in [Å]). The NOE labels refer to the formula shown on the right, where given as e.g. H<sup>A</sup>H<sup>B</sup>, NOEs were recalculated from structures as  $r^{-6}$  averages over all pairs of atom-atom distances.

NOE		distances [Å]			
		$d_{mean}$	$d_{min} \dots d_{max}$	$d_{calc}$	$\Delta d$
H3X	H7	3.316	2.984-3.648	3.068	-
H4	H1	4.164	3.748-4.580	3.738	-0.010
H4	H1A1	2.958	2.662-3.253	3.354	0.101
H4	H1A2	3.416	3.074-3.758	3.783	0.025
H4	H2	3.014	2.712-3.315	3.294	-
H4	H7	2.710	2.439-2.981	3.208	0.227
H7	H1	4.709	4.238-5.179	4.582	-
H7	H2	3.574	3.216-3.931	3.834	-
H9	H1	5.200	4.680-5.719	5.133	-
H9	H15	6.381	5.743-7.019	5.383	-0.360
H9	H2	2.906	2.615-3.197	3.238	0.041
H9	H7	3.559	3.204-3.915	3.804	-
H12	H1	2.568	2.311-2.825	2.213	-0.098
H12	H14	3.200	2.880-3.520	3.238	-
H12	H15	3.255	2.929-3.580	3.900	0.320
H12	H1B1	3.077	2.770-3.385	2.673	-0.097
H12	H1B2	3.812	3.431-4.193	3.717	-
H12	H2	3.377	3.039-3.714	3.792	0.078
H12	H7	3.566	3.209-3.923	4.005	0.082
H12	H9	4.641	4.177-5.105	4.225	-
H14	H1	3.398	3.058-3.739	3.873	0.134
H14	H15	2.951	2.656-3.246	2.817	-
H14	H1B1	2.839	2.555-3.123	2.468	-0.087
H14	H1B2	3.342	3.008-3.676	3.434	-
H14	H2	3.519	3.168-3.871	3.778	-
H1A1	H1	2.650	2.385-2.915	2.321	-0.064
H1A1	H15	2.821	2.539-3.103	3.424	0.321
H1A1	H1A2	1.780	1.602-1.958	1.817	-
H1A1	H2	3.218	2.897-3.540	3.463	-
H1A2	H1	2.722	2.450-2.994	3.067	0.073
H1A2	H15	3.054	2.748-3.360	2.892	-
H1A2	H2	2.949	2.654-3.244	2.522	-0.132
H1B1	H1	2.776	2.499-3.054	3.255	0.201
H1B1	H15	2.893	2.603-3.182	2.943	-
H1B2	H1	2.742	2.467-3.016	3.125	0.109
H1B2	H15	2.492	2.243-2.741	2.174	-0.069
H1B2	H1B1	2.002	1.801-2.202	1.777	-0.024

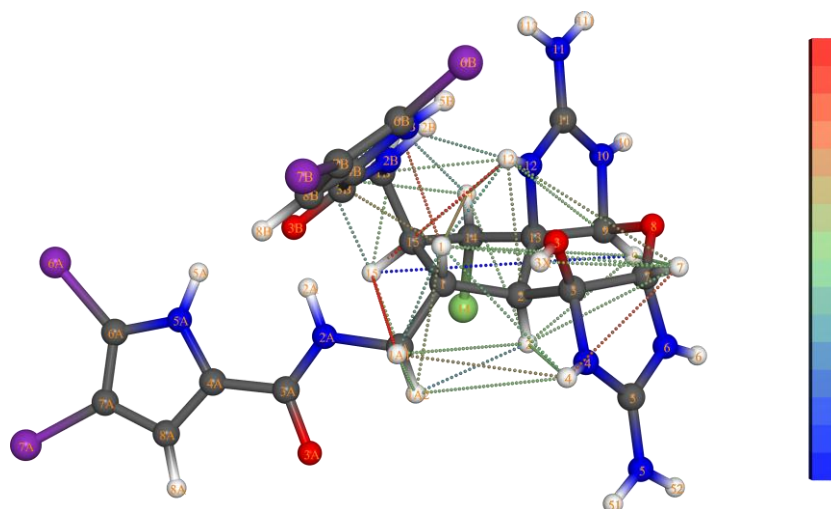
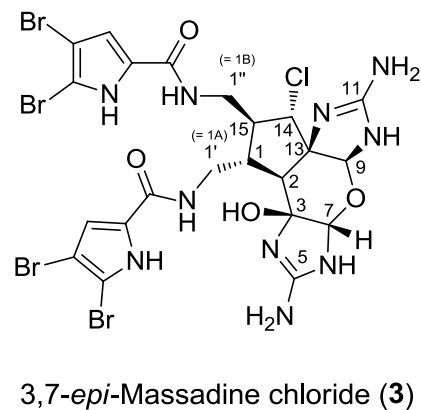


Figure S10. Plot of the best-fit (minimum pseudo energy) DG structure of 3,7-*epi*-Massadine chloride (3) with color-coded representation of all NOE contacts used in the configurational and conformational analysis. The color scale was adapted from calculated final NOE violations, ranging from -0.40 Å (blue) to +0.40 Å (red).



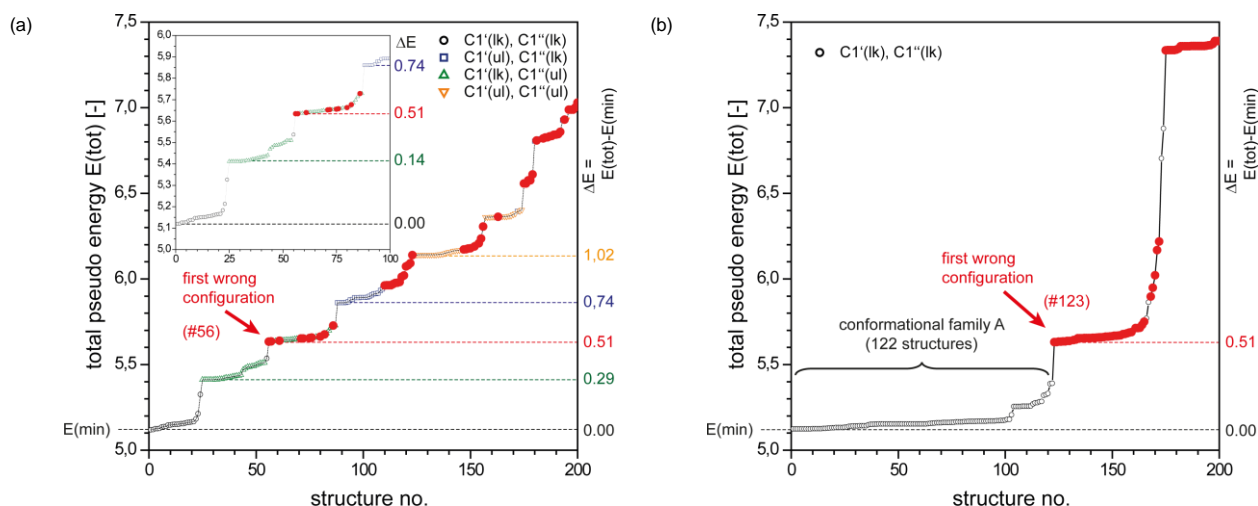


Figure S11. Detailed analysis of the assignments of diastereotopic methylene protons of 3,7-*epi*-Massadine chloride (**3**). (a) The *left plot* shows pseudo energy sorted and ranked rDG structures of **3** as discussed in the main paper. In addition, the color-coded symbols designate rankings of alternative assignments of CH<sub>2</sub>-protons (methylene groups C1' and C1''), where the relative stereodescriptors "lk" (*like*) and "ul" (*unlike*) refer to the global pseudo energy minimum "lk/lk" assignment; the right scale gives  $\Delta E$  values relative to  $E(\min)$ . Different CH<sub>2</sub>-assignments were found (total number of structures generated: lk/lk: 25 (black), ul/lk: 0 (blue), lk/ul: 30 (green), and ul/ul: 0 (orange), with rankings of first occurrence lk/lk: #1 ( $\Delta E = 0.00$ ), ul/lk: #88 ( $\Delta E = 0.74$ ), lk/ul: #25 ( $\Delta E = 0.29$ ), and ul/ul: #124 ( $\Delta E = 1.02$ )), which were ranked below the first wrong configuration of a stereogenic center (ranked no. #56,  $\Delta E = 0.51$ ). (b) The *right plot* shows the pseudo energy of ranked rDG structures emerging from a simulation in which chiral volume restraints were used to restrict the pseudo configuration of both methylene groups in the correct low-energy configuration of plot (a). The sampling quality of correct lk/lk structures increases to 122 located below the occurrence of the first structure of wrong configuration ranked no. #123. The energy steps become significantly more pronounced as alternative assignments of methylene groups are discarded, and the low-energy structures cluster into a single conformational family A. Below, a plot of these superimposed structures is given (Figure S12).

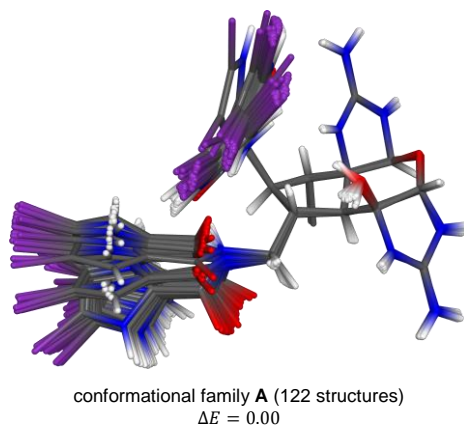


Figure S12. Superimposed structures for the main low-pseudo energy conformational family A of 3,7-*epi*-Massadine chloride (**3**) as identified from the rDG simulation depicted in Figure S11b.

## NOE, RDC, and Structure Data for Tubocurarine (4)

The following table provides data on the RDCs ( $D^{exp}$ ) used for Tubocurarine (4, three alignment media labeled [A]-[C]), their back-calculated values ( $D^{calc}$ ), and residuals ( $\Delta D = D^{exp} - D^{calc}$ ).

Table S4. RDC data used for Tubocurarine (4) ( $N = 16$  RDCs, best-fit back-calculated RDCs  $D^{calc}$  for each alignment medium (AM) labeled [A], [B], and [C], and residuals  $\Delta D = D^{exp} - D^{calc}$ , all values in [Hz]). Only bold face entries were used as parameters for the RDC analysis, regular font entries designate the calculated split terms of compound RDCs (where applicable, sums of RDCs are denoted as  $C-H^A+C-H^B = D(CH^A) + D(CH^B)$ , averages of RDCs are denoted as  $C-H^A|C-H^B = (D(CH^A) + D(CH^B))/2$ , methyl-RDCs were considered as three-state averages  $C-H^A|H^B|H^C$ ); the RDC labels refer to the formula shown on the right).

RDC	AM [A]			AM [B]			AM [C]		
	$D^{exp}$	$D^{calc}$	$\Delta D$	$D^{exp}$	$D^{calc}$	$\Delta D$	$D^{exp}$	$D^{calc}$	$\Delta D$
<b>C1-H1</b>	<b>-9.13</b>	<b>-9.17</b>	<b>0.04</b>	<b>-4.33</b>	<b>-4.37</b>	<b>0.04</b>	<b>-0.04</b>	<b>-0.12</b>	<b>0.08</b>
<b>C3-H3A+C3-H3B</b>	<b>2.18</b>	<b>2.16</b>	<b>0.02</b>	<b>-11.53</b>	<b>-11.51</b>	<b>-0.02</b>	<b>24.69</b>	<b>24.68</b>	<b>0.01</b>
C3-H3A	-	-23.29	-	-	-18.27	-	-	-19.61	-
C3-H3B	-	25.45	-	-	6.76	-	-	5.07	-
<b>C4-H4A+C4-H4B</b>	<b>19.99</b>	<b>19.98</b>	<b>0.01</b>	<b>6.87</b>	<b>6.89</b>	<b>-0.02</b>	<b>1.42</b>	<b>1.43</b>	<b>-0.01</b>
C4-H4A	-	14.53	-	-	7.09	-	-	14.14	-
C4-H4B	-	5.45	-	-	-0.20	-	-	-12.71	-
<b>C6-H6</b>	<b>-19.54</b>	<b>-19.57</b>	<b>0.03</b>	<b>8.00</b>	<b>8.04</b>	<b>-0.04</b>	<b>9.06</b>	<b>9.06</b>	<b>0.00</b>
C18-H18 C19-H19	-1.09	-1.15	0.06	-3.48	-3.50	0.02	4.76	4.68	0.08
C18-H18	-	23.98	-	-	0.51	-	-	-6.11	-
C19-H19	-	-26.28	-	-	-7.50	-	-	15.47	-
<b>C20-H20 C21-H21</b>	<b>-1.55</b>	<b>-1.53</b>	<b>-0.02</b>	<b>-4.52</b>	<b>-4.37</b>	<b>-0.15</b>	<b>3.19</b>	<b>3.31</b>	<b>-0.12</b>
C20-H20	-	-25.58	-	-	-8.69	-	-	15.22	-
C21-H21	-	22.52	-	-	-0.04	-	-	-8.60	-
<b>C23-H23A+C23-H23B</b>	<b>-4.67</b>	<b>-4.66</b>	<b>-0.01</b>	<b>-16.38</b>	<b>-16.40</b>	<b>0.02</b>	<b>-5.03</b>	<b>-5.05</b>	<b>0.02</b>
C23-H23A	-	-23.42	-	-	-18.64	-	-	19.00	-
C23-H23B	-	18.77	-	-	2.24	-	-	-24.04	-
<b>C24-H24</b>	<b>-24.11</b>	<b>-24.09</b>	<b>-0.02</b>	<b>-18.45</b>	<b>-18.59</b>	<b>0.14</b>	<b>19.33</b>	<b>19.33</b>	<b>0.00</b>
<b>C26-H26A+C26-H26B</b>	<b>7.52</b>	<b>7.48</b>	<b>0.04</b>	<b>10.11</b>	<b>10.16</b>	<b>-0.05</b>	<b>12.14</b>	<b>12.10</b>	<b>0.04</b>
C26-H26A	-	-6.30	-	-	0.75	-	-	24.81	-
C26-H26B	-	13.79	-	-	-9.41	-	-	-12.71	-
<b>C27-H27A+C27-H27B</b>	<b>1.62</b>	<b>1.66</b>	<b>-0.04</b>	<b>3.54</b>	<b>3.61</b>	<b>-0.07</b>	<b>2.29</b>	<b>2.35</b>	<b>-0.06</b>
C27-H27A	-	-13.50	-	-	-15.79	-	-	13.38	-
C27-H27B	-	15.16	-	-	19.40	-	-	-11.03	-
<b>C29-H29</b>	<b>-23.06</b>	<b>-22.88</b>	<b>-0.18</b>	<b>-2.94</b>	<b>-2.83</b>	<b>-0.11</b>	<b>10.20</b>	<b>10.37</b>	<b>-0.17</b>
<b>C32-H32</b>	<b>-22.20</b>	<b>-22.48</b>	<b>0.28</b>	<b>-3.65</b>	<b>-3.63</b>	<b>-0.02</b>	<b>10.36</b>	<b>10.15</b>	<b>0.21</b>
<b>C39-H39</b>	<b>12.20</b>	<b>12.33</b>	<b>-0.13</b>	<b>2.24</b>	<b>2.04</b>	<b>0.20</b>	<b>-3.98</b>	<b>-4.11</b>	<b>0.13</b>
<b>C42-H42</b>	<b>11.53</b>	<b>11.31</b>	<b>0.22</b>	<b>0.62</b>	<b>0.84</b>	<b>-0.22</b>	<b>-3.70</b>	<b>-3.63</b>	<b>-0.07</b>
<b>C43-H43</b>	<b>-24.30</b>	<b>-24.19</b>	<b>-0.11</b>	<b>-14.21</b>	<b>-14.32</b>	<b>0.11</b>	<b>17.12</b>	<b>17.14</b>	<b>-0.02</b>
<b>C45-H45A+C45-H45B</b>	<b>-22.14</b>	<b>-22.21</b>	<b>0.07</b>	<b>-26.90</b>	<b>-26.74</b>	<b>-0.16</b>	<b>6.48</b>	<b>6.48</b>	<b>0.00</b>
C45-H45A	-	-11.01	-	-	-15.26	-	-	-2.03	-
C45-H45B	-	-11.20	-	-	-11.47	-	-	8.51	-

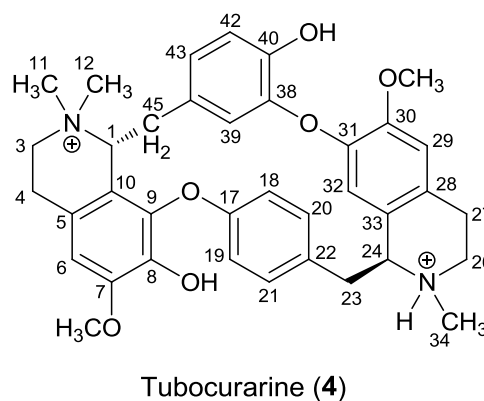


Figure S13. Plot of the experimental RDCs ( $D^{exp}$ ) vs. their back-calculated values ( $D^{calc}$ ) used for Tubocurarine (4, three alignment media labeled [A]-[C]). The corresponding best-fit (lowest total pseudo energy) structure model (see plot below) was obtained from the DG simulation using all three AM data sets.

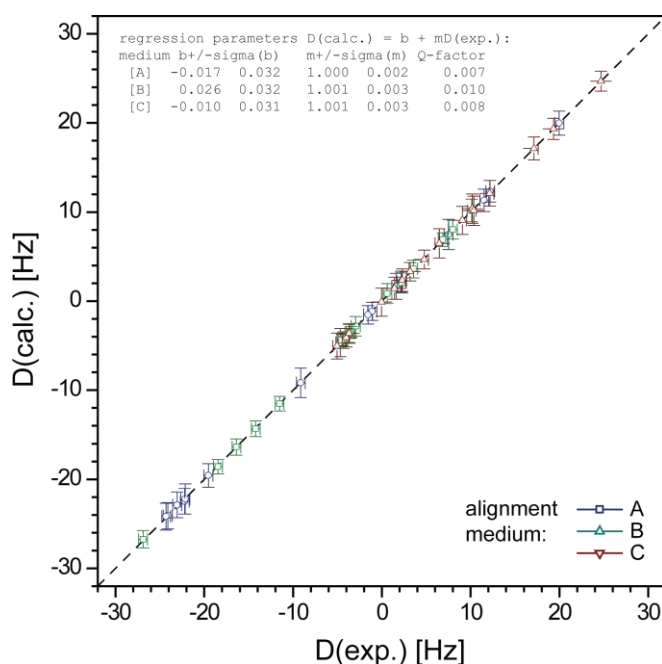
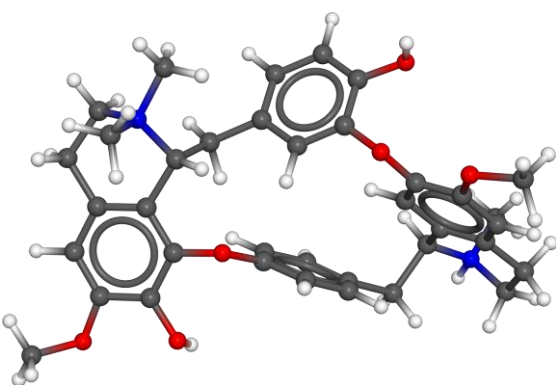


Table S5. NOE data used for Tubocurarine (4) ( $N = 17$  NOEs, the NMR-derived expectation values are denoted as  $d_{mean}$ , and the allowed lower and upper bounds – usually  $d_{mean} \pm 10\%$  – are labeled as  $d_{min} \dots d_{max}$ ; the averaged distances back-calculated from structural data are labeled  $d_{calc}$ , and the corresponding residuals are listed only if this value falls out of range, i.e.  $d_{calc} < d_{min}$  or  $d_{calc} > d_{max}$ ; all distance are given in [Å]). The NOE labels refer to the formula shown on the right, where given as e.g. H<sup>A</sup>|H<sup>B</sup>, NOEs were recalculated from structures as  $r^{-6}$  averages over all pairs of atom-atom distances.

NOE		distances [Å]			
		$d_{mean}$	$d_{min} \dots d_{max}$	$d_{calc}$	$\Delta d$
H1	H39	2.166	1.949-2.383	2.300	-
H1	H45A H45B	2.639	2.375-2.903	2.654	-
H3A H3B	H4A H4B	2.473	2.226-2.720	2.488	-
H4A H4B	H6	2.690	2.421-2.959	2.724	-
H6	H14A H14B H14C	2.476	2.228-2.724	2.414	-
H18 H19	H39	3.414	3.073-3.755	3.131	-
H18 H19	H45A H45B	2.525	2.272-2.778	2.548	-
H20 H21	H23A H23B	2.646	2.381-2.911	2.767	-
H20 H21	H24	3.279	2.951-3.607	3.289	-
H23A H23B	H24	3.024	2.722-3.326	2.663	-0.059
H23A H23B	H26A H26B	2.336	2.102-2.570	2.561	-
H24	H32	2.338	2.104-2.572	2.385	-
H26A H26B	H27A H27B	2.438	2.194-2.682	2.480	-
H27A H27B	H29	2.669	2.402-2.936	2.701	-
H29	H36A H36B H36C	2.365	2.129-2.602	2.347	-
H39	H45A H45B	2.972	2.675-3.269	2.879	-
H43	H45A H45B	3.287	2.958-3.616	2.730	-0.228

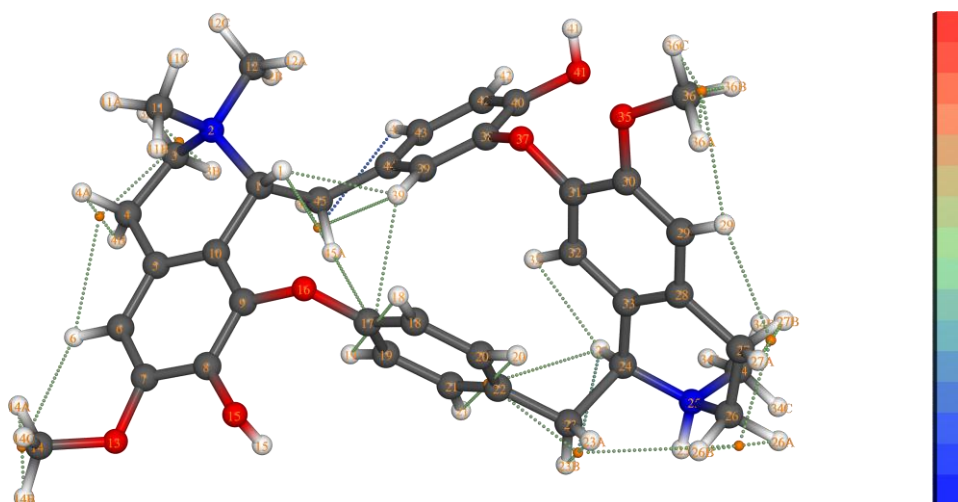
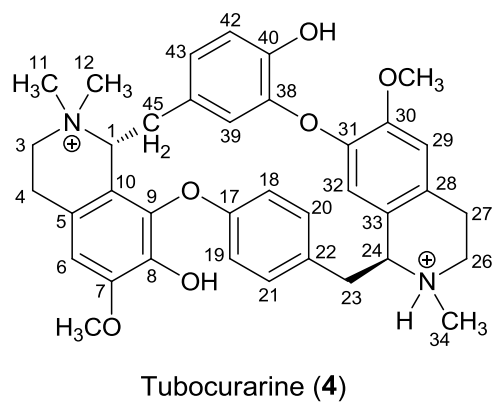


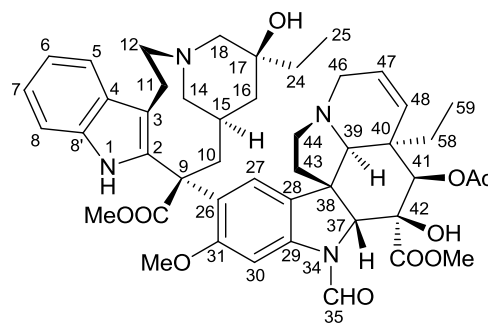
Figure S14. Plot of the best-fit (minimum pseudo energy) DG structure of Tubocurarine (4) with color-coded representation of all NOE contacts used in the configurational and conformational analysis. The color scale was adapted from calculated final NOE violations, ranging from -0.40 Å (blue) to +0.40 Å (red).

## NOE, RDC, and Structure Data for Vincristine (5)

The following table provides data on the RDCs ( $D^{exp}$ ) used for Vincristine (**5**, three alignment media labeled [A]-[C]), their back-calculated values ( $D^{calc}$ ), and residuals ( $\Delta D = D^{exp} - D^{calc}$ ).

Table S6. RDC data used for Vincristine (**5**) ( $N = 24$  RDCs, best-fit back-calculated RDCs  $D^{calc}$  for each alignment medium (AM) labeled [A], [B], and [C], and residuals  $\Delta D = D^{exp} - D^{calc}$ , all values in [Hz]). Only bold face entries were used as parameters for the RDC analysis, regular font entries designate the calculated split terms of compound RDCs (where applicable, sums of RDCs are denoted as  $C-H^A+C-H^B = D(CH^A) + D(CH^B)$ , averages of RDCs are denoted as  $C-H^A|C-H^B = (D(CH^A) + D(CH^B))/2$ , methyl-RDCs were considered as three-state averages  $C-H^A|H^B|H^C$ ); the RDC labels refer to the formula shown on the right).

RDC	AM [A]			AM [B]			AM [C]		
	$D^{exp}$	$D^{calc}$	$\Delta D$	$D^{exp}$	$D^{calc}$	$\Delta D$	$D^{exp}$	$D^{calc}$	$\Delta D$
<b>C5-H5</b>	<b>18.60</b>	<b>18.68</b>	<b>-0.08</b>	<b>-25.15</b>	<b>-25.28</b>	<b>0.13</b>	<b>4.92</b>	<b>5.16</b>	<b>-0.24</b>
<b>C6-H6</b>	<b>4.47</b>	<b>4.49</b>	<b>-0.02</b>	<b>20.86</b>	<b>20.87</b>	<b>-0.01</b>	<b>19.24</b>	<b>19.33</b>	<b>-0.09</b>
<b>C7-H7</b>	<b>-0.13</b>	<b>-0.14</b>	<b>0.01</b>	<b>10.27</b>	<b>10.24</b>	<b>0.03</b>	<b>12.44</b>	<b>12.50</b>	<b>-0.06</b>
<b>C8-H8</b>	<b>19.98</b>	<b>19.92</b>	<b>0.06</b>	<b>-24.19</b>	<b>-24.18</b>	<b>-0.01</b>	<b>5.26</b>	<b>5.19</b>	<b>0.07</b>
<b>C10-H10A+C10-H10B</b>	<b>-4.79</b>	<b>-4.80</b>	<b>0.01</b>	<b>0.49</b>	<b>0.49</b>	<b>0.00</b>	<b>15.57</b>	<b>15.52</b>	<b>0.05</b>
C10-H10A	-	-16.23	-	-	-22.31	-	-	-0.54	-
C10-H10B	-	11.43	-	-	-22.79	-	-	16.07	-
<b>C11-H11A+C11-H11B</b>	<b>-8.62</b>	<b>-8.65</b>	<b>0.03</b>	<b>8.17</b>	<b>8.20</b>	<b>-0.03</b>	<b>-18.08</b>	<b>-18.08</b>	<b>0.00</b>
C11-H11A	-	-27.51	-	-	-6.36	-	-	-18.44	-
C11-H11B	-	18.85	-	-	14.56	-	-	0.36	-
<b>C12-H12A+C12-H12B</b>	<b>29.22</b>	<b>29.20</b>	<b>0.02</b>	<b>-10.72</b>	<b>-10.65</b>	<b>-0.07</b>	<b>5.25</b>	<b>5.19</b>	<b>0.06</b>
C12-H12A	-	16.79	-	-	13.76	-	-	-1.84	-
C12-H12B	-	12.41	-	-	-24.41	-	-	7.03	-
<b>C14-H14A+C14-H14B</b>	<b>-13.51</b>	<b>-13.51</b>	<b>0.00</b>	<b>10.35</b>	<b>10.35</b>	<b>0.00</b>	<b>-11.89</b>	<b>-11.88</b>	<b>-0.01</b>
C14-H14A	-	-14.07	-	-	1.75	-	-	-22.71	-
C14-H14B	-	0.56	-	-	-8.60	-	-	10.83	-
<b>C15-H15</b>	<b>-8.57</b>	<b>-8.57</b>	<b>0.00</b>	<b>-27.71</b>	<b>-27.68</b>	<b>-0.03</b>	<b>1.00</b>	<b>0.98</b>	<b>0.02</b>
<b>C16-H16A+C16-H16B</b>	<b>-3.06</b>	<b>-3.07</b>	<b>0.01</b>	<b>17.72</b>	<b>17.74</b>	<b>-0.02</b>	<b>-16.21</b>	<b>-16.22</b>	<b>0.01</b>
C16-H16A	-	18.92	-	-	16.34	-	-	3.92	-
C16-H16B	-	-21.99	-	-	1.40	-	-	-20.14	-
<b>C18-H18A+C18-H18B</b>	<b>-17.52</b>	<b>-17.52</b>	<b>0.00</b>	<b>-25.70</b>	<b>-25.70</b>	<b>0.00</b>	<b>-20.39</b>	<b>-20.38</b>	<b>-0.01</b>
C18-H18A	-	-12.45	-	-	0.78	-	-	-23.66	-
C18-H18B	-	-5.07	-	-	-26.48	-	-	3.28	-
<b>C24-H24A+C24-H24B</b>	<b>0.94</b>	<b>0.94</b>	<b>0.00</b>	<b>15.75</b>	<b>15.75</b>	<b>0.00</b>	<b>-9.08</b>	<b>-9.09</b>	<b>0.01</b>
C24-H24A	-	13.46	-	-	20.27	-	-	15.55	-
C24-H24B	-	-12.51	-	-	-4.51	-	-	-24.64	-
<b>C27-H27</b>	<b>14.52</b>	<b>14.49</b>	<b>0.03</b>	<b>18.78</b>	<b>18.67</b>	<b>0.11</b>	<b>15.29</b>	<b>15.24</b>	<b>0.05</b>
<b>C30-H30</b>	<b>17.02</b>	<b>17.00</b>	<b>0.02</b>	<b>14.74</b>	<b>14.84</b>	<b>-0.10</b>	<b>14.06</b>	<b>14.14</b>	<b>-0.08</b>
<b>C35-H35</b>	<b>7.91</b>	<b>8.01</b>	<b>-0.10</b>	<b>6.56</b>	<b>6.36</b>	<b>0.20</b>	<b>-11.24</b>	<b>-11.17</b>	<b>-0.07</b>
<b>C37-H37</b>	<b>-16.61</b>	<b>-16.63</b>	<b>0.02</b>	<b>8.66</b>	<b>8.65</b>	<b>0.01</b>	<b>-15.02</b>	<b>-14.97</b>	<b>-0.05</b>
<b>C39-H39</b>	<b>-24.87</b>	<b>-24.93</b>	<b>0.06</b>	<b>2.00</b>	<b>1.90</b>	<b>0.10</b>	<b>4.18</b>	<b>4.31</b>	<b>-0.13</b>
<b>C41-H41</b>	<b>-5.03</b>	<b>-5.03</b>	<b>0.00</b>	<b>-4.67</b>	<b>-4.65</b>	<b>-0.02</b>	<b>-19.53</b>	<b>-19.49</b>	<b>-0.04</b>
<b>C43-H43A+C43-H43B</b>	<b>-30.83</b>	<b>-30.77</b>	<b>-0.06</b>	<b>3.45</b>	<b>3.46</b>	<b>-0.01</b>	<b>13.99</b>	<b>13.95</b>	<b>0.04</b>
C43-H43A	-	-16.03	-	-	-24.48	-	-	-1.86	-
C43-H43B	-	-14.74	-	-	27.94	-	-	15.81	-
<b>C44-H44A+C44-H44B</b>	<b>-14.42</b>	<b>-14.41</b>	<b>-0.01</b>	<b>6.81</b>	<b>6.79</b>	<b>0.02</b>	<b>2.47</b>	<b>2.45</b>	<b>0.02</b>
C44-H44A	-	14.27	-	-	2.35	-	-	14.36	-
C44-H44B	-	-28.68	-	-	4.44	-	-	-11.91	-
<b>C46-H46A+C46-H46B</b>	<b>-22.40</b>	<b>-22.40</b>	<b>0.00</b>	<b>-2.47</b>	<b>-2.48</b>	<b>0.01</b>	<b>-10.39</b>	<b>-10.39</b>	<b>0.00</b>
C46-H46A	-	-16.83	-	-	-0.89	-	-	-23.50	-
C46-H46B	-	-5.57	-	-	-1.59	-	-	13.11	-
<b>C47-H47</b>	<b>-0.88</b>	<b>-0.95</b>	<b>0.07</b>	<b>-3.29</b>	<b>-3.27</b>	<b>-0.02</b>	<b>-0.91</b>	<b>-0.89</b>	<b>-0.02</b>
<b>C48-H48</b>	<b>15.49</b>	<b>15.47</b>	<b>0.02</b>	<b>-13.54</b>	<b>-13.56</b>	<b>0.02</b>	<b>3.53</b>	<b>3.48</b>	<b>0.05</b>
<b>C58-H58A+C58-H58B</b>	<b>22.26</b>	<b>22.26</b>	<b>0.00</b>	<b>-24.94</b>	<b>-24.94</b>	<b>0.00</b>	<b>-2.45</b>	<b>-2.44</b>	<b>-0.01</b>
C58-H58A	-	25.15	-	-	-16.08	-	-	1.17	-
C58-H58B	-	-2.89	-	-	-8.86	-	-	-3.61	-



Vincristine (**5**)

Figure S15. Plot of the experimental RDCs ( $D^{exp}$ ) vs. their back-calculated values ( $D^{calc}$ ) used for Vincristine (**5**, three alignment media labeled [A]-[C]). The corresponding best-fit (lowest total pseudo energy) structure model (see plot below) was obtained from the DG simulation using all three AM data sets.

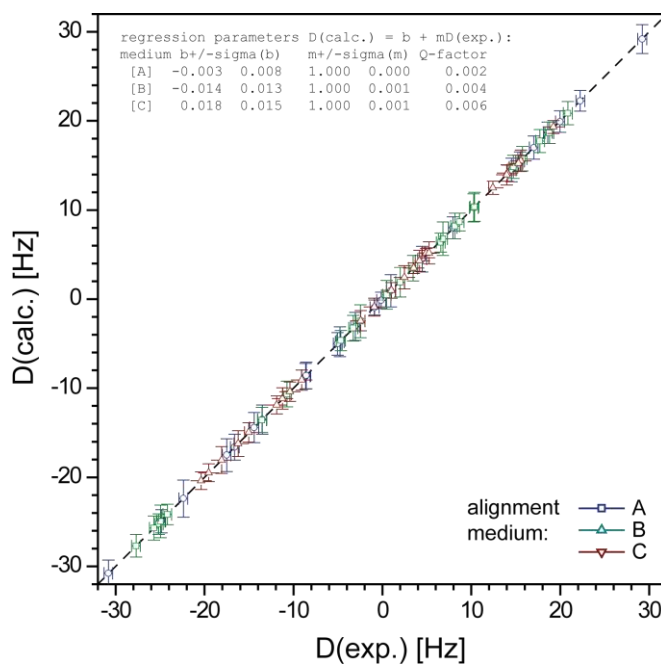
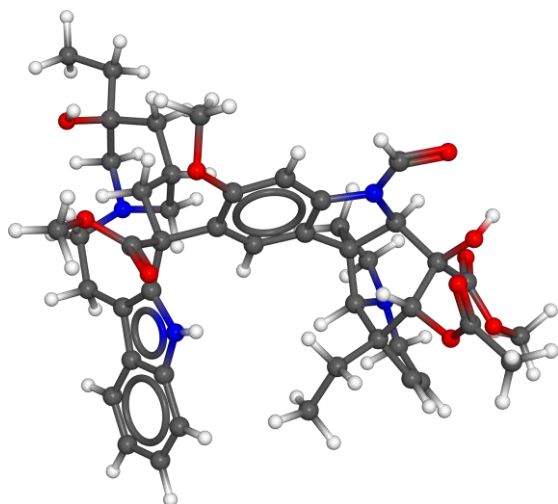


Table S7. NOE data used for Vincristine (**5**) ( $N = 23$  NOEs, the NMR-derived expectation values are denoted as  $d_{mean}$ , and the allowed lower and upper bounds – usually  $d_{mean} \pm 10\%$  – are labeled as  $d_{min} \dots d_{max}$ ; the averaged distances back-calculated from structural data are labelled  $d_{calc}$ , and the corresponding residuals are listed only if this value falls out of range, i.e.  $d_{calc} < d_{min}$  or  $d_{calc} > d_{max}$ ; all distance are given in [Å]). The NOE labels refer to the formula shown on the right, where given as e.g.  $H^A|H^B$ , NOEs were recalculated from structures as  $r^{-6}$  averages over all pairs of atom-atom distances.

NOE	distances [Å]				
	$d_{mean}$	$d_{min} \dots d_{max}$	$d_{calc}$	$\Delta d$	
H30	H35	2.206	1.985-2.426	2.149	-
H27	H39	2.458	2.212-2.704	2.565	-
H1	H27	2.672	2.405-2.939	2.877	-
H15	H27	2.684	2.416-2.952	2.752	-
H10A H10B	H12A H12B	2.176	1.958-2.394	2.290	-
H10A H10B	H16A H16B	2.783	2.505-3.061	2.809	-
H12A H12B	H18A H18B	2.705	2.435-2.976	2.703	-
H14A H14B	H16A H16B	3.100	2.790-3.410	3.162	-
H14A H14B	H18A H18B	2.926	2.633-3.219	2.940	-
H14A H14B	H27	2.598	2.338-2.858	2.621	-
H16A H16B	H18A H18B	3.292	2.963-3.621	3.310	-
H27	H43A H43B	2.894	2.605-3.183	2.725	-
H27	H58A H58B	3.304	2.974-3.634	3.563	-
H37	H43A H43B	2.562	2.306-2.818	2.533	-
H37	H44A H44B	3.287	2.958-3.616	3.319	-
H39	H41	3.463	3.117-3.809	3.448	-
H39	H43A H43B	3.140	2.826-3.454	3.190	-
H39	H44A H44B	3.330	2.997-3.663	3.415	-
H39	H46A H46B	3.014	2.713-3.315	3.091	-
H39	H58A H58B	2.653	2.388-2.918	2.611	-
H41	H58A H58B	2.361	2.125-2.597	2.369	-
H44A H44B	H46A H46B	2.829	2.546-3.112	2.798	-
H48	H58A H58B	2.864	2.578-3.150	2.946	-

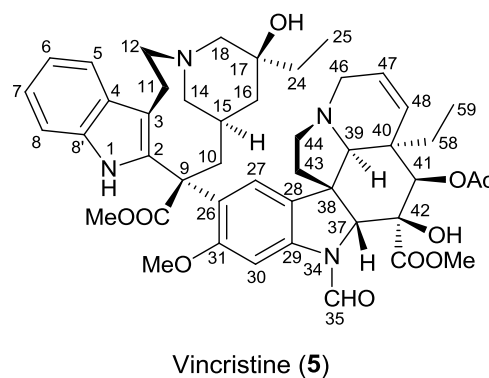


Figure S16. Plot of the best-fit (minimum pseudo energy) DG structure of Vincristine (**5**) with color-coded representation of all NOE contacts used in the configurational and conformational analysis. The color scale was adapted from calculated final NOE violations, ranging from -0.40 Å (blue) to +0.40 Å (red).

