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STRUCTURE AND REACTIVITY OF HIGHLY SUBSTITUTED CYCLOBUTYL TOSYLATES*†

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Abstract—The solvolyses, in 80% aqueous ethanol, of *cis*- and *trans*-3-hydroxy-2,2-4,4-tetramethylcyclobutyl tosylates and of *cis*- and *trans*-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylates have been studied. The observed rate differences are explained in terms of steric effects on the transition states for the reactions.

HASEK *et al.* reported the extremely interesting observation that the acid-catalyzed cleavage of *trans*--2,2,4,4-tetramethyl-1,3-cyclobutanediol goes to completion under conditions which do not affect the *cis*-isomer.

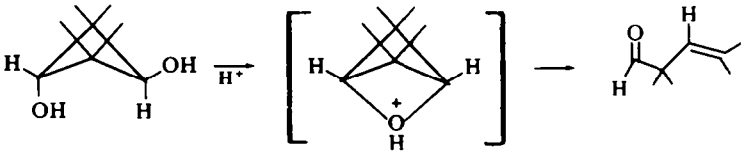

FIG. 1

These workers estimated the rate ratio (K_{trans}/K_{cis}) as approximately 1000 and proposed anchimeric assistance *via* bicyclic oxonium ion (2) for the *trans*-isomer as an explanation for the rate disparity. Similar four-membered oxonium ions have been proposed as intermediates in a number of reactions,[3–5] but no unequivocal evidence for their intermediacy has been found. In fact, solvolysis studies give no evidence for stabilization of a developing carbonium ion by formation of a four-membered cyclic oxonium ion.[6, 7]

These intriguing facts lead us to study the solvolysis of the monotosylates of the aforementioned diols with two objectives in mind. First, by a product study of the two deuterated tosylates (4) we would ascertain whether a symmetrically bridged intermediate (or transition state) such as (2) did, in fact, intervene. If this was the case, then the product aldehyde (3) should have an equal distribution of deuterium at the aldehyde and vinyl positions. Second, we hoped by kinetic studies of the tosylates to obtain an accurate and quantitative measure of the rate ratio—making the reasonable assumption that tosylate reactivity would parallel diol reactivity.

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Additionally, we wanted to measure the secondary deuterium isotope effect on the reaction rate.

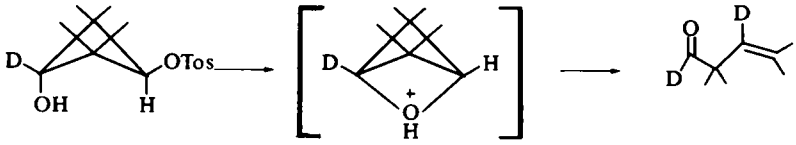


FIG. 2

Meanwhile, Wilcox and Nealy reported the results of their study of the solvolysis of these same compounds in 90% aqueous acetone.[8] They found that the *trans*-monotosylate solvolyzed some 800 times faster than the *cis*- at 75°. Interestingly, they found a comparable rate ratio for the *ditosylates* although somewhat more vigorous conditions were required to effect solvolysis. Further, they found that 2,2,4,4-tetramethylcyclobutyl tosylate solvolyzed *faster* than either of the 3-hydroxy-substituted compounds. These results cast even more doubt on the four-membered oxonium ion proposal, since it seems quite doubtful that a hydroxyl and a tosyl group could render anchimeric assistance with equal facility. Further, the similarity of the rates of solvolysis of *trans*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate and 2,2,4,4-tetramethylcyclobutyl tosylate suggests that the observed rate differences arise as a result of a *retardation* of the *cis*- solvolysis rate rather than from enhancement of the *trans*- solvolysis rate. Wilcox and Nealy suggested[8] that the rate differences arose partly as a result of steric effects on ground state stability and partly from an "inversion" of relative steric effects in a cyclopropylcarbinyl transition state.

The required labelled tosylates were obtained by reduction of 3-keto-2,2,4,4-tetramethylcyclobutyl tosylate. Reduction with lithium aluminium deuteride afforded *cis*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate-3-*d* in 65% yield whereas reductlon with hexadeuteriodiborane afforded a mixture of *cis*- and *trans*- hydroxy tosylate. However, the difference in reactivity between the *cis*- and *trans*-hydroxy tosylates is sufficient to allow complete solvolysis of the *trans*-isomer under conditions which do not affect the *cis*-isomer.

Our study of the solvolysis of the deuterotosylates (4) in 80% aqueous ethanol has yielded the following results: (1) *all* the deuterium in the product olefinic aldehyde was found at the aldehyde position, *none* at the vinyl position (control experiments show as little as 5% of the isomer could have been detected); (2) K_H/K_D for the *cis*-tosylate is 1·11, indicating the reaction is concerted (due to experimental difficulties we did not measure the corresponding rate ratio for the *trans*-isomer). This data, together with that of Wilcox and Nealy[8] prove conclusively that a symmetrical intermediate or transition state such as (2) does not intervene in these reactions. Furthermore, it seems reasonable to extend this conclusion to the acid-catalyzed cleavage of the diols since a similar difference in reactivity is observed.

With these data in hand, the problem was to provide a satisfactory alternative explanation of the facts, i.e. the *trans*-/*cis*-rate ratios of 800–1000. From the available data, it appeared that steric effects were important and that these effects cause a retardation of solvolysis rates for the *cis*-isomers, rather than an enhancement for

the *trans*-isomers which were exhibiting the so-called "normal" rate of solvolysis. We would propose the following hypothesis.

(1) Ring-opening is sterospecific and concerted.

(2) The direction of ring opening is such that the minimum rotation about the C2-C3 bond is required.

(3) The electron demand is at the rear side of the carbon bearing the departing tosyl group and this demand is supplied by the C2-C3 bonding electrons.

These points are illustrated with the *cis*-hydroxy tosylate in Fig. 3. This model enables us to make a number of interesting predictions. Among them is the prediction that substitution of a methyl group for the hydrogen on C3 would cause a dramatic reduction in the *trans/cis* rate ratio. Reference to models shows that for the *cis*-isomer illustrated, a methyl group must rotate toward a hydroxyl group, thus engendering a steric interaction in the transition state. In the *trans*-isomer the analogous interaction is between a hydrogen and a methyl, allowing a faster rate for the *trans*. Considering the case when methyl has been substituted for the C_3 hydrogen, the *cis*-isomer (with respect to the two oxygen functions) will still experience a methyl-hydroxyl interaction, but the *trans*-isomer now will have a methyl–methyl interaction at the transition state. Thus, for the pentamethyl compounds, a dramatic decrease or perhaps even inversion in the *trans*-/cis-rate ratio would be predicted.

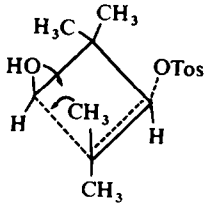
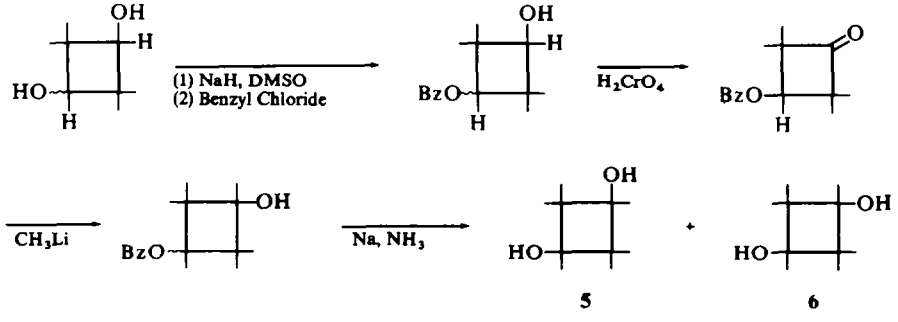


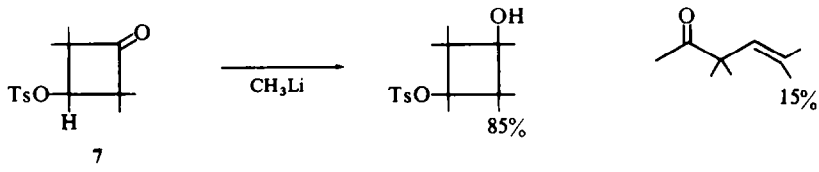
FIG. 3

The required *cis*- and *trans*-pentamethylcyclobutyl tosylates were prepared by the following scheme. The diols were separated by column chromatography and converted to the tosylate esters in the usual manner. An alternate synthesis of the *cis*-monotosylate was found in the treatment of ketotosylate (7) with methyl lithium.



SCHEME 1

The sterochemical assignments for diols (5) and (6) were made on the basis of IR and NMR spectral data. We have assigned the higher melting diol (6) the *trans*-configuration and the lower melting diol (5) the *cis*-configuration. The single ring



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SCHEME 2

proton in the isomeric pentamethylcyclobutane-1,3-diol is expected to appear at lower field in the *trans*-isomer, since in this isomer it is *cis* to the hydroxyl group. Accordingly, the C_3 proton of *trans*-pentamethylcyclobutane-1,3-diol appears at τ 6·29 whereas the C_3 proton of the *cis* isomer appears at τ 6·60. A similar difference is noted in the hydroxy tosylates. That this is indeed the effect of a *cis*-oxygen function is demonstrated by the NMR data for the 2,2,4,-4-tetramethylcyclobutane-1,3-diols and their derivatives of known configuration. These data are summarized in Table 1.

TABLE 1. NMR AND IR SPECTRAL DATA FOR CYCLOBUTYL TOSYLATES AND DIOLS

	Chemical shift* of C_1-H τ	IR (cm^{-1})† in CCl_4
A. Cyclobutyl tosylates:		
cis-3-Hydroxy-2,2,4,4-tetramethyl-	6·05	3625
		3636
trans-3-Hydroxy-2,2,4,4-tetramethyl-	5·88	3630
cis-3-Hydroxy-2,2,3,4,4-pentamethyl-	6·04	3621
		3638
trans-3-Hydroxy-2,2,3,4,4-pentamethyl-	5·73	3620
cis-3-Tosyloxy-2,2,4,4-tetramethyl-	6·10	
trans-3-Tosyloxy-2,2,4,4-tetramethyl-	5·88	
B. Cyclobutane 1,3-diols:		
cis-2,2,4,4-tetramethyl-‡	6·38	
trans-2,2,4,4-tetramethyl-‡	6·17	
cis-2,2,3,4,4-pentamethyl-	6·60	
trans-2,2,3,4,4-pentamethyl-	6·29	

* Internal tetramethylsilane reference in $CDCl_3$.
† Conc. = 0·015M.
‡ Determined using pyridine as solvent.

The IR spectrum in carbon tetrachloride (*ca.* 10^{-2} molar) of the known *cis*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate shows two peaks in the hydroxyl region, suggestive of intramolecular hydrogen bonding, while the *trans*-isomer shows only one. Similarly, the *cis*-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylate shows two peaks while only one is found for the *trans* isomer.

The solvolysis of both the isomeric hydroxypentamethylcyclobutyl tosylates gave

quantitative yields of the expected cleavage product 3,3,5-trimethylhex-4-ene-2-one, which was also prepared from 2,2,4-trimethyl-3-pentenal, the cleavage product of the tetramethylcyclobutane-1,3-diols, by the action of methyl lithium followed by chromic acid oxidation. The results of our solvolysis studies are presented in Tables 2 and 3, along with some pertinent data on the solvolysis of *cis*- and *trans*-2,2,3,4,4-pentamethylcyclobutyl tosylate which Wilcox and Engen have reported in a preliminary communication.[9]

TABLE 2. RELATIVE RATES OF SOLVOLYSIS OF SUBSTITUTED CYCLOBUTYL TOSYLATES IN 80% AQUEOUS ETHANOL AT 50

Cyclobutyl tosylate	Relative rate	10^5 k (sec^{-1})
2,2,4,4-Tetramethyl-	1	69·0*
trans-2,2,3,4,4-Pentamethyl-	5	360·0*
trans-3-Hydroxy-2,2,4,4-tetramethyl-	6×10^{-1}	37·9
trans-3-Hydroxy-2-2,3,4,4-pentamethyl-	5×10^{-2}	3·37†
cis-2,2,3,4,4-Pentamethyl-	4×10^{-2}	2·85*
cis-3-Hydroxy-2,2,3,4,4-pentamethyl-	1×10^{-2}	0·926†
cis-3-Hydroxy-2,2,4,4-tetramethyl-	4×10^{-4}	0·025†

* Extrapolated from 90% acetone rate constants given by Wilcox by multiplying the rate constants by 15, the average of the solvent effects on the 3-hydroxy-2,2,4,4-tetramethylcyclobutyltosylate solvolyses.

† Extrapolated from $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ data.[2]

TABLE 3. DEUTERIUM ISOTOPE EFFECT ON SOLVOLYSIS IN 80% ETHANOL

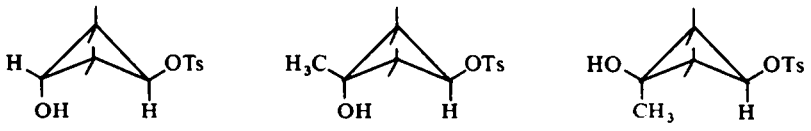
Compound	Temperature	10^5 k (sec^{-1})
cis-3-Hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate	99·90	7·78 ± 0·26
cis-3-Hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate-3-d	99·90	7·00 ± 0·24
$k_H/k_D = 1{\cdot}11 \pm 0{\cdot}05$		

The most striking fact, in examining the data in Table 2, is that the K_{trans}/K_{cis} ratio, which was over 1000 in the case of the 3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylates has been reduced to less than 4 by the substitution of a methyl group for the hydrogen at the 3-position. This result is in good accord with our model, which invokes steric effects on the transition states as the primary determinant of the *trans/cis* rate ratio.

An alternative explanation for the rate ratio observed in the solvolysis of the 3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylates has been advanced by Wiberg.[10] His CNDO calculations for the cyclobutyl cation show that the equatorial cation (8) has a much larger cross ring (1–3) bond index than the axial cation (9). Thus, the *cis*-isomer is said to be greatly reduced in reactivity due to the possibility for the

FIG. 4

equatorial hydroxyl group to exert a destabilizing influence *via* this 1–3 interaction, while the possibility of such interaction in the *trans*-isomer is considerably reduced. A similar explanation has been offered for the reduced rate ratio in the 2,2,3,4,4-pentamethylcyclobutyl tosylate case[9] (i.e. in that case a preferential stabilization of the transition state for the *cis* methyl compound would lead to a reduction in the rate ratio K_{trans}/K_{cis}). The data of the present study are not consistent with this explanation.



10 11 12

FIG. 5

Consider the effect of substituting a methyl group for the hydrogen on tosylate 10 to give tosylate 11. The Wiberg hypothesis predicts that 11 must be more reactive than 10 since an electron donating methyl group is being introduced *cis* to the leaving group. This substitution should also serve to increase the population of the more reactive equatorial tosylate conformational isomer. However, tosylate 10 solvolyzes at least ten times more rapidly than tosylate 11. Furthermore, application of the Wiberg hypothesis to the effect of this methyl substitution on the *trans/cis* rate ratio leads to the conclusion that, if anything, the ratio would be larger for the pentamethyl compounds than for the tetramethyl compounds. As stated previously, the *trans*-tosylate 11 would be expected to solvolyze faster than 10. However, the *cis*-tosylate 12 is subject to a combination of opposing effects. The introduction of a methyl group should lead to an inductive effect which would enhance the rate but this would be offset by a decrease in the population of the more reactive equatorial tosylate conformational isomer. The combined effects predict that tosylate 12 should solvolyze not much faster or even slower than *cis*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate. On this basis it would be expected that the *trans/cis* rate ratio should remain on the order of 10^3 whereas we find this ratio to be near unity.

EXPERIMENTAL

General

All m.ps and b.ps are uncorrected; distillations were carried out, unless otherwise stated, using a 70 cm modified Podbielniak tantalum spiral column. IR spectra were determined in chloroform or carbon tetrachloride solution using a Beckman IR-7 infrared spectrophotometer. PMR spectra were measured at 60 mc in carbon tetrachloride or deuterochloroform, using tetramethylsilane as internal standard with a Varian A-60 spectrometer. GLC was carried out with an Aerograph Model A-90-P gas chromatograph with helium as carrier gas.

cis *and* trans-2,2,4,4-*Tetramethyl*-1,3,3-*cyclobutanediol*

Separated from the commercially available mixture by means of the published procedure. In this way the pure *cis*-diol, mp 162·5–163·5° (lit.[2] m.p. 162·5–163·5°) and the pure *trans*-diol, m.p. 147·0–148·0° (lit.[12] m.p. 147·0–148·0°) were obtained.

3-*Tosyloxy*-2,2,4,4-*tetramethylcyclobutanone.*

A mixture of the *cis*- and *trans*-2,2,4,4-tetramethyl-1, 3-cyclobutanediol monotosylates was prepared by

treating the diol mixture with one equivalent of *p*-toluenesulfonyl chloride at room temperature in pyridine solution. A solution of this mixture of tosylates (124 g, 0·417 mol) in 600 ml of acetone was cooled to 0°. To this solution was added, with vigorous stirring and continued cooling, an oxidizing solution made by adding 154 ml of water to a solution of chromium trioxide (53.4 g. 0·534 mol) in 46 ml of concentrated H_2SO_4. After the addition was complete (approximately 5 min) the stirring was continued an additional 5 min and then the reaction mixture was poured into 2 l. of ice–water. The white precipitate was filtered, rinsed with water and recrystallized from absolute EtOH. The yield was 118 g (95%) of 3-tosyloxy-2,2,4,4-tetramethylcyclobutanone, m.p. 121·5–123·0°. The NMR spectrum (deuterochloroform) showed aromatic protons (A_2B_2 pattern) between τ 2 and 3, CH (singlet) τ 5·58, $ArCH_3$ (singlet) τ 7·53, CCH_3 (singlets) τ 8·83 and 8·87; the IR spectrum showed strong carbonyl absorption at 1782 cm^{-1} and no hydroxyl absorption. (Found: C, 60·57; H, 6·63; O, 21·66; S, 10·84. $C_{15}H_{20}O_4S$ requires: C, 60·78; H, 6·81; O, 21·62; S, 10·82%).

cis-3-*Hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*

A. *From* cis-2,2,4,4-*tetramethyl*-1, 3-*cyclobutanediol.* The *cis*- diol (2 g, 0·014 mol) was dissolved in dry pyridine (10 ml) and a solution of *p*-toluenesulfonyl chloride (2·7 g, 0·014 mol) in 10 ml of dry pyridine was added dropwise at 0° with stirring over a period of 10 min after which the mixture was then allowed to come to room temperature and stirring was continued an additional 1·5 hr. At the end of this time, the reaction mixture was poured into ice water and the precipitate was filtered. The product was rinsed with several portions of 5% H_3PO_4 and recrystallized from benzene–hexane to give 2·1 g (48%) of the *mono-p*-toluenesulfonate, m.p. 109·0–110° (lit.[3] 111·0–112·0°). The IR spectrum of a 0·015M solution in carbon tetrachloride showed peaks at 3625 and 3637 m^{-1}.

B. *By LAH reduction of* 3-*tosyloxy*-2,2,4,4-*tetramethylcyclobutanone.* The ketone (1·9 g, 0·0065 mol) was dissolved in 12 ml of THF (freshly distilled from LAH) and the solution was added dropwise over a period of 25 min to slurry of LAH (0·29 g, 0·0034 mol) in 10 ml anhydrous THF with cooling (ice bath) and stirring. When the addition was complete, the cooling was discontinued and stirring was continued 1 hr at room temperature. Ice water was then added cautiously with cooling and stirring. The mixture was then acidified with 12 ml of 3N HCl and poured into ice water. The water solution was then concentrated in *vacuo* and the resulting white precipitate filtered, dried, and recrystallized from benzene–hexane. The yield was 1·5 g (75%) of the *cis*-monotosylate m.p. 109–110°.

C. *By sodium borohydride reduction of* 3-*tosyloxy*-2,2,4,4-*tetramethylcyclobutanone.* The ketone (1·9 g, 0·0065 mole) was slurred with 60 ml of absolute EtOH. This slurry was added dropwise with stirring at room temperature to a slurry of $NaBH_4$ (0·883 g, 0·0022 mole) in 25 ml absolute EtOH. After 30 min the mixture became homogeneous. Stirring was continued for 1 hr and then the reaction mixture was poured into 200 ml of ice water. The precipitate was filtered and the water solution extracted with several portions of ether. The ether extract was dried over anhydrous $MgSO_4$ and evaporated to yield additional product. The combined product was recrystallized from benzene–hexane to yield 0·7 g (35%) of the *cis*-monotosylate, m.p. 109–110°.

trans-3-*Hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*

A. *From* trans-2,2,4,4-*tetramethyl*-1, 3-*cyclobutanediol.* The *trans*-diol (8·34 g, 0·028 mol) was treated with *p*-toluenesulfonyl chloride in pyridine as described for the *cis*- diol. The yield of *trans*-monotosylate was 5·5 g (65%), m.p. 97·5–98·5° (lit.[8] m.p. 96·0–96·8°). The IR spectrum of a 0·015M solution in carbon tetrachloride showed a peak at 3630 cm^{-1}.

B. *By diborane reduction of* 3-*tosyloxy*-2,2,4,4-*tetramethylcyclobutanone.* The ketone (1·0 g, 0·0034 mol) was dissolved in anhydrous THF (40 ml). Diborane was generated under dry nitrogen by the addition of LAH (0·57 g, 0·015 mol) in 15 ml anhydrous ether to a solution of freshly distilled boron trifluoride etherate (2·13 g, 0·015 mole) in 15 ml of anhydrous ether.[13] The evolved diborane was bubbled through a gas dispersion tube into the ketone solution with a stream of dry nitrogen. The reaction mixture was cooled with an ice bath throughout the reaction. After the hydride addition was complete, the nitrogen flow was continued an additional 30 min. The reaction mixture was then poured into ice water and extracted with several portions of ether. The combined ether extracts were dried over anhydrous Na_2SO_4 and evaporated to yield 0·90 g (90%) of a mixture of *cis*- and *trans*-monotosylates, which were not separated. The mixture was approximately 40% *trans*-3-hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate (estimated by comparison

of the integrals of the peaks appearing at τ 5·88 (*trans*-CTosH) and τ 6·10 (*cis*-CTosH) in the NMR spectrum of the mixture).

cis-3-*Hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*-3-d

3-Tosyloxy-2,2,4,4-tetramethylcyclobutanone was reduced as previously described using LAD instead of LAH. The product thus obtained was recrystallized from benzene–hexane to give the pure labelled monotosylate (65% yield)m.p. 109–110°. The tosylate was greater than 98% deuterated at the 3-position as judged from its NMR spectrum.

trans-3-*Hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*-3-d

3-Tosyloxy-2,2,4,4-tetramethylcyclobutanone was reduced as previously described using LAD to generate hexadeuterodiborane. This yielded a mixture of *cis*- and *trans*-3-hydroxy tosylates which were not separated.

3-*Benzyloxy*-2,2,4,4-*tetramethylcyclobutanol*

A 1:1 mixture of *cis*- and *trans*-2,2,4,4-tetramethyl-1,3-cyclobutanediol (100 g, 0·7 mol) was dissolved in anhydrous dimethyl sulfoxide (200 ml) and added dropwise with stirring at room temperature to a suspension of sodium hydride (36 g, 1·5 mol, separated from a 50% mineral oil dispersion by the method of Corey)[14] in 250 ml of anhydrous dimethyl sulfoxide, under nitrogen. Addition of the diol solution was complete in 4 hr. Stirring was continued an addition hour, then benzyl chloride (95 g, 0·75 mol) dissolved in anhydrous dimethyl sulfoxide (150 ml) was added dropwise with stirring during 3 hr period. Stirring was continued an additional 6·5 hr, then 50 ml of water was added dropwise. The reaction mixture was then poured into 3 l. of water and extracted with several portions of ether (total 500 ml). The combined ether layers were dried over anhydrous sodium sulfate and evaporated to give 141 g of crude product as a yellow oil. On standing, 7 g of stilbene precipitated. The NMR spectrum of the crude product showed that it contained dibenzyl ethers in addition to the desired monobenzyl ethers.

3-*Benzyloxy*-2,2,4,4-*tetramethylcyclobutanone*

The crude reaction product (134 g) from the preparation of the monobenzyl ethers of the tetramethylcyclobutanediols was dissolved in 550 ml of acetone and a solution of chromium trioxide (64·4 g, 0·644 mol), 58 ml concentrated H_2SO_4 and 192 ml of water was added dropwise with stirring over a 2·5 hr period. The reaction mixture was cooled with an ice bath during the addition. After stirring an additional 17 hr at room temperature, the reaction mixture was poured into 3 l. of water and extracted with ether. The combined ether layers were dried and evaporated to give 97 g of yellow oil which was distilled to give pure 3-benzyloxy-2,2,4,4-tetramethylcyclobutanone b.p. 92·5–95·5° (0·25 mm). The yield was 32·2 g (20% based on starting diol). The NMR spectrum (carbon tetrachloride) showed aromatic protons τ 2·72 (singlet), benzylic protons τ 5·50 (singlet), CH τ 6·42 (singlet), CCH_3 (singlets) τ 8·83 and 8·87; the IR spectrum showed strong carbonyl absorption at 1781 cm^{-1} and no hydroxyl absorption. (Found: C, 77·32; H, 8·31. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%).

3-*Benzyloxy*-1,2,2,4,4-*pentamethylcyclobutanol*

To a solution of 3-benzyloxy-2,2,4,4-tetramethylcyclobutanone (12·5 g, 0·054 mol) in 200 ml of ether was added with stirring 67 ml of an ether solution of methyl lithium (1·67 M) at room temperature. When addition was complete, the solution was stirred an additional 25 min. Ammonium chloride (10 g, 0·19 mol) in water (75 ml) was then cautiously added. The ether layer was separated and the water layer extracted with several portions of ether. The combined ether layers were dried over anhydrous Na_2SO_4 and evaporated to give a mixture of *cis*- and *trans*-3-benzyloxy-1,2,2,4,4-pentamethylcyclobutanol, 12·8 g (96%). The composition of the mixture was estimated by comparison of the integrals of the peaks appearing in the NMR spectrum (carbon tetrachloride solution) at τ 6·77 (*trans*-HCOBz) and τ 6·98 (*cis*-HCOBz). The mixture was approximately 25% *trans*-isomer.

2,2,3,4,4-*Pentamethyl*-1,3-*cyclobutanediol*

The mixture of 3-benzyloxy-1,2,2,4,4-pentamethylcyclobutanol isomers (12·8 g, 0·052 mol) was dissolved in anhydrous ether (300 ml) and added to 500 ml freshly distilled liquid ammonia. Sodium (6 g, 0·26 g atom) was then added rapidly with stirring and the reaction mixture was allowed to reflux for 5 hr. Solid

NH_4Cl (13 g. 0·24 mol) was then added and the ammonia was allowed to evaporate. Water (150 ml) was added to the reaction mixture, the ether layer was separated and the water layer extracted with several portions of ether (total 150 ml). The combined ether solution was dried and evaporated to give 8 g (94%) of crystalline diol mixture, which was estimated (by comparison of the integrals of the peaks at τ 6·29 (*trans*-CH) and τ 6·60 (*cis*-CH) in the NMR spectrum (deuterochloroform) of the mixture to be approximately 25% *trans*-2,2,3,4,4-pentamethyl-1,3-cyclobutanediol.

This mixture was chromatographed on a column (52 × 5 cm) of Alcoa F-20 alumina (500 g). Elution was begun with benzene with 25 ml fractions being collected. Fractions 1–163 (benzene eluent) contained neither of the diols; likewise, fractions 164–303 (1% ethyl acetate–benzene eluent) contained neither diol. Fractions 304–353 (5% ethyl acetate–benzene eluent) yielded 800 mg of pure *trans*-2,2,3,4,4-pentamethyl-1,3-cyclobutanediol, m.p. 118–119·5° (after sublimation). The NMR spectrum (deuterochloroform) showed peaks at τ 6·26 CH (singlet), τ 8·30 OH (broad), τ 8·88 COHMe (singlet, τ 8·92 and 8·97 CCH_3 (singlets). (Found: C, 68·23; H, 11·45. $C_9H_{18}O_2$ requires: C, 68·31, H, 11·47%).

Fractions 354–395 (5% ethyl acetate–benzene eluent) gave 1·8 g of a mixture of *cis*- and *trans*-diols. Fractions 396–on (ethyl acetate eluent) gave 5·1 g of *cis*-2,2,3,4,4-pentamethyl-1,3-cyclobutanediol, m.p. 98–99° (after sublimation). The NMR spectrum (deuterochloroform) showed peaks at τ 6·60 CH (singlet), τ 8·30 OH (broad), τ 8·85 $COHCH_3$ (singlet), τ 8·92 and 8·97 CCH_3 (singlets). (Found: C, 68·21; H, 11·48. $C_9H_{18}O_2$ requires: C, 68·31; H, 11·47.)

trans-3-*Hydroxy*-2,2,3,4,4-*pentamethylcyclobutyl tosylate*

A solution of *trans*-2,2,3,4,4-pentamethyl-1,3-cyclobutanediol (400 mg, 0·0025 mol) and *p*-toluenesulfonyl chloride (580 mg, 0·0025 mol) in 1·5 ml of anhydrous pyridine was stirred at room temperature for 13 hr. The reaction mixture was then poured into water and the water was extracted with ether. The combined ether layers were washed with several portions of 5% H_3PO_4, dried and evaporated. The resulting crystalline product was recrystallized from chf-hexane to give the pure *trans*-tosylate, 728 mg (91%), m.p. 115–116°. The NMR spectrum (deuterochloroform) showed, in addition to the expected aromatic, aromatic methyl, and hydroxyl peaks, peaks at τ 5·73 CH (singlet), τ 8·90 $COHCH_3$ (singlet), τ 8·97 and 9·07 CCH_3 (singlets); the IR spectrum of a 0·015M solution in carbon tetrachloride showed a hydroxyl peak at 3620 cm^{-1}. (Found: C, 61·09; H, 7·43. $C_{16}H_{24}O_4S$ requires: C, 61·51; H, 7·74%).

cis-3-*Hydroxy*-2,2,3,4,4-*pentamethylcyclobutyl tosylate*

A. *From* cis-2,2,3,4,4-*pentamethyl*-1,3-*cyclobutanediol.* The *cis*-diol (2·0 g, 0·0128 mol) was treated with *p*-toluenesulfonyl chloride in pyridine as described for the *trans*-isomer to give the *mono* tosylate, 3·0 g (77%), m.p. 122·5–123·0° after crystallization from chf–hexane. The NMR spectrum (deuterochloroform) showed, in addition to the expected aromatic, aromatic methyl, and hydroxyl peaks, peaks at τ 6·04 CH (singlet), τ 8·90 $COHCH_3$ and CCH_3 (broad singlet), and τ 9·12 CCH_3 (singlet); the IR spectrum of a 0·015M solution in carbon tetrachloride showed peaks at 3621 and 3638 cm^{-1}. (Found: C, 61·01; H, 7·65. $C_{16}H_{24}O_4S$ requires: C, 61·51; H, 7·74%).

B. *From* 3-*tosyloxy*-2,2,4,4-*tetramethylcyclobutanone.* A solution of the ketone (7·0 g, 0·0236 mole) in anhydrous ether (500 ml) was cooled to −60° (acetone–dry ice bath and 100 ml of an ether solution of methyl lithium (1·62M) was added with stirring. After addition was complete, the solution was kept at −60° to −50° and stirred an additional 30 min. An excess of saturated ammonium chloride solution was then added. The ether layer was separated and the water layer extracted with ether. The combined ether layers were dried and evaporated to yield 6·9 g of crude products. NMR and IR spectra indicated this was a mixture of *cis*-3-hydroxy-2,2,3,4,4-pentamethylcyclobutyl tosylate (*ca.* 85%) and 3,3,5-trimethylhex-4-ene-2-one (*ca.* 15%). The pure *cis*- tosylate could be isolated from this mixture by recrystallization from hexane–chf.

2,2,4-*Trimethyl*-3-*pentenal*

Synthesized by the method previously described.[2] The product had b.p. 51–53° (20 mm), n_D^{20} 1·4341 [lit.[2] b.p. 81–83·5° (100 mm), n_D^{20} 1·4357–1·4361]. The 2,4-dinitrophenylhydrazone was prepared in the usual way and had m.p. 142–143° (lit.[2] m.p. 142–143°).

3,3,5-*Trimethylhex*-4-*ene*-2-*ol*

To solution of 2,2,4-trimethyl-3-pentenal (15 g, 0·119 mol) in anhydrous ether (200 ml) was added 125 ml

of an ether solution of methyl lithium (1·62M) dropwise with stirring at room temperature. After the addition was complete, the stirring was continued an additional 10 min, then an excess of saturated NH_4Cl solution was added. The ether layer was separated and the water layer extracted with an additional portion of ether. The combined ether layers were dried over anhydrous Na_2SO_4 and the ether was evaporated. The product alcohol was distilled to yield 3.3.5-trimethylhex-4-ene-2-ol, 13·7 g (81%), b.p. 79–80° (15 mm), n_D^{20} 1·4565. A portion of a middle fraction was taken for analysis. (Found: C, 75·89; H, 12·25. $C_9H_{18}O$ requires: C, 76·00; H, 12·76%).

3,3,5-*Trimethylhex-4-ene-2-one*

A solution of chromium trioxide (4·6 g, 0·046 mol) in 1 ml of concentrated sulfuric acid and 13 ml of water was added dropwise with stirring to a solution of 3,3,5-trimethylhex-4-ene-2-ol (5·0 g, 0·035 mol) in 57 ml of acetone. The reaction mixture was stirred an additional 15 min, and then poured into 250 ml of water. The water was extracted with several portions of ether. The combined ether layers were dried and the ether evaporated. The residual oil was distilled to give a fraction b.p. 61–63° (15 mm), n_D^{20} 1·4380 which was the pure ketone 2·41 g (54%). A higher boiling fraction, b.p. 63–83° (15 mm) contained a mixture of starting material and product ketone (total 0·60 g). The IR spectrum of the ketone showed a strong carbonyl peak at 1700 cm^{-1}. (Found: C, 77·40; H, 11·63. $C_9H_{16}O$ requires: C, 77·09; H, 11·50.)

The 2,4-dinitrophenylhydrazone, m.p. 113–114°, was made in the usual way and crystallized from EtOH. (Found: C, 56·28; H, 6·47; N, 17·24. $C_{15}H_{20}O_4N_4$ requires: C, 56·24; H, 6·29; N, 17·49%).

Kinetic measurements

Commercial Solvents Corp., "Gold Shield" absolute EtOH was used without further purification to prepare 80% aqueous EtOH (v/v/25°). Rate measurements were performed by the sealed ampoule technique. Aliquots of approximately 0·03M solutions of the esters were sealed in ampoules, placed in a constant temperature bath and withdrawn and quenched in ice water at intervals. Water (50–60 ml) was added to the samples and they were titrated to a phenolphthalein end-point with standard $Ba(OH)_2$ solution. All reactions were followed to at least three half-lives. Infinity points were taken at ten or more half-lives. In the cases where the deuterium isotope effect was measured, the reactions of the deuterated and non-deuterated esters were run simultaneously in the same constant temperature bath. The thermometers used were calibrated against a platinum resistance thermometer. Rate constants and activation parameters were calculated by the least squares method using the University of Oregon computer program Rate VI and an IBM 1620 computer.

Product of the solvolysis of trans-3-*hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*

trans-3-Hydroxy-2,2,4,4-tetramethylcyclobutyl tosylate (0·743 g, 0·0025 mol) was added to 20 ml of 80% EtOH and the mixture refluxed for 35 min. The solution was then cooled, 25 ml of water added and extracted with three portions of ether (total 60 ml). The combined ether layers were washed with 5% Na_2CO_3 solution, dried and evaporated to give the crude products 0·31 g (100%). The aldehyde was converted to its 2,4-dinitrophenylhydrazone, 0·6 g (85%), m.p. 142–143°.

Product of the solvolysis of cis-3-*hydroxy* 2,2,4,4-*tetramethylcyclobutyl tosylate*

The ester (0·253 g, 0·008 mole) was added to 10 ml of 80% aq EtOH in a combustion tube. The tube was then sealed and placed in a steam bath for 42 hr. At the end of this time, the tube was cooled, opened and the reaction mixture poured into 10 ml of ice water. An excess of 2,4-dinitrophenylhydrazine reagent was added. The precipitated 2,2,4-trimethyl-3-pentenal 2,4-dinitrophenylhydrazone was filtered, dried and weighed. The yield was 93·4 mg (45%), m.p. 142–143°. Gas–liquid chromatography of the crude product on a 5 ft × ¼ in. column of 20% carbowax/60–80-firebrick at 110° showed that, in addition to the aldehyde, there was another unidentified component in approximately the same quantity.

Determination of the position of deuterium in the solvolysis product of cis-3-*hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*-3-d

A sample of the deuterated ester was placed in a tube with 80% EtOH and allowed to solvolyze at 100° for 24 hr. At the end of this time, the reaction mixture was worked up in the normal manner. The product aldehyde was taken up in carbon tetrachloride and the NMR spectrum was measured. No aldehyde proton (τ 0·64) was visible. The spectrum was in all other respects identical with that of an authentic

sample. The vinyl proton (τ 4·92, septet) integrated correctly for one proton. The aldehyde was then converted to the 2,4-dinitrophenylhydrazone in the usual manner. The NMR spectrum of the dinitrophenylhydrazone was determined in deuterochloroform. No aldimine proton peak (τ 2·43) was visible. The spectrum was in all other respects identical with that of an authentic sample. The vinyl proton (τ 4·75. septet) integrated correctly for one proton.

Position of deuterium in the solvolysis product of trans-3-*hydroxy*-2,2,4,4-*tetramethylcyclobutyl tosylate*-3-d

A sample of a mixture of the *cis*- and *trans*- esters (*ca.* 40% *trans*-) was placed in a tube with 80% EtOH and allowed to solvolyze at 100° for 7 min. The reaction mixture was then poured into ice water, filtered (to remove unreacted *cis*- tosylate, 62% recovery) and treated with 2,4-dinitrophenylhydrazine reagent. The NMR spectrum of the dinitrophenylhydrazone thus produced was measured. No aldimine proton peak was observed. The vinyl proton peak integrated correctly for one proton.

Sensitivity of the deuterium analysis

A mixture of deuterium labelled, 2,2,4-trimethyl-3-pentenal 2,4-dinitrophenylhydrazone and unlabelled dinitrophenylhydrazone was prepared. The mixture contained 5% of the unlabelled material. The aldimine proton peak (τ 2·43) was easily observable.

Product of the solvolysis of cis-3-*hydroxy*-2,2,3,4,4-*pentamethylcyclobutyl tosylate*

A sample of the ester (101 mg, 0·33 m-mol) was placed in a tube with 5 ml of 80% EtOH. The tube was sealed and heated in an oil bath at 100° for 2 hr. At the end of this time the tube was opened and the sample neutralized with sodium hydroxide solution. *p*-Cymene (39·2 mg, 0·292 m-mol) was then added and the mixture was analyzed by GLC at 95° on a 5% Dow 710/60–80 firebrick column (5 ft × ¼ in.). The ratio of 3,3,5-trimethylhex-4-ene-2-one/*p*-cymene was found to be 1·11 (100% yield). The relative thermal response of the ketone and *p*-cymene was found to be 1·0 by analysis of known mixtures.

Product of the solvolysis of trans-3-*hydroxy*-2,2,3,4,4-*pentamethylcyclobutyl tosylate*

The solvolysis reaction mixture of a sample of the *trans*-ester in 80% EtOH was analyzed as described for the *cis*- isomer. The yield of 3,3,5-trimethylhex-4-ene-2-one was quantitative.

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