were rapid at lower temperature. The deuterium which is introduced asymmetrically in the isotopic perturbation experiment would further lower the tunneling rate by breaking the degeneracy. In any event, a double-minimum energy surface would be expected to produce a substantial equilibrium isotope effect and thus would lead to a large isotope-induced splitting in the NMR which was not observed.

MINDO/3 is reported to yield an energy difference of 7.3 kcal/mol between "classical" and symmetrically bridged structures for the 1,2-dimethylnorbornyl cation.[1] However, the NMR spectrum of this ion in solution shows conclusively that the barrier to interconversion of the unsymmetrical classical ions is less than 2.5 kcal/mol.[10,11] The prediction of tunneling, or the lack of it, for dimethylnorbornyl cation[1] is therefore based on a barrier height clearly in contradiction to the experimental facts. Recent high level ab initio SCF and CI calculations[12,13] on the norbornyl cation indicate only a single sharp minimum corresponding to the symmetrically bridged structure.

At the present, a substantial body of data[14] indicates that the norbornyl cation strongly prefers the symmetrical bridged structure in solution and in the gas phase and that participation of the 1,6 bond is important at the transition state for the solvolysis reaction of norbornyl derivatives. The nature of the results and the great variety of methods used go far beyond the usual scientific criteria for acceptance. These results are completely in accord with all accepted principles of bonding and analogous to results obtained in a number of other comparable cations. Therefore, at this point, we should carefully examine proposals that the situation is different. Any new proposals should consider *all* the previously reported data on this much investigated system.

(10) Saunders, M.; Telkowski, L.; Kates, M. H.; *J. Am. Chem. Soc.* **1977**, *99*, 8070.

(11) Perhaps in the spirit of the semiempirical MINDO idea, we should *correct* this value by 4.8 kcal to fit the experimental data. If so, a similar correction to the 1.9-kcal barrier predicted by MINDO/3 for norbornyl itself would lead to the conclusion that the "corrected" MINDO/3 value should be −2.9 kcal (the symmetrically bridged ion predicted to be more stable).

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On the Stereochemistry of the Bistetrahydrofuranyl Moiety of Uvaricin: Proton Chemical Shifts Can Play a Crucial Role in Complex Structure Determination

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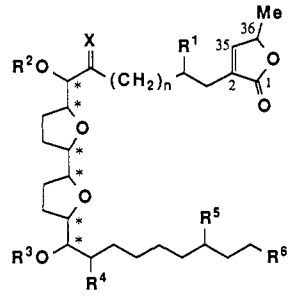
Uvaricin (**1**)[2a] is a member of a growing family of bistetrahydrofuran-containing, polyether natural products that includes desacetyluvaricin (**2**),[2b] rollinicin (**3**),[2c] isorollinicin (**4**),[2c] rollinone (**5**),[2d] asimicin (**6**),[2e] cherimoline (**7**),[2f] and dihydrocherimoline (**8**).[2f] In no case has it been possible to assign any of the relative stereochemical features of these molecules.[3] All are described by such terms as waxy, amorphous, or microcrystalline and have thus far proven to be unsuitable for crystallographic study. The assignment of relative and/or absolute stereochemical properties of the bistetrahydrofuranyl portions of **1–8** is a nontrivial task,

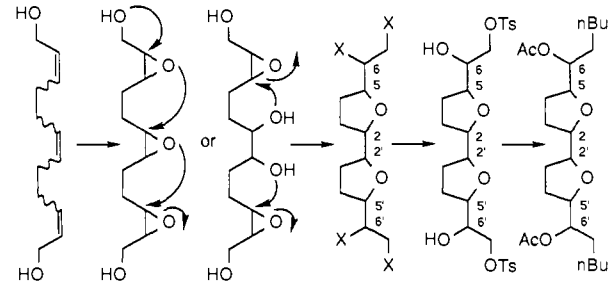


	X	R^1	R^2	R^3	R^4	R^5	R^6	n
1	HH	H	H	Ac	H	H	Et	9
2	HH	H	H	H	H	H	Et	9
‡3	HH	H	H	H	HO	H	Et	9
‡4	HH	H	H	H	HO	H	Et	9
‡‡5	=O	H	H	H	H	H	Et	9
6	HH	HO	H	H	H	H	Et	9
7	HH	H	H	H	HO	HO	Me	10
‡‡8	HH	H	H	H	HO	HO	Me	10
16	HH	H	Ac	Ac	H	H	Et	9

‡ **3** is epimeric with **4** at some center(s)
‡‡ **5** and **8** are $\Delta^{2,35}$-dihydro

yet those features could well be critical in imparting the in vivo inhibitory activity against various leukemias observed for **1**, **3**, **4**, and **5** and the cytotoxic, pesticidal, and antimicrobial behaviors of **6**, **7**, and **8**. As a prelude to the synthesis of uvaricin (**1**), we have determined the relative configuration of six of its seven[3] stereogenic centers (marked *) by comparison with the series of "dibutylated diacetates" **9a-l** as described here. Of paramount importance in this determination was the realization that stereochemical information could be extracted from iterative and synergistic analyses of very small differences in high-field proton chemical shift and chromatographic retention data.

There exist 20 diastereomers of **9**.[4] The 12 which contain identical stereo relationships (i.e., either both threo or both erythro) between C(5)/C(6) and C(5′)/C(6′) (**9a–l**) have been previously synthesized[5] by end-to-end triepoxide cascade reactions of **10** and/or by complementary inside-out closures of diol diepoxides **11** via the tetrols **12** (which were isolated and characterized as their tetraacetate derivatives **13**) and ditosylates **14**. These 12



15a E,Z,E
b E,E,E
c Z,Z,Z
d Z,E,Z

10 **11** **12** X = OH; **13** X = OAc **14** **9**

■ = hydrogen up □ = hydrogen down for **9**, **12**, **13**, and **14**

	6	5	2	2′	5′	6′		6/5	5/2	2/2′	2′/5′	5′/6′	symmetry
a	■	□	□	■	■	□	≡	eryth	cis	threo	cis	eryth	C_2
b	■	□	■	□	□	■	≡	eryth	trans	threo	cis	eryth	none
c	■	□	■	□	■	□	≡	eryth	trans	threo	trans	eryth	C_2
d	■	□	□	□	□	■	≡	eryth	cis	eryth	cis	eryth	C_s
e	■	□	■	■	■	□	≡	eryth	trans	eryth	cis	eryth	none
f	■	□	■	■	□	■	≡	eryth	trans	eryth	trans	eryth	C_s
g	□	□	□	■	■	■	≡	threo	cis	threo	cis	threo	C_2
h	□	□	■	□	□	□	≡	threo	trans	threo	cis	threo	none
i	□	□	■	□	■	■	≡	threo	trans	threo	trans	threo	C_2
j	□	□	□	□	□	□	≡	threo	cis	eryth	cis	threo	C_s
k	□	□	■	■	■	■	≡	threo	trans	eryth	cis	threo	none
l	□	□	■	■	□	□	≡	threo	trans	eryth	trans	threo	C_s

were generated in four sets of three diastereomers each, and each set arose, formally at least,[5b] from one of the four trienes **15a–d** which possess either C_{2v} or C_{2h} symmetry (i.e., those four that have

(1) Fellow of the Alfred P. Sloan Foundation.

(2) (a) Jolad, S. D.; Hoffmann, J. J.; Schram, K. H.; Cole, J. R.; Tempesta, M. S.; Kriek, G. R.; Bates, R. B. *J. Org. Chem.* **1982**, *47*, 3151. (b) Jolad, S. D.; Hoffmann, J. J.; Cole, J. R.; Barry, C. E.; III; Bates, R. B.; Linz, G. S.; Konig, W. A. *J. Nat. Prod.* **1985**, *48*, 644. (c) Dabrah, T. T.; Sneden, A. T. *Phytochemistry* **1984**, *23*, 2013. (d) Dabrah, T. T.; Sneden, A. T. *J. Nat. Prod.* **1984** *47*, 652. (e) Rupprecht, J. K.; Chang, C. J.; Cassady, J. M.; McLaughlin, J. L.; Mikolajczak, K. L.; Weisleder, D. *Heterocycles* **1986**, *24*, 1197. (f) Cortes, D.; Rios, J. L.; Villar, A.; Valverde, S. *Tetrahedron Lett.* **1984**, *25*, 3199.

(3) However, the absolute configuration of C(36) of uvaricin has recently been determined by degradation of natural material to (*S*)-lactic acid.[2b]

(4) There are six stereogenic centers in **9**, which dictates a maximum of 64 stereoisomers or 32 diastereomeric pairs of enantiomers. Symmetry factors reduce this number to 20: **9a**-l plus 8 more unsymmetrical isomers which have C(5)/C(6) threo and C(5′)/C(6′) erythro relationships.

(5) (a) Hoye, T. R.; Suhadolnik, J. C. *Tetrahedron* **1986**, *42*, 2855. (b) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312.

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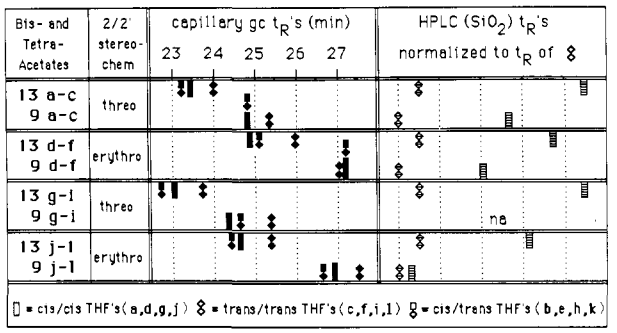

Figure 1. Capillary GC and HPLC retention times of **13a–l** and **9a–l**.

terminal olefin geometries which are either both *E* or both *Z*). Within any set of three isomers, the pair containing two cis- or two trans-disubstituted tetrahydrofuran rings was easily distinguished after separation by HPLC (at the stage of the tetraacetates **13**) by their C_s or C_2 symmetry from the third, unsymmetrical isomer which always had one each of *cis*- and *trans*-THF rings (e.g., **13a** and **13c** vs. **13b**). The two symmetrical isomers **13a** and **13c** were assigned by an unambiguous synthesis of the former by the inside-out process[5] on **11c** and, thereafter, by correlation of ^{1}H NMR (vide infra) and chromatographic data.

Figure 1 summarizes both the capillary gas chromatography (CGC) and normal-phase SiO_2 HPLC retention times (t_R's) for the series of tetraacetates **13a–l** and dibutylated diacetates **9a–l**. Notice, first, that the group of six compounds having a threo relationship[6] between C(2) and C(2′) (**a–c** and **g–i**) all possess shorter CGC t_R values than any of the group of six having erythro C(2)/C(2′) stereochemistry[6] (**d–f** and **j–l**) for both the tetra- and diacetates, **13** and **9**, respectively. This fact provided clear indication that correlations between chromatographic retention times and stereochemistry could be expected even within series of molecules of this complexity. Notice, now, that in every instance in which there is a significant difference between the t_R's of the cis/cis and trans/trans isomers for any one set of three compounds, the isomer eventually assigned the trans/trans stereochemistry always elutes faster by HPLC and slower by CGC than its cis/cis partner, thus considerably increasing the confidence level in those assignments.

Proton NMR chemical shift data (300 MHz) for **9a–l**, uvaricin (**1**), and uvaricin acetate (**16**) are summarized in Figure 2. Many trends are apparent, and from these the stereochemistries of the cis/cis (**a**, **d**, **g**, **j**) vs. the trans/trans (**c**, **f**, i, l) isomers of **9** (and **13**)[7] were deduced. In every instance among **9** (and **13**),[7] (i) H(5) and H(2) appear further downfield (by 0.04–0.08 ppm) in the trans/trans compounds than in the cis/cis isomers, (ii) for a given cis/cis or trans/trans bistetrahydrofuran configuration H(2) is shifted downfield whenever the C(2)/C(2′) relationship is threo[6] compared with when it is erythro,[6] and (iii) for the unsymmetrical cis/trans isomers (**b**, **e**, **h**, **k**) H(2) and H(2′) are nearly superimposed in the C(2)/C(2′) erythro[6] isomers and significantly shift-separated in the C(2)/C(2′) threo[6] compounds. Finally, the methyl resonances for the C(6) and C(6′) acetate groups in the **a–f** isomers of **9** (and **13**)[7] having C(6(′))/C(5(′)) erythro[6] stereochemistry always appear ~0.03 ppm upfield (e.g., δ 2.051 ± 0.007 in **9**) of those for the **g–l** threo[6] isomers (e.g., δ 2.075 ± 0.006 in **9**).

Comparison of the ^{1}H chemical shifts for uvaricin acetate (**16**) with those of **9** led to the establishment of the relative configuration within **16** (and therefore **1**) shown in Figure 2. Thus, the presence of one 3 H singlet at δ 2.049 in uvaricin (**1**) and a pair at δ 2.074 and 2.046 in uvaricin acetate (**16**) strongly suggested a C(15)/C(16) threo and C(23)/C(24) erythro relationship, respectively. A trans/trans bistetrahydrofuran assignment was supported by

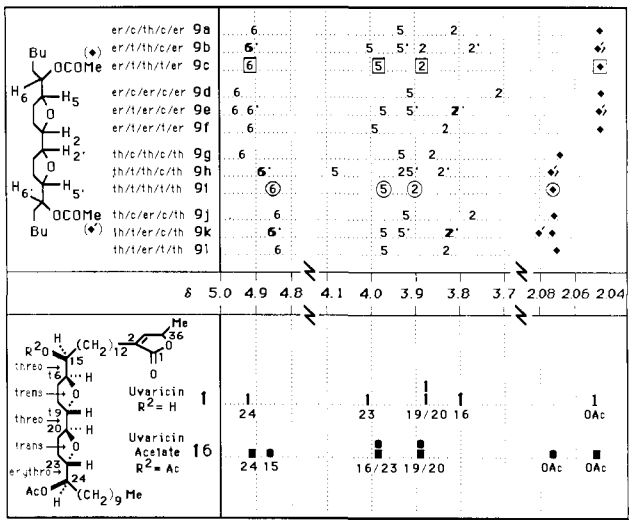

Figure 2. Proton NMR chemical shifts of diagnostic protons in the 12 isomers of dibutylated diacetates **9a–l** and of uvaricin (**1**) and uvaricin acetate (**16**).

the similarity of the H(16) and H(23) δ's with those for H(5) of any of the *trans,trans*-**9** isomers. The final relationship, C(19)/C(20), was assigned as threo since the δ's of H(19) and H(20) in **16** are very similar to those of H(2) in **9c** and **9i** (5-2/2-2′/2′-5′ trans/threo/trans compounds) and significantly different from H(2(′)) in any other environment. It is apparent and ironic that the relative configuration deduced for **16** (and **1**) which has C(15)/C(16) threo and C(23)/C(24) erythro linkages, does not correspond to any one of the 12 isomers of our model compounds **9**, each of which has stereochemically identical C(5)/C(6) and C(5′)/C(6′) linkages. However, it is gratifying and confirmatory to observe the near perfect proton chemical shift correlation between **16** and the two symmetrical models **9i** and **9c** (cf. boxes and circles in Figure 2), which embody, respectively, the stereo relationships found among C(15) through C(20) and C(19) through C(24) in uvaricin acetate (**16**).

It is interesting to recognize that the concepts used to reach the above stereochemical conclusion, differential chemical shift and differential chromatographic retention, are the most fundamental ideas associated with those particular analysis methods. However, because of the small magnitude of the differences involved, this problem would likely have been insoluble before the instrumental advances of, say, this decade. Moreover, although differential chemical shift analysis has routinely been used in conjunction with ^{13}C NMR spectroscopy, that approach in the present instance was fruitless in our hands.[8] This study, coupled with the more routine availability of largely if not completely assignable ^{1}H NMR spectra, suggests that proton chemical shift analyses may have considerable merit.[9] Although it is difficult to decide what constitutes a proof of stereochemistry by the above class of arguments, we are sufficiently confident of the relative configuration of uvaricin (**1**) to be currently engaged in its synthesis.

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Supplementary Material Available: ^{1}H NMR data for **13a–l** (cf. Figure 2) and complete spectral data for **16** (2 pages). Ordering information is given on any current masthead page.

(6) This stereochemistry rests on firm mechanistic grounds since it derives directly from the *E* or *Z* nature of a precursor olfin.

(7) Entirely analogous ^{1}H NMR data (see supplementary material) from and arguments for assignment of stereochemistry within the series of tetraacetates **13a–l** exist which further solidify the conclusion.

(8) Moreover, homonuclear proton coupling data, although sufficiently reproducible to be useful as fingerprints for specific protons in analogous stereochemical environments, were not adequately distinctive to allow a priori assignments.

(9) For a recent comment of similar thrust, see ref 10 in: Daub, G. W. Griffith, D. A. *Tetrahedron Lett.* **1986**, *27*, 6311.