farnesyl pyrophosphate. However, since the *endo*-bergamotenes[22,27] as well as other sesquiterpenes[28] having the endo stereochemistry are known natural products, the generality of least-motion mechanisms is uncertain at this time.

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Effects of Tunneling on NMR Spectra. The Question of Heavy Atom Tunneling in Norbornyl Cations Reexamined

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Recently Dewar and Merz[1] have suggested that the NMR results concerning norbornyl cation can be explained by invoking heavy atom tunneling, as was previously suggested by Fong.[2] Aside from the serious question of whether the theoretical method employed by them is able to give anything like an adequate prediction of the tunneling frequency, it is relevant to consider what the observable effects of tunneling would be if it *did* occur. Johnson and Mottley[3,4] studied the solid-state proton spectrum in 1,1-dideuterioethyl iodide, where light atom tunneling must be considered in the rotation of the methyl group. At 127 K they observed broadening in the methyl spectrum, which they ascribed to thermally activated passage over the barrier. At 87 K, the spectrum changed to that expected for a fixed methyl group. However, on further cooling to 4.2 K, a number of additional lines appeared which were interpreted as clearly being due to tunneling. A tunneling frequency of 21 kHz was used to calculate a theoretical spectrum which fit the observed spectrum. The apparent tunneling frequency was found to strongly decrease with increasing temperature! It is a common feature of such systems that free quantum tunneling effects are averaged out as the temperature increases and thermally driven incoherent processes dominate at higher temperature.[5]

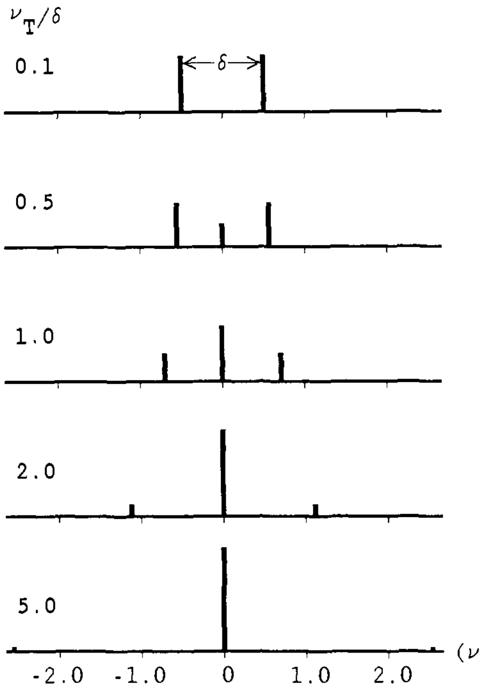

Figure 1. Calculated NMR spectra for a spin $^1/_2$ nucleus in a symmetrical double-well potential for various values of tunneling frequency, ν_T.

An important point[6] is that tunneling alone *does not* lead to the familiar broadening phenomena in the NMR but instead produces shifts and new lines. To produce broadening and coalescence, an incoherent, random process such as thermal passage over a barrier is needed. In contrast, tunneling, a coherent process, leads to splitting of states, which yields shifted and new lines, all sharp. As a model for this process, we consider two spin $^1/_2$ nuclei with chemical shifts separated by δ but no dipole–dipole interactions. The spatial motion is constrained by a symmetrical double potential well such that the tunneling splitting of the ground state is ΔE and the rate at which the spin tunnels to the adjacent well is $\nu_T = 2\Delta E/h$. A simple calculation of the NMR spectrum was performed in the spirit of the previous calculation for CH_2D with basis functions of the form $|i\rangle = G(x - x_j)|\sigma\rangle$ where $G(x \simeq x_j)$ is a sharply peaked spatial function centered at x_j (j = 1, 2), σ represents the spin state α or β, and i = 1–4. The results, details of which are published elsewhere,[7] are illustrated in Figure 1. If norbornyl had a double-minimum surface with tunneling in the appropriate frequency range, such spectra would be expected. If the apparent tunneling frequency decreased at higher temperature, as in the methyl case, and thermal passage over the barrier increased in rate, the side peaks due to tunneling might shift and broaden, and substantial broadening might be expected in the central peak. Since *no* such splitting appeared in the spectrum of norbornyl cation at 4 K observed by Yannoni, Macho, and Myhre,[8] nor was any broadening seen at higher temperatures, it can be concluded that tunneling is not an adequate explanation of these results. The simplest conclusion is that norbornyl has a single-minimum energy surface. Only very high frequency tunneling at all temperatures or an extremely low barrier permitting rapid thermal passage at very low temperature might also be consistent with the spectra. The calculations reported here suggest that NMR might be useful for detecting tunneling effects associated with rearrangements or conformational changes at low temperature; however, intermolecular interactions in solids might well destroy the symmetry of the expected double-well potential curves and thus attenuate the effect. This expected attenuation also makes it less likely that the single line seen in the low-temperature spectrum of norbornyl is due to tunneling.

The isotopic perturbation results[9] also cannot be explained by tunneling. In the first place, the experiments were done at much higher temperatures where the apparent tunneling frequency in the NMR might be expected to be much smaller even if tunneling

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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.

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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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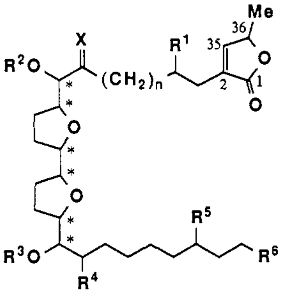
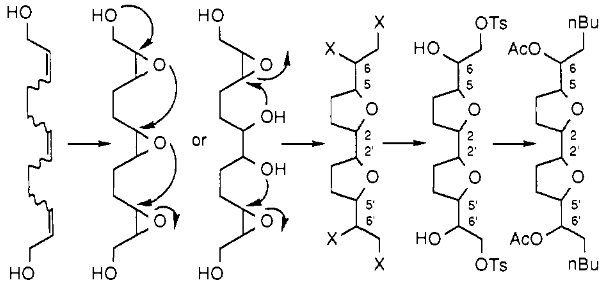
Uvaricin (**1**)[2a] is a member of a growing family of bistetrahydrofuran-containing, polyether natural products that includes desacetyluvaricin (**2**),[2b] rollinicin (**3**),[2c] isorollinicin (**4**),[2c] rollinone (**5**),[2d] asimicin (**6**),[2e] cherimoline (**7**),[2f] and dihydrocherimoline (**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, 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.



	X	R¹	R²	R³	R⁴	R⁵	R⁶	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

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



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

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[1] Fellow of the Alfred P. Sloan Foundation.

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[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.

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