chiral alkoxy groups, such as **1e**),[13] together with the use of controlled polymerization techniques,[14] can give rise to materials exhibiting interesting and useful solid-state properties.

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Supplementary Material Available: Physical, spectroscopic, and analytical data for compounds **1a-f** (2 pages). Ordering information is given on any current masthead page.

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Trehalose Conformation in Aqueous Solution from Optical Rotation

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Trehalose (α-D-glucopyranosyl-(1→1)-α-D-glucopyranoside) apparently has several important biological functions. One of the most recently discovered, with potential biotechnological importance, is its effectiveness in stabilizing membrane structure in the dry state and, perhaps, inhibiting biological damage at low temperature.[1-4] The detailed mechanism by which trehalose produces these stabilizing effects has not yet been established. It is known that trehalose binds to the head group of lipids in dry bilayers,[5] but the nature of the important molecular interactions in solution is not yet known.[6-8] We report here a determination of the solution conformation of trehalose based on optical rotation; the relative inflexibility that it displays may prove to be relevant to its cryobiological effectiveness.

Because of its symmetrical chemical structure, the two glucose rings are NMR equivalent; i.e., only one set of ^1H or ^{13}C resonances is observed. Conventional NMR techniques involving the measurement of chemical shifts, relaxation times, coupling constants, or NOEs cannot be applied to deduce the linkage geometry in solution. Attempts to make the two glucose rings distinguishable by NMR, as through isotopic substitution, have not yet been reported.

Chiroptical measurements are very sensitive to saccharide conformation as well as configuration, and a reliable semiempirical calculational model has recently been developed that allows the prediction of optical rotation as a function of disaccharide conformation.[9] We have here applied that model to trehalose with no variation of the model parameters originally reported. Linkage conformations are specified by the dihedral angles ϕ and ψ; because of molecular symmetry the conformation specified as $\phi, \psi = a, b$ can equivalently be specified as $\phi, \psi = b, a$. For a given linkage geometry, we considered four combinations of the exocyclic hydroxymethyl groups, allowing for both *gt* and *gg* conformations in each glucose residue. With statistical weights of 0.67 for the *gt* conformation and 0.33 for the *gg* conformation,[10] the average we require is

$$[\bar{M}]^{calc} = 0.45[M]_{gt,gt} + 0.22[M]_{gt,gg} + 0.22[M]_{gg,gt} + 0.11[M]_{gg,gg}$$

where $[M]$ is the Na_D molar rotation on a disaccharide basis, $0.45 = (0.67)^2$, $0.22 = (0.67)(0.33)$, and $0.11 = (0.33)^2$. Calculated results are displayed in Figure 1 superimposed on a hard-sphere conformational ϕ, ψ map, generated by using the atom-atom contact distances of Rees and Scott.[11] Molecular symmetry leads to the symmetric arrangement of rotations with respect to the diagonal of the figure.

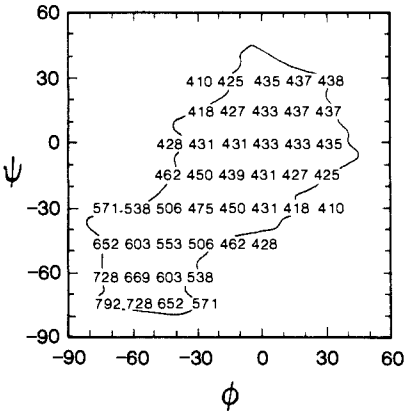

Figure 1. Na_D molar rotations of trehalose calculated as a function of linkage angles ϕ and ψ, superimposed on a hard-sphere conformation map.

The observed trehalose optical rotation[12] of +681 deg cm^2 dmol^{-1} in water is that expected for conformations in the region near $\phi, \psi = -60°, -60°$ (Figure 1). The significant features of conformations in that region are that the C(1)-C(2) bond of each glucose ring is trans to the O(1)-C(1) bond of the other, and the O(1)-C(1) bond of each ring is gauche to the C(1)-O(5) bond of the other.

The solid-state conformation of trehalose ($\phi, \psi = -60°, -59°$)[13] and that of trehalose dihydrate ($\phi, \psi = -58°, -45°$)[14] are located in the same region of the ϕ, ψ map, as is the energy-minimized calculated conformation of Tvaroska and Vaclavik ($\phi, \psi = -61°, -56°$).[15] An earlier, somewhat more empirical, analysis of optical rotation by Rees and Thom[16] led to an averaged solution conformation of $\phi, \psi = -72°, -72°$, indicating a strong preference for the same region of conformational ϕ, ψ space as found by us.

Moreover, the present results indicate that the extent of conformational excursions in aqueous solution is extremely limited, inasmuch as any significant conformational averaging would lead to a substantially reduced optical rotation (Figure 1). Conformations in which either ϕ or ψ is decreased by as little as 30° have molar rotations 100 deg cm^2 dmol^{-1} less than what is observed in aqueous solution. Whether trehalose stabilizes biological membranes through direct binding[17] or indirectly through in-

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teractions with water, its relative inflexibility in linkage conformation may play a role in its particular effectiveness.

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Synthesis of Bryostatin 7

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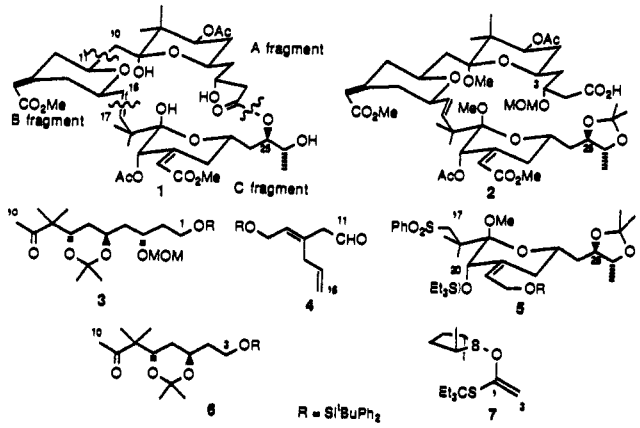
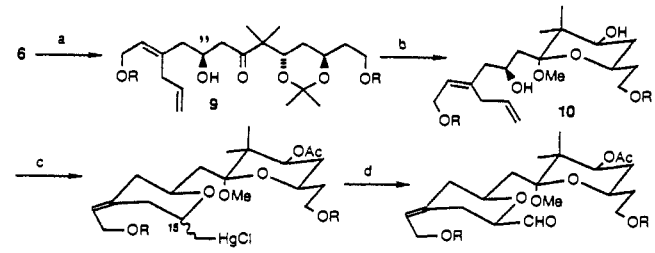
We record herein the synthesis of bryostatin 7 (**1**), a representative member of potent antileukemic agents isolated from the invertebrate filter feeder *Bugula neritina*.[1,2] As previously documented,[3] our earlier efforts toward this objective reached seco-acid derivative **2** corresponding to **1** through the connection of fragments A (**3**), B (**4**), and C (**5**). Unfortunately, deprotection of the C(3)-OMOM group (of **2**), which had been introduced at an early stage and had served well by surviving throughout the course of the synthesis of **2**, turned out to be problematic.[4] This led to a revision of the synthetic route that placed the creation of the C(3) stereogenic center at the end of the seco-acid synthesis. Thus, sequential connection of fragment A′ (**6**) [C(3)–C(10)] [instead of A (**3**) [C(1)–C(10)]], B (**4**), C (**5**), and a C(1)–C(2) unit (**7**) in this order, followed by macrolactonization, completed the synthesis of **1**. All of these fragments were available in our earlier work.[3]

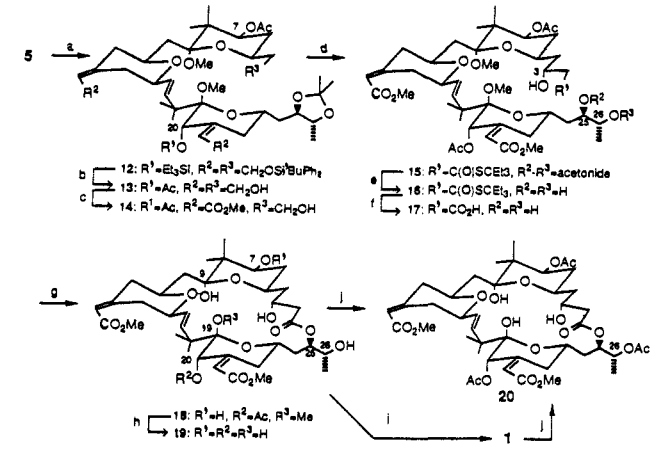


Scheme I[a]



[a] R = SiᵗBuPh₂. (a) (*R,R*)-2,5-Dimethylborolanyl triflate, $^{i}Pr_2EtN$, Et_2O, then **4** (86%, 11*S*:11*R* = 8:1); (b) MeOH, PPTS, $(MeO)_3CH$ (84%); (c) (i) $Hg(OAc)_2$, THF–MeOH, then KCl, (ii) Ac_2O, pyridine, DMAP (93%, two steps, 15*S*:15*R* = 1:1); (d) (i) $NaBH_4$, O_2, DMF–CH_2Cl_2 (77%), (ii) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C, (iii) Al_2O_3 (3% H_2O), CH_2Cl_2 (60%, two steps).

Scheme II[a]



[a] (a) (i) PhLi, THF, −78 °C, then **8**, then PhCOCl and DMAP, −78 °C → 25 °C, (ii) Na–Hg, MeOH–EtOAc, Na_2HPO_4, −20 °C (60%, two steps); (b) (i) $^{n}Bu_4NF$, THF, (ii) $^{t}BuMe_2SiCl$, DMF, imidazole, (iii) Ac_2O, pyridine, DMAP, (iv) $^{n}Bu_4NF$, THF (100%, four steps); (c) MnO_2, THF, then MeOH, NaCN, and AcOH (61%); (d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, −78 °C → 0 °C, (ii) **7**, $^{i}Pr_2EtN$, Et_2O, −100 °C → −78 °C (83%, two steps, 3*R*:3*S* = 3:1); (e) CSA, MeOH (40%); (f) (i) Et_3SiOTf, CH_2Cl_2, lutidine, 0 °C, (ii) $Hg(O_2CCF_3)_2$, Na_2HPO_4, THF, (iii) HF·pyridine, THF, −20 °C (64%, three steps); (g) DCC, PPTS, pyridine, $ClCH_2CH_2Cl$, reflux (51%); (h) K_2CO_3, MeOH, then 5% HCl aqueous workup (54%); (i) (i) $^{t}BuMe_2SiCl$, DMF, Et_3N, DMAP, (ii) Ac_2O, pyridine, (iii) HF–MeCN (40%, two steps); (j) Ac_2O, pyridine.

Synthesis of the A′B Fragment (8). The aldol reaction of **4** with the enolate derived from **6** and (*R,R*)-2,5-dimethylborolanyl triflate proceeded with a stereoselection of 8:1 to provide the desired diastereomer **9** as the major product (Scheme I). The two chiral components, **6** and the triflate, constitute a matched pair.[5] With all the carbons in place, **9** was further modified to fragment A′B (**8**). Construction of the two pyran rings was accomplished by deacetonization (step b) to secure **10** followed by Hg-mediated cyclization (step c). The stereorandomness of the latter process as shown in **11** was not critical as this pyran side chain was equilibrated to become equatorial at the aldehyde stage (see **8** and step d, reaction iii) in the manner already detailed for the synthesis of fragment AB.[3b]

Connection of Fragment A′B, C, and the C(1)–C(2) Unit. The synthesis of fragment C (**5**) has been described elsewhere,[3a] and the characterization of its precursors and an updated synthetic route are provided in the supplementary material. The stereostructure assigned to **5** was confirmed by X-ray analysis of its C(20) hydroxyl compound generated from **5**.[6]

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(6) We thank Dr. O. Yamashita and Mr. J. Okada for carrying out this analysis, which is detailed in the supplementary material.

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