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The stereochemistry of glabrescol

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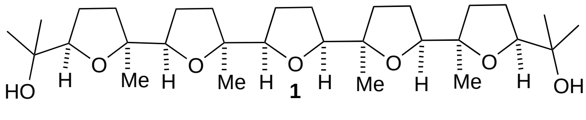
Abstract—The structure of glabrescol has been proposed and revised. Could the revised structure have been predicted without the need for total synthesis? Molecular modelling studies showed that the natural product structure proposed for glabrescol was not the most thermodynamically favourable form. When a lithium ion was incorporated, the natural product proved to be the lowest in energy of all symmetric isomers of glabrescol. Further modelling studies have led to the discovery of an asymmetric isomer lower in energy than the natural product when bound to a variety of ions. © 2001 Elsevier Science Ltd. All rights reserved.

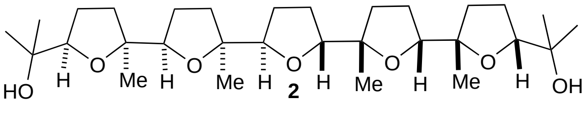
Glabrescol, a pentacyclic oxasqualenoid isolated from *Spathelia glabrescens*[1] was originally assigned the C_s-symmetric structure **1**. Total synthesis[2] of this has shown the initial assignment to be incorrect, and recent total syntheses by Corey[3] and Morimoto[4] have proven **2** is the true structure of glabrescol (Fig. 1).

One possible reason why glabrescol has this C_2-symmetric structure, rather than the alternative C_s-structure initially proposed, is that nature has selected this structure to perform a particular function especially well. The structures of ionophores lasalocid A, ulapualide A and nonactin have been investigated by comparing the relative affinity of different isomers to a cationic species. Still found that the natural form of lasolocid A[5] bound barium ions more tightly than any of its epimers by two to three orders of magnitude. Pattenden used molecular modelling in an ambitious attempt to predict the then unknown stereochemistry of ulapualide A,[6] a prediction shown by a later total synthesis[7] to be largely correct. More recently, modelling studies on nonactin[8,9] have shown that the natural product is the most thermodynamically stable of all possible isomers when bound to a potassium ion.

Molecular modelling studies were carried out on all 16 possible C_2-symmetric isomers of glabrescol, along with the initially proposed C_s-symmetric structure **1**. A genetic algorithm[10] was used to search possible conformations, and energies were minimised using the MM2* force field within MacroModel[11] to find the global minimum energy conformation for each structure. The natural product **2** was found to have only the fifth lowest energy of the C_2-symmetric structures, and was also 3.65 kJ mol^{-1} higher in energy than C_s-symmetric **1**. The role of glabrescol has been proposed to involve ion binding,[12] so the procedure was repeated using ACCA[13] to incorporate a lithium ion[†] in each structure, and a modified version of the genetic algorithm to search conformations. When bound to lithium, the natural product **2** was found to be considerably lower in energy than the originally proposed structure **1**. The calculated difference in energy (35.5 kJ mol^{-1}) corresponds to a ratio of about a million to one, whereas without lithium the predicted ratio is approximately 1:5.[‡] A summary table of calculated energies and predicted relative populations is available as supplementary information upon request.



1



2

Figure 1. Structures proposed for the natural product glabrescol.

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[†] Lithium was chosen for convenience, as parameters for this were already available ($r = 1.500$ Å, $\varepsilon = 0.050$ kcal/mol).

[‡] Energy differences are converted to relative populations using Boltzmann factors (Ref. 14), and assuming ions are in thermodynamic ratios.

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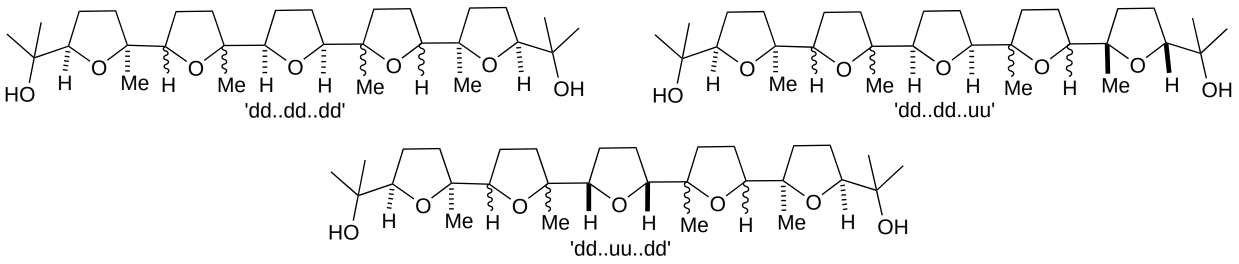

'dd..dd..dd'

'dd..dd..uu'

'dd..uu..dd'

Figure 2. Three patterns possible with *cis* terminal and central rings

Modelling all 1024 possible isomers of glabrescol to find which is the lowest energy would require unrealistic computational power. It was, therefore, desirable to eliminate some possibilities. Considering the symmetry of the backbone and ignoring enantiomers reduces the number of unique isomers. Further elimination is possible; of the cases considered, all structures with a *cis* central ring bind more strongly to lithium than the equivalent structure with a *trans* central ring, even though natural product **2** has a *trans* central ring. *cis* Terminal rings also appear to be favoured; in all cases where a direct comparison was made, a structure with *trans* terminal rings had an equivalent structure with *cis* terminal rings that was lower in energy.

There are three possible patterns for the relative stereochemistry of isomers with *cis* terminal and central rings as illustrated in Fig. 2. Isomers with the pattern dd..dd..uu (where 'd' indicates that a substituent is pointing down, and 'u' indicates up) showed more affinity for lithium than corresponding structures with one of the other two patterns. This leaves only four variable stereocentres and therefore 16 likely candidates for the minimum energy structure. One of these isomers, **3** (Fig. 3), differing from **2** only in the configuration of one of its stereocentres, giving a *cis* central ring, was found to bind lithium more strongly than the natural product (E = +10.97 kJ mol^{-1} unbound, −3.2 kJ mol^{-1} bound to Li$^+$). Based on the trends observed, **3** is likely to be the thermodynamically most favoured form of glabrescol when bound to a lithium ion.

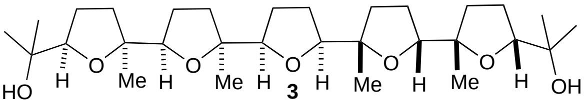

Figure 3.

The conformations of the different isomers (Fig. 4) are very similar and show, as expected, the seven oxygen atoms pointing inwards towards the lithium ion.[§] Average Li–O distances are greater for **1**, indicating weaker stabilisation of the cation, whereas those for **2** and **3** are similar. It is likely that orientating the *trans* central ring of **2** to obtain good Li–O interaction introduces more strain than that for the *cis* central ring in **3**.

Table 1. Energy (kJ mol^{-1}) of glabrescol isomers incorporating a cation. Energies quoted relative to Li$^+$(**2**)

Isomer	Ion bound			
	Li$^+$	Na$^+$	K$^+$	Ca^{2+}
1	35.5	42.3	121.3	−320.6
2	0	7.8	110.0	−372.9
3	−3.2	4.3	108.6	−382.8

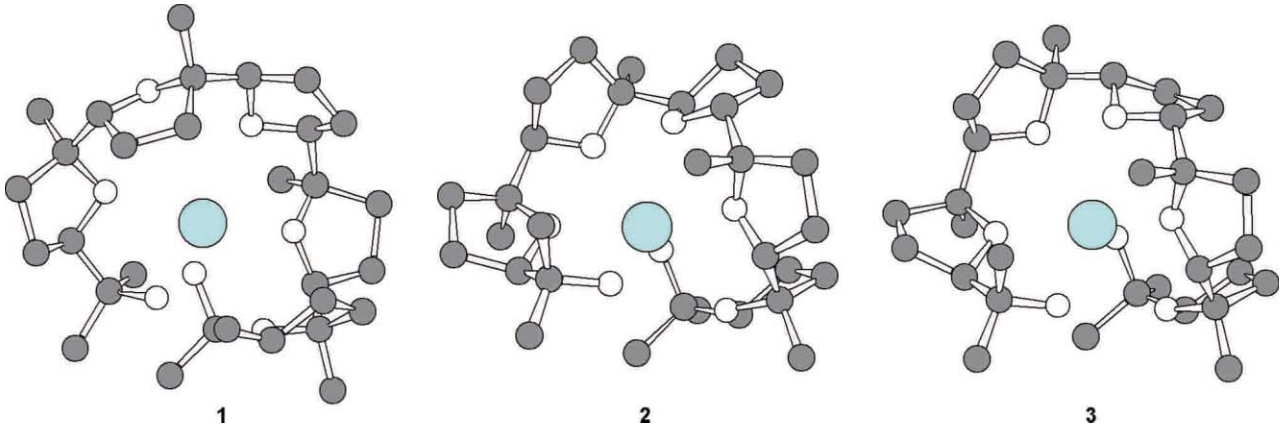

Figure 4. Minimum energy conformations of isomers of glabrescol bound to lithium. Note the difference between the top right hand rings of **2** and **3**.

[§] Structures are available on the World Wide Web at http://www.ch.cam.ac.uk/MMRG/glabrescol/

Table 2. Calculated change in energy for reaction shown (kJ mol^{-1})

Entry	Reaction	Ion (M)			
		Li^+	Na^+	K^+	Ca^{2+}
1	$\mathbf{1}+M(H_2O)_7 \rightarrow M(\mathbf{1})+7H_2O$	67.1	70.5	21.5	285.2
2	$\mathbf{2}+M(H_2O)_7 \rightarrow M(\mathbf{2})+7H_2O$	27.9	32.3	6.5	229.3
3	$\mathbf{3}+M(H_2O)_7 \rightarrow M(\mathbf{3})+7H_2O$	23.0	27.1	3.4	217.7
4	$Li^+(\mathbf{1})+M(H_2O)_7 \rightarrow M(\mathbf{1})+Li^+(H_2O)_7$	0	3.4	−45.6	218.1
5	$Li^+(\mathbf{2})+M(H_2O)_7 \rightarrow M(\mathbf{2})+Li^+(H_2O)_7$	0	4.4	−21.4	201.3
6	$Li^+(\mathbf{3})+M(H_2O)_7 \rightarrow M(\mathbf{3})+Li^+(H_2O)_7$	0	4.1	−19.6	194.6

The relative energy of **1**, **2** and **3** when bound to potassium, sodium and calcium was calculated in the same manner as for lithium;[¶] for all ions studied the non-natural **3** was found to be lower in energy (Table 1).

The energies of the metal hydrates $M^{x+}(H_2O)_7$ were calculated using MM2* for the same ions.[‖] The relative affinity of isomers **1**, **2** and **3** for the four ions studied was estimated by calculating energies for the equilibria shown in Table 2. This model predicts that, relative to the metal hydrates, glabrescol will bind most strongly to potassium, then to sodium and lithium, with calcium showing the weakest binding (entries 1–3). The isomers bind with similar selectivities, however the natural product is predicted to bind potassium more selectively than **3** (entries 5, 6).

Structure **2** is the lowest in energy of all C_2-symmetric isomers when bound to lithium, but one of the possible non-symmetric structures is even more thermodynamically favoured. It is possible that the symmetry of **2** may allow for a simpler biosynthesis, and the evolutionary advantage gained by increased ion affinity could be outweighed by the need for a more complex route to produce it. Furthermore, the higher selectivity for potassium ions of **2** may be necessary for the role of glabrescol in natural systems, and compensate for its slightly lower overall ion affinity.

Acknowledgements

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References

1. Harding, W. W.; Lewis, P. A.; Jacobs, H.; McLean, S.; Reynolds, W. F.; Tay, L. L.; Yang, J. P. *Tetrahedron Lett*. **1995**, *36*, 9137–9140.
2. Xiong, Z. M.; Corey, E. J. *J. Am. Chem. Soc*. **2000**, *122*, 4831–4832.
3. Xiong, Z. M.; Corey, E. J. *J. Am. Chem. Soc*. **2000**, *122*, 9328–9329.
4. Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc*. **2000**, *122*, 7124–7125.
5. Still, W. C.; Hauck, P.; Kempf, D. *Tetrahedron Lett*. **1987**, *28*, 2817–2820.
6. Maddock, J.; Pattenden, G.; Wight, P. G. *J. Computer-Aided Mol. Des*. **1993**, *7*, 573–586.
7. (a) Chattopadhyay, S. K.; Pattenden, G. *Tetrahedron Lett*. **1998**, *39*, 6095–6098; (b) Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc*., *Perkin Trans. 1* **2000**, *15*, 2429–2454.
8. Goodman, J. M.; Hoyer, R., in preparation.
9. Rowan, S. J.; Hamilton, D. G.; Brady, P. A.; Sanders, J. K. M. *J. Am. Chem. Soc*. **1997**, *119*, 2578–2579.
10. Nair, N.; Goodman, J. M. *J. Chem. Inf. Comp. Sci*. **1998**, *2*, 317–320.
11. Allinger, N. L. *J. Am. Chem. Soc*. **1977**, *99*, 8127.
12. Morimoto, Y.; Iwai, T.; Yoshimura, T.; Kinoshita, T. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2005–2010.
13. Acca is a program that aids conformation searching by rapidly transforming structures. The executable is available on the World Wide Web (http://www.ch.cam.ac.uk/MMRG/software/). See also: Goodman, J. M.; Leach, A. G. *J. Chem. Soc*., *Perkin. Trans. 2* **1997**, 1205–1208.
14. Goodman, J. M.; Kirby, P. D.; Haustedt, L. O. *Tetrahedron Lett*. **2000**, *41*, 9879–9882.
15. Burgess, J. *Metal Ions in Solution*; Ellis Horwood: Chichester, UK, 1978; pp. 137–159.

[¶] Force field parameters for MM2* were approximated based on those from the AMBER force field (Na^+ $r=1.60$ Å, $\varepsilon=0.031$ kcal/mol; K^+ $r=2.00$ Å, $\varepsilon=0.13$ kcal/mol; Ca^{2+} $r=1.70$ Å, $\varepsilon=0.23$ kcal/mol).

[‖] Calculations were carried out with six and seven molecules, and the differences were found not to be significant. The actual hydration number in solution is debatable (Ref. 15).