476210). Potassium and ammonium cation activities were determined by a Corning monovalent cation electrode, Model No. 476220. A Corning Ag/AgCl reference electrode (Model 476029) was used with each of the ion-selective electrodes. A water bath, placed on a magnetic stirrer, was maintained at 25 ± 0.2 °C with a Cole Parmer circulator heater (Model 125200). Sample cells were constructed from 50-mL rimless beakers (50-mm height by 41-mm diameter) capped by a Teflon top (50 mm diameter, tapered to fit) drilled with three holes. Two holes were drilled to accommodate the electrodes (each approximately 12 mm), and a third hole approximately 8 mm was drilled to accommodate a digital thermocouple inserted in the sample cell to monitor temperature.

Procedure. New electrodes were conditioned in 1 M salt solutions stepwise to 100% MeOH over a 10-day period, starting with 1 M salt in 90% H_2O-10% MeOH solution. The MeOH was increased by 10% per day while the H_2O was decreased by 10%. The salt concentration was kept constant at 1 M. NaCl was used to condition the Na^+ ISE, and KCl was used for the monovalent ISE. Once at 100% MeOH, the electrodes were thereafter kept in a 4 mM salt solution. Each ion-selective electrode was tested as described in its manual for Nernstian response.

A 2.000 mM stock salt solution (50 mL) and a 5.000 mM (25 mL) stock crown solution were prepared. A 1.000 mM salt reference sample was prepared in a sample cell by pipetting 10 mL of stock salt solution and 10 mL of MeOH. Three crown plus salt samples were prepared as follows: 10 mL of salt + 10 mL of crown, 10 mL of salt + 8 mL of crown + 2 mL of MeOH, and 10 mL of salt + 6 mL of crown + 4 mL of MeOH. The samples were 2.500, 2.000, and 1.500 mM with respect to crown. The potential of the reference sample was measured at 25 °C by taking readings at 5-min intervals until three successive readings differed by 0.2 mV or less. The solution was stirred except while recording a voltage. Potentials of the crown and salt samples were determined in the same manner. At least two trials of all samples were measured.

Calculations. The stability constant for a 1:1 crown–metal complex is defined as

$$K_S = [MCr^+]/[M^+][Cr]$$

assuming activity coefficients of 1. The concentration of free $[M^+]$ was calculated at 25 °C by the Nernst equation as follows:

$$\Delta E = E_{ref}\,(V) - E_{crown}\,(V) \quad (1)$$

$$[M^+]_{free} = e^{-\Delta EnF/RT}[M^+]_{ref}$$

$$[M^+]_{free} = 10^{-\Delta E/0.0591}[M^+]_{ref} \quad (2)$$

The complex concentration is calculated by subtracting $[M^+]_{free}$ from the total salt concentration added to the sample. In the samples described the total salt concentration was 0.001 000 M.

$$[MCr^+] = [M^+]_{total} - [M^+]_{free}$$

$$[MCr^+] = 0.001\,000 - [M^+]_{free} \quad (3)$$

From the total crown concentration and the complex concentration, $[Cr]_{free}$ was calculated. In the samples described the total crown concentrations were 0.002 500, 0.002 000, and 0.001 500 M.

$$[Cr]_{free} = [Cr]_{total} - [MCr^+] \quad (4)$$

The equilibrium constant, K_S, is calculated from the values of $[M^+]_{free}$, $[Cr]_{free}$, and $[MCr^+]$. The log K_S values of all the trials were averaged. If the standard deviation was more than +0.04 log unit, then the experiment was repeated. If the values still had a standard deviation >0.04, the situation is probably complicated by the presence of second-order or higher equilibria. In such a case, the titration method and calculations described by Frensdorff[14] were used.

Discussion

When we first began routinely determining cation binding constants, the experiment was done in a glovebox using a di-*n*-butyl phthalate bath for temperature control. After much study, we found that the results are the same in a water bath open to the atmosphere. If the electrodes give less than a Nernstian slope, it generally means the membrane is clogged. Sodium ion selective electrode membranes can be cleaned with pumice as described in the instruction manual. We have found that both the sodium and monovalent cation electrodes can be cleaned by sonicating them in a 4 mM salt solution for 15 min. The minimum lifetime of properly handled electrodes is 6 months, but our electrodes have usually remained serviceable for periods up to 18 months. Stability constants of 18-crown-6 in MeOH measured in our laboratory[15] using this procedure are log $K_S(Na^+)$ = 4.35 and log $K_S(K^+)$ = 6.08. Literature values obtained calorimetrically[16] and spectrophotometrically[17] are log $K_S(Na^+)$ = 4.36, 4.32 and log $K_S(K^+)$ = 6.06, 6.10, respectively. These values are within experimental error of our values validating the procedure.

Acknowledgment. We warmly thank the National Institutes of Health and W. R. Grace & Co. for support of this work.

Registry No. MeOH, 67-56-1; 18-crown-6-Na^+, 31270-12-9; 18-crown-6-K^+, 31270-13-0.

(15) Gokel, G. W.; Goli, D. M.; Minganti, C.; Echegoyen, L. *J. Am. Chem. Soc.* **1983**, *105*, 6786.
(16) Haymore, B. L.; Lamb, J. D.; Izatt, R. M.; Christensen, J. J. *Inorg. Chem.* **1982**, *21*, 1598.
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Determination of Solvolysis Products from 1-Substituted Tetracyclodecanes by 2D-NMR and Molecular Mechanics

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In a previous paper[1] we reported the kinetic results of the solvolysis of some 1-substituted tetracyclononanes and tetracyclodecanes. This study included the acetolysis of *trans*-(tetracyclo[3.3.2.$0^{2,4}$.$0^{6,8}$]dec-1-yl)methyl tosylate (**1**) and *endo,exo*-(tetracyclo[3.3.1.$0^{2,4}$.$0^{6,8}$]non-1-yl)methyl tosylate (**2**). It was concluded that adding a second cyclopropane ring did not substantially increase the amount of participation by the corner of a cyclopropane ring compared to similar tricyclic systems with only one cyclopropane ring analogously situated,[2,3] as shown by the similarity in solvolytic rates.

During this study an interesting and challenging problem developed in attempting to determine the structure of the solvolysis products of tosylates such as **1** and **2**.

(1) Chenier, P. J.; Christie, D. M., Goettl, V. M. *J. Org. Chem.* **1985**, *50*, 3213.
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(3) Chenier, P. J.; Jenson, T. M.; Wulff, W. D. *J. Org. Chem.* **1982**, *47*, 770.

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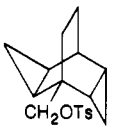

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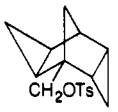


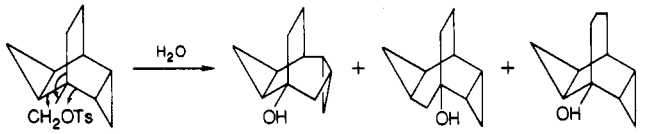
2

Ring expansion and rearrangement to a bridgehead derivative with one additional carbon in the ring system is the common mode by which the solvolysis takes places. When only one cyclopropane ring is present the bridge that expands is usually quite selective, but even then special techniques such as 500-MHz NMR are necessary to determine which of the three possible ring expansions is preferred in the formation of the product.[3] In determining the products in the solvolysis of tosylate **1**, we found that it was necessary to use even more sophisticated methods of analyzing the major product in order to determine its structure. These included two-dimensional proton–proton and proton–carbon correlations and some NOE experiments. The structure was further confirmed by strain energy calculations via molecular mechanics.

Results and Discussion

Analysis of the acetolysis products of tetracyclodecyl tosylate **1** showed a GC distribution of four products as 2.4, 81.6, 9.9, and 6.1%, definitely favoring the formation of one particular product. We were able to crystallize this major product from the mixture with hexane and it was found to be an alcohol rather than an acetate, formed during the relatively mild aqueous workup. However, this hydrolysis does not change the solvolytic conclusions. The acetate to alcohol conversion does not affect the rest of the structure since a bridgehead moiety is involved.

The three possible ring expansions of tosylate **1** would give alcohols **3**, **4**, and **5** via one of two cyclopropano migrations or an ethano movement. The difference in



1 3 4 5

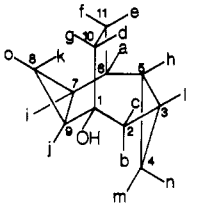
structure between alcohols **3** and **4** is subtle and cannot be differentiated easily. X-ray crystallography could not be done on the major product because acceptable crystals were not obtained. We therefore turned to NMR and molecular mechanics to determine the structure of the main product and found it to be **3** by the following analysis (see Table I for the proton and carbon analysis).

In the ^1H spectrum most of the resonances are well separated at 500 MHz; only i/j and l/m overlap. In the two-dimensional COSY experiment[4] a is found to couple with e, f, h, and i (or j). Similarly, we see that b is coupled to c, g, and l (or m). Other couplings for the remaining protons were found similarly. Particularly obvious in the COSY spectrum is the d, e, f, g cluster of coupled protons from the ethano bridge, ruling out alcohol **5** as a possible structure. Also shown is a coupling of e and f with a and a coupling of g (but not d) to b, the latter caused by the long-range W effect.

Two groups of cyclopropyl protons are easily identified as l, j, k, o and h, l, m, n, all of which couple in their own group but show no coupling between the two groups. i (or j) does show a coupling with a, and h is coupled to a. l (or m) is coupled to b and c.

(4) Bax, A. *Two-Dimensional Nuclear Magnetic Resonance in Liquids*; D. Reidel Publishing Co.: Boston, 1982.

Table I. Chemical Shifts and Coupling Constants for Alcohol 3



3

proton	δ	pattern	coupled protons	carbon	ppm
a	2.45	m	e, f, h, i	2	43.8
b	2.20	ddd	c, g, l	3	5.0
c	2.10	dd	b, l	4	9.1
d	1.82	m	e, f, g, j	5	22.6
e	1.65	tm	a, d, f, g, i	6	27.8
f	1.57	m	a, d, e, g	7	21.3
g	1.42	m	b, d, e, f	8	6.9
b	1.06	tt	a, l, m, n	9	13.6
i, j	not separable			10	33.0
k	0.71	dt	i, j, o	11	23.3
l, m	not separable				
n	0.55	td	h, l, m		
o	0.50	td	i, j, k		

J values: ah = 6, bc = 13.5, bg = 1, bl = 2.5, cl = 9, de = 12, ef = 13, hl = 9, hm = 6, hn = 9, ik = 4.5, io = 8, jk = 4.5, jo = 8, ko = 5.5, ln = 9, mn = 4

A model of structure **4** shows that the endo proton of the methylene group at C-2 should show two large couplings, a geminal coupling as well as a vicinal coupling with a dihedral angle close to 0°, and a smaller coupling to the ethano bridge by the W effect. This is not the case. The exo proton should show a large geminal coupling and a small vicinal coupling with a dihedral angle close to 90°. This is not seen. However, for compound **3** the endo proton b should and does show the large geminal coupling to c, a small vicinal coupling with angle 90° to l, and a long-range small coupling to g. The exo proton c should and does show the large geminal coupling to b and a large vicinal coupling with angle 0° to l. Alcohol **3** therefore is the only structure consistent with the spectra.

A ^{13}C–^1H chemical shift correlation spectrum confirms the assignment of protons, since b and c are shown to occupy the same carbon, as well as d/g, e/f, k/a, and m/n for the other methylene proton pairs. The carbon bearing the hydroxyl does not appear. Table I gives the complete ^{13}C assignments.

The only remaining question is the assignment of individual stereochemistries to the methylenes rather than assigning them as pairs. Classical one-dimensional NOE experiments confirm our assignments. This shows k as being close to f and g. Since o has the same multiplicity as n, both of these must be protons with cis vicinal couplings as well as a geminal coupling. Thus, m and n are differentiated and structure **3** with its assignments is completely proven.

MM2 force field calculations by the method of Allinger[5,6] were employed to predict which of the three structures is most stable and has the lowest energy. Results for alcohols **3**, **4**, and **5** are given in Table II. Alcohol **3** is of lower energy and would be predicted to be the most stable product. This is in accord with structure **3** being the major

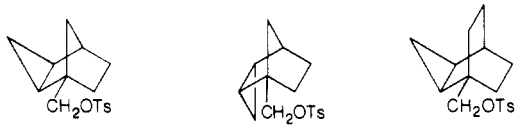
(5) Allinger, N. L. In *Advances in Physical Organic Chemistry*; Gold, V., Bethell, D., Eds.; Academic Press: New York, 1976; Vol. 13, pp 2–82.
(6) Allinger, N. L.; Burkert, J. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

Table II. Calculated Steric Energies of Alcohols

factor	contribution, kcal/mol 3	4	5
compression	5.5554	5.5431	7.7925
bending	35.2898	36.6245	36.1047
stretch-bend	1.3639	1.2974	0.7970
van der Waals			
1,4 energy	8.4177	8.7266	8.1102
other	−1.7654	−0.9883	−0.8238
torsional	26.9803	29.8725	36.3605
dipole	0.1016	0.1055	0.0343
total steric energy	75.9433	81.1813	88.3754

product as analyzed in the NMR interpretation. The main difference lies in torsional strain, which varies nearly 10 kcal/mol as we proceed from alcohol **3** through **5**. Apparently, the methylene at C-2 prefers to be next to an endo cyclopropane ring as in **3** rather than the exo cyclopropane as in **4**. Alcohol **5** is most certainly less stable because both cyclopropanes are attached to the more strained two-carbon bridges, which are also less flexible.

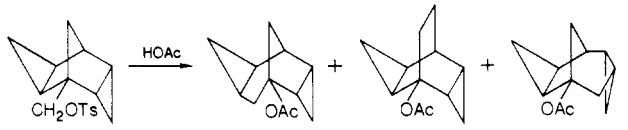
In the tricyclic systems previously studied, it was found that an exo cyclopropane ring as in tosylate **6** prefers to rearrange but an endo ring as in tosylate **7** does not. A rate increase as well as product preference was caused by the stereochemical requirements of corner participation by cyclopropane. The cyclopropane ring also migrated easily when it was fused to the [2.2.2] skeleton, as in tosylate **8**. In tetracyclodecyl tosylate **1**, one of the cyclo-



6 7 8

propano groups still migrates. It makes no difference in terms of corner participation which one is preferred, since they are both on the symmetrical [2.2.2] skeleton. The one which does migrate is determined by product stability and **3** is thermodynamically the more stable.

Tetracyclononyl tosylate **2** was solvolyzed and the products were analyzed by gas chromatography. The

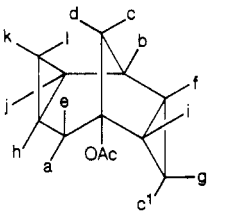


2 9 10 11

three main products were found to be formed in a 41:36:21 proportion.[7] A full identification of these products was not undertaken since little selectivity in the three possible bridge migrations (methano, *exo*-cyclopropano, and *endo*-cyclopropano) was apparent. Mechanistically it would have served little purpose to identify which product was which, since a slight favoritism of one product over the other would not yield any new conclusions about preferred solvolytic pathways in this system.

However, we were able to assign the product occurring to the extent of 36% via a 500-MHz spectrum with decoupling as acetate **9**. Proton assignments are given in Table III. Proton C^1 had to be inferred since its chemical shift is directly under the acetate methyl but it makes its presence known through changes in the spectrum when it is irradiated. MM2 calculations on acetates **9**, **10**, and **11** give total energies of 51.2, 60.0, and 50.3 kcal/mol, respectively. Because of the nearness in energies it is not surprising that a mixture results from this solvolysis, with no major product predominating, although it is understandable that the one assigned product, **9**, formed in the second largest amount, does have a low energy.

Table III. Multiplicity and Coupling Constants for Acetate 9



9

proton	pattern	coupled proton
a	ddd	c, e, h
b	td	c, f, j
c	ddd	a, b, d
d	dd	c, i
e	d	a
f	m	b, g, i
g	td	f, i, C^1
h	gd	a j, k, l
i	m	
j	m	
k	td	h, j, l
l	q	h, j, k
C^1		f, g, i

J values: ac = 2.5, ae = 13, ah = 9, bc = 6, bf = 6, bj = 2.5, cd = 10.5, di = 1.5, fg = 9, gi = 9, gC^1 = 4, hj = 9, hk = 9, hl = 5, jl = 5, kj = 9, kl = 5

We believe that a similar approach involving 2-D NMR together with molecular mechanics calculations will be of value to us in determining the structure of other compounds in this series.

Experimental Section

Melting points are uncorrected and were taken on a Thomas-Hoover apparatus. The following instruments were used: Varian T-60 and Bruker AM-500 NMR spectrometers, Perkin-Elmer 283, 727, and 1420 infrared spectrophotometers, and Varian Aerograph A-90-P and 700 Autoprep gas chromatographs with helium as carrier gas. NMR data are given in parts per million (δ) relative in Me_4Si in $CDCl_3$. Microanalyses were performed by Micro-Tech Laboratories, Skokie, IL. MM2 calculations were done on a VAX 8600 computer.

Tosylate **1** (1.28 g, 4.03 mmol)[8] was studied by dissolution in 170 mL of 0.05 M sodium acetate in glacial acetic containing 0.3% acetic anhydride to give a tosylate concentration of 0.025 M as in the kinetic studies previously reported.[1] The solution was heated at 103 °C for 16 h. Water was added (1 L) and the products were extracted with ether (2 × 200 mL). The combined ether layer was washed with 10% sodium bicarbonate (3 × 300 mL), water (300 mL), and brine (25 mL). The resulting solution was dried with anhydrous magnesium sulfate and filtered. The filtrate was rotary evaporated and the products were partially solidified.

Gas chromatography of a solution showed three main peaks with QF-1 at 150 °C and 192 °C but four main peaks with OV-17 at 155 °C, 180 °C, and 198 °C in a distribution of 2.4, 81.6, 9.9, and 6.1% (in order of increasing t_R). Recrystallization of the solid isomer from hexane, mp 164–168 °C, showed it to be the main product through mixing experiments and identical t_R. The solution left from the recrystallization was also shown to be partially depleted in the main product. IR spectroscopy in chloroform showed both free and hydrogen bonded OH stretching. NMR

(7) We thank V. M. Goettl of the University of Wisconsin—Eau Claire and Prof. W. D. Wulff of the University of Chicago for aiding us in this study.

(8) We thank D. M. Christie of the University of Wisconsin—Eau Claire for this preparation.

data is summarized in Table I. Three additional recrystallizations from hexane gave a pure sample of alcohol **3**, mp 162–164 °C. Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.63; H, 9.71.

Acknowledgment. This research was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the University of Wisconsin—Eau Claire University Research Fund.

Registry No. **1**, 63180-69-8; **2**, 97235-07-9; **3**, 105019-13-4; **4**, 105087-99-8; **5**, 105019-14-5; **9**, 105019-15-6; **10**, 105019-16-7; **11**, 105088-00-4.

A Short Efficient Synthesis of Trichodiene

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The trichothecene mycotoxins such as deoxynivalenol (vomitoxin, **1**) have been identified as harmful contaminants of grain in many parts of the world.[1] From precursor incorporation studies,[2] the hydrocarbon trichodiene, **2**, has been shown to be the first unique intermediate in the biosynthetic pathway leading to the trichothecenes. Since **2** has only been isolated in trace quantities from natural sources,[3] considerable effort has been directed toward the synthesis of this natural product. This interest is due both to the pivotal biosynthetic role occupied by **2** and to the synthetically challenging nature of the two contiguous quaternary centers inherent in the structure of **2** (Figure 1).

Some elegant and igenious total syntheses have been reported for racemic **2**[4] and also for its biogenetically divergent diastereomer bazzanene, **3**.[4b,f,5] To supplement our trichothecene biosynthetic studies,[6] a synthetic route to **2** was desired that would be amenable to isotopic labeling and was also as direct as possible from commercially available starting materials. The approach we devised employs an ester–enolate Claisen rearrangement as the key carbon–carbon bond-forming step enabling simultaneous introduction of the two quaternary centers.

Commercially available[7] methyl ketone **4** can be readily converted to allylic alcohol **5** via the two-step sequence[8]

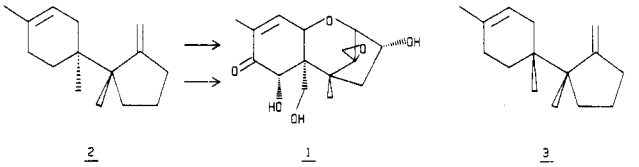


Figure 1. Outline of trichothecene iosynthesis.

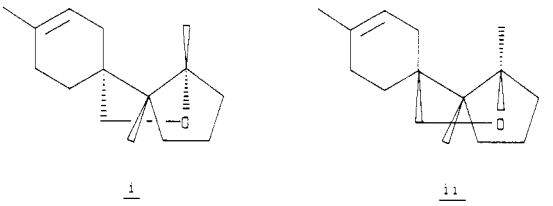
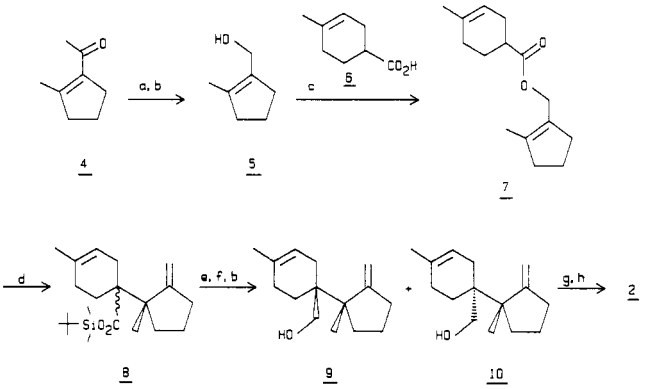


Figure 2. Structures of enol–ether byproducts.

Scheme I. Synthetic Route to Trichodiene[a]



[a] (a) KOCl; (b) $LiAlH_4$; (c) DCC, DMAP; (d) i. LDA, *t*-$BuMe_2SiCl$; ii. reflux; (e) *n*-Bu_4NF; (f) CH_2N_2; (g) PCC; (h) Me_3COK, NH_2NH_2.

shown in Scheme I. Diels–Alder adduct **6**[9] is then esterified with **5** under very mild conditions[10] in the presence of DCC to yield ester **7**. The complete carbon skeleton of trichodiene is then obtained in short order by subjecting ester **7** to the Ireland modification[11] of the Claisen rearrangement, which gives rise to **8** as a 60:40 mixture of diastereomers.

As has been observed[4g] for an analogous highly hindered neopentyl silyl ester, hydride reducing agents simply hydrogenolyzed **8** to the derived acid, necessitating the three-step route to alcohols **9** and **10** shown in Scheme I. By careful silica gel chromatography, diastereomers **9** and **10** could be separated with the desired **10** exhibiting the lower R_f. Alcohol **10** could then be converted to racemic trichodiene by PCC oxidation[12,13] to the aldehyde followed by Wolff–Kishner reduction using the reported conditions.[4f] In a comparison of its specral and chromatographic properties, the synthetic material proved identical in all respects (except optical rotation) with an authentic sample of natural trichodiene.[6b]

This direct synthesis of **2** has been employed to obtain standards of racemic trichodiene useful as carriers in on-

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(3) (a) Machida, Y.; Nozoe, S. *Tetrahedron Lett.* **1972**, 1969. (b) Evan, R.; Hanson, J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 326.

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