Stereochemical Course of the Allylic Hydroxylation : Reaction of 1-*tert*-Butyl-4-alkylidenecyclohexanes with Selenium Dioxide

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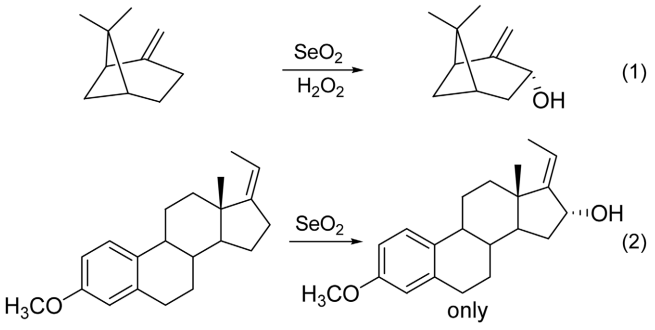
Selenium dioxide-mediated oxidation of substituted olefins is regarded as one of the most reliable and predictable methods for introducing a hydroxy group into the allylic position.[1] The reaction reveals a very useful regio- and stereo-selectivity when applied to trisubstituted olefins, producing (E)-allylic alcohol predominantly.[2] Many aspects concerning selectivity of this reaction has been summarized with pertinent examples in a review.[1c] The mechanism of this highly selective process had been a subject of interest for many years until Sharpless[3] proposed a mechanism, a generally accepted, consisting of two consecutive pericyclic reactions (an electrophilic ene reaction followed by the 2,3-sigmatropic rearrangement) (Scheme 1).

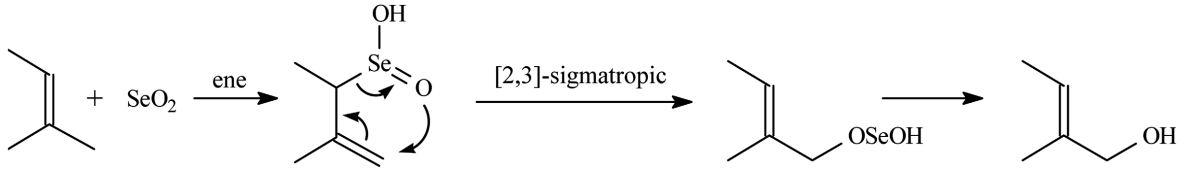
A recent mechanistic study[4] on the selenium dioxide-mediated allylic oxidation of the acyclic olefin, 2-methyl-2-butene clarified the stereochemical aspect of the ene step in this reaction successfully. Later, the overall profile of the allylic oxidation of 2-methyl-2-butene has been explained based on *ab initio* studies by us.[5] Synthetically very useful aspect in this conversion of the nonactivated C=C double bond into the allylic alcohol intermediate lies in its high stereoselectivity as demonstrated in the synthesis of *trans*-pinocarveol and a steroid compound.[6,7]

Although this reaction has been proved very useful for producing an allylic alcohol from an olefinic moiety in various cyclic systems,[8] the systematic account on the stereochemical course for cyclic systems has been scarce. The above cyclic systems, due to their stereochemical features already crafted as highly biased, might be prone to produce a high stereoselectivity and still remain as specific cases. We were interested in understanding detailed features of the stereochemical control in the allylic oxidation for more general cyclic systems. Thus, we have performed stereochemical studies on selenium dioxide-mediated oxidation of 1-*tert*-butyl-4-alkylidene cyclohexanes **3** whose structural elements would be built in such a way that the selenium reagent may respond aptly. Accordingly, the selenium reagent would arrange the hydrogen of three positions (a-c) to the corresponding hydroxyl functional group (**4**-**6**) (Scheme 2).

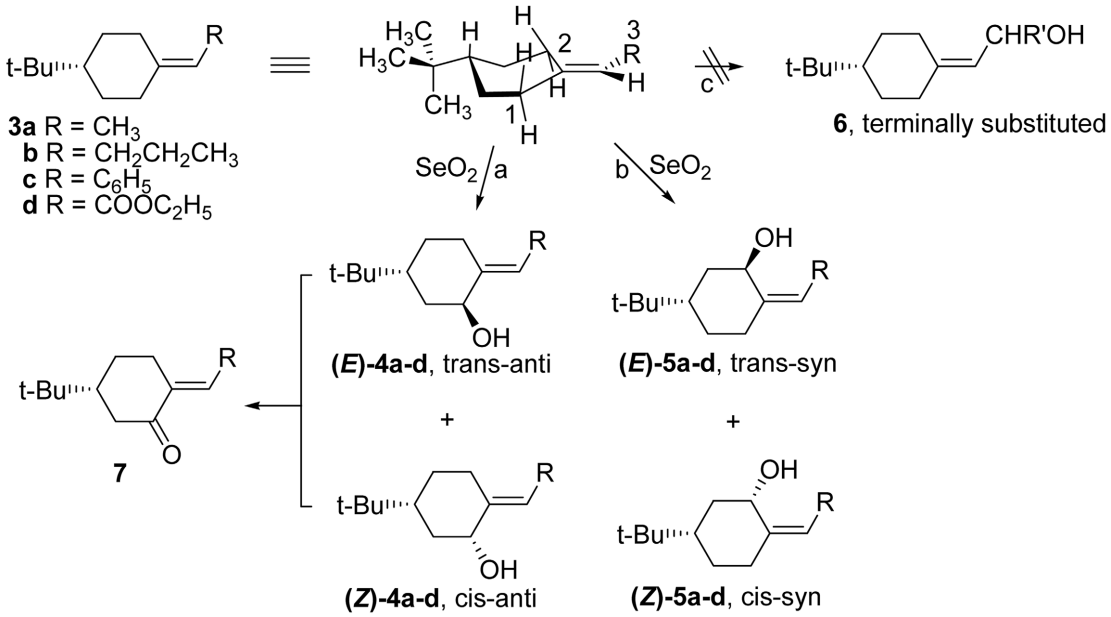
Parallel *ab-initio* calculation studies for transition states of two major steps (an ene step and a [2,3]-sigmatropic rearrangement) were made to analyze the stereochemical course of this reaction using HF/3-21G* method. Calculation results were compared with the experimental observations and the overall stereochemical course of the whole transformation could be described on the basis of the comparative analysis of two data.

4-*tert*-Butylalkylidenecyclohexanes **3** were prepared from 4-*tert*-butylcyclohexanone by known procedure.[9a-d] Allylic oxidation was carried out by reacting **3a**-**e** with 1 equivalent of selenium dioxide in ethanol for 15 h at room temperature. Reaction products were purified by flash column chromatography on silica gel. Allylic alcohols were isolated as a mixture of diastereomeric isomers. The ratios of diastereomeric isomers were determined by analyzing areas of distinct





Scheme 1



Scheme 2. Possible isomers (**4**-**6**) from the allyic oxidation of 4-*tert*-butylethylidene cyclohexane. Description '*trans*' and '*cis*' is used when the substituting hydroxy function points above and below the ring respectively, where the 4-*tert*-butyl group adopts the equatorial position. 'Anti' and 'syn' are used to describe the side of the hydrogen in locating toward and against the substituent of the alkylidene moiety respectively.

protons adjacent to hydroxy group and vinylic protons in ^{1}H NMR. The reaction was selective in several ways: strong preference of anti-products over the face of the alkylidene moiety, *i.e.*, anti-products **4** were favored (88-94%) over syn-products **5** (6-12%) and the trans attack away from the tertiary butyl group was favored, *i.e.*, ratios of (***E***)-**4** : (***Z***)-**4** ranges from 2-4 : 1. Products from the syn-cis route, (***Z***)-**5**, and terminally substituted products, **6** were not observed (Table 1 and Scheme 2). (***E***)-Configuration of allylic alcohols **4** could be confirmed by analyzing the single product **7** obtained from the reaction in the presence of excess amount of selenium dioxide. Chemical shifts at typically downfield region around 6.5 ppm indicate vinylic protons belong to (***E***)-isomers.[10] Reduction *via* an axial attack of isolated enone product, **7a** with sodium borohydride expectedly gave a single product as expected, (***Z***)-**4a** whose NMR spectra exactly matched with that of the allylic alcohol obtained from the SeO_2 oxidation. Spectral assignment of diastereomers was made on the basis of discussions for alkylidenecyclohexanols.[11] The protons adjacent to the hydroxy groups in (***E***)-**4** and (***E***)-**5** nearly axial to allylic systems are noted for smaller vicinal coupling constants (*ca.* 2.8 Hz), while the protons of (***Z***)-**4** show larger coupling constants (*ca.* 11 Hz). Table 1 summarizes the yields and isomeric ratios of the reaction.

Table 1. Allylic hydroxylation by selenium dioxide of 4-*tert*-butylalkylidene cyclohexanes **3**

compd	substituents, R	isomer ratio, % (***E***)-**4** : (***Z***)-**4** : (***E***)-**5**	yield, %
3a	CH_3	75 : 17 : 8	48 (**4a** + **5a**), 12 (**7a**)
3b	CH_2CH_3	72 : 19 : 9	50 (**4b** + **5b**), 18 (**7b**)
3c	$CH_2CH_2CH_2CH_3$	64 : 24 : 12	46 (**4c** + **5c**), 15 (**7c**)
3d	Ph	65 : 29 : 6	34 (**4d** + **5d**), 18 (**7d**)

There are several stereochemical issues to be considered in the allylic hydroxylation (Figure 1): (i) the regioselectivity in substitution (internal *vs* terminal position), (ii) the orientation of the other Se=O function (which will not participate in the ene reaction) toward the olefinic function, (iii) two kinds of stereo-selectivity in the attack of selenium reagent (*trans* / *cis* and *anti* / *syn*), and (iv) stereochemical sequences for [2,3]-sigmatropic rearrangement of the ene products.

Terminal approach (**c**) of selenium oxide on the olefin function (Scheme 2) would be energetically very unfavorable because the selenic acid moiety should locate near the cyclic rim in the intermediate formed after the ene step in the reaction **3a** (R = CH_3).[12a] Now favorable approaches are two internal ones (**a** and **b**, Scheme 2) and the following rearrangement may have two possibilities for each ene intermediate, yielding totally four possible modes of addition (**A**-**D**); *trans-anti* addition (**A**), *trans-syn* addition (**B**), *cis-anti* addition (**C**), and *cis-syn* addition (**D**) (Figure 1). Stereochemical details could be clarified by theoretical calculations on transition states for compound **3a** (Table 2). Table shows transition state energies of three favorable approaches (**A**-**C**) for the ene step in order (**A**) > (**B**) >> (**C**).[12b] The most favorable compound, (***E***)-**4a** is produced *via* (**A**) approach in the ene step and *in-situ* [2,3]-rearrangement prior to rotation of allylselenic acid moiety of the ene intermediate. A minor compound, (***Z***)-**4a** turned out to originate from the ene reaction *via* a *trans-syn* attack (**B**) of selenium dioxide followed by rotation of initially formed allylselenic acid

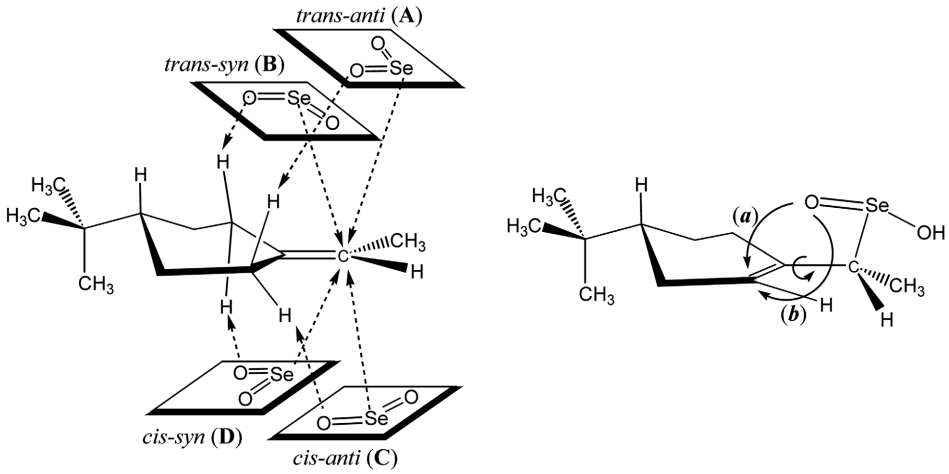
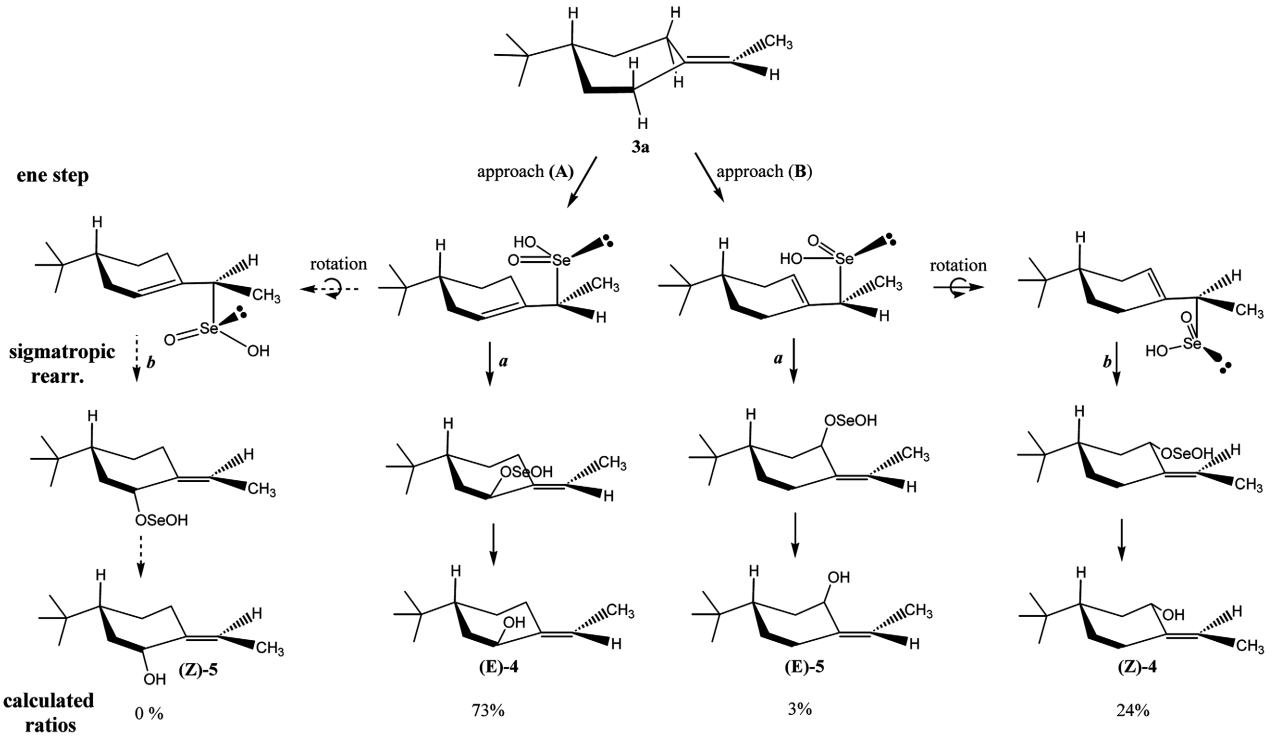


Figure 1. Four possible topologies (**A-D**) for 'ene' reaction and two pathways (**a**, **b**) for [2,3]-sigmatropic rearrangement of the ene product formed through '*trans-anti*' mode.

Table 2. Energies of **TS1**s and **TS2**s for the allylic hydroxylation of compound **3a** and predicted ratios of isomeric allylic products at HF/3-21G*

TS1 for ene reaction			**TS2** for 2,3-rearrangement			Predicted ratios	product
	E_{total} [a]	E_{rel} [b]		E_{total} [a]	E_{rel} [b]		
A	−3002.120162	0.00	**a**	−3002.135937	0.84	73	(***E***)-**4a**
			b	−3002.130411	4.31	0	
B	−3002.119149	0.63559	**a**	−3002.131823	3.42	3	(***E***)-**5a**
			b	−3002.133729	2.23	24	(***Z***)-**4a**
C	−3002.116603	2.23334	**a**	−3002.132206	3.18	0	
			b	−3002.132555	2.96	0	

[a]Total energies (hartree): −3002.1174354 for complex of $SeO_2\cdots$**3a**. [b]Relative energies (kcal/mol) from the complex energy.



Scheme 3. Stereochemical pathways of the allylic hydroxylation of compound **3a**.

prior to the sigmatropic rearrangement. The least favorable compound, (*E*)-**5a** is produced *via* (**B**) approach in the ene step followed by the [2,3]-rearrangement (Scheme 3). The ratios of three stereoisomeric products ((*E*)-**4**, (*Z*)-**4** and (*E*)-**5**) obtained from the reaction are in good agreement with the predicted values from *ab initio* calulation studies of transition states for two major steps.

In summary, stereochemical course of selenium dioxide-mediated allylic oxidation of 1-*tert*-butyl-4-alkylidene cyclohexanes **3** was investigated by a combination of experimental and theoretical studies. The ratios of three stereoisomeric products ((*E*)-**4**, (*Z*)-**4** and (*E*)-**5**) obtained from the reaction are in good agreement with the predicted values from *ab initio* calulation studies of transition states for two major steps (an ene step and a [2,3]-sigmatropic rearrangement). A comparative analysis of two results showed that the overall transformation was controlled by two competing pathways: the major path corresponds to an trans-anti mode ene step followed by a stereospecific [2,3]-sigmatropic rearrangement and the minor is *via* the rotation of allylselenic acid initially formed by the *trans-syn* attack of selenium oxide prior to the sigmatropic rearrangement.

Experimental Section

Computational methods. All calculations were performed with Gaussian-98 package.[13] The structures of the intermediates and transition states were then fully optimized using HF/3-21G* method. Frequency calculations were subsequently carried out for the transition state structures and in each case one imaginary frequency was found, confirming that the structures obtained were indeed transition states.

General procedure for allylic oxidation of 1-*tert*-butyl-4-alkylidene cyclohexanes 3 with selenium dioxide. Selenium dioxide (122 mg, 1.10 mmol) was dissolved in absolute ethanol (15 mL). Compound **3** (1.10 mmol) was added and the mixture was stirred at room temperature for 15h. The reaction mixture was concentrated and the residue was partitioned between ether and water and extracted with ether 3 × 20 mL. The organic layers was dried over anhydrous magnesium sulfate, filtered and concentrated. The concentrate was subject to flash column chromatography (silica gel, elution with 2% ethylacetate in *n*-hexane) to give **7** and mixures of allylic alcohols (**4** and **5**) as oil.

5-*tert*-Butyl-2-ethylidenecyclohexanol. (*E*)-**4a**. NMR (300 MHz, $CDCl_3$) δ5.40 (dq, J = 6.9, 1.7 Hz, 1H), 4.25 (t, J = 2.8 Hz, 1H), 2.76-1.12 (series of m, 8H), 1.61 (dd, J = 6.9, 1.7 Hz, 3H,), 0.85 (s, 9H); (*Z*)-**4a**. NMR (300 MHz, $CDCl_3$) δ5.46 (tq, J = 6.7, 1.6 Hz, 1H), 4.00 (brd, J = 11.3 Hz, 1H), 2.75 (m, 1H), 2.15 (series of m, 7H), 1.65 (dt, J = 6.7, 1.6 Hz, 3H), 0.87 (s, 9H); (*E*)-**5a**. NMR (300 MHz, $CDCl_3$) δ 5.27 (dq, J = 6.7, 1.6 Hz, 1H), 4.83 (brt, J = 2.7Hz, 1H), 2.74-1.12 (series of m, 8H), 1.65 (dd, J = 6.7, 1.6 Hz, 3H), 0.86 (s, 9H).

(*E*)-5-*tert*-Butyl-2-ethylidenecyclohexanone (7a). NMR (300 MHz, $CDCl_3$) δ6.72 (tq, J = 7.2 Hz, 2.3 Hz, 1H,), 2.73 (m, 1H), 2.57 (m, 1H), 2.20-1.21 (series of m, 5H), 1.74 (dd, J = 7.4, 1.4 Hz, 3H), 0.90 (s, 9H).

(*E*)-5-*tert*-Butyl-2-*n*-propylidenecyclohexanol. (*E*)-**4b**. NMR (300 MHz, $CDCl_3$) δ5.34 (dt, J = 7.5, 1.8 Hz, 1H), 4.24 (t, J = 3.0 Hz, 1H), 2.12-1.21 (series of m, 8H), 1.99 (q, J = 7.5 Hz, 2H), 0.96 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H); (*Z*)-**4b**. δ5.38 (tq, J = 7.2, 1.8 Hz, 1H), 4.00 (dd, J = 10.7, 4.1 Hz, 1H), 2.10-1.22 (series of m, 8H), 1.97 (q, J = 7.5 Hz, 2H), 0.99 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H); (*E*)-**5b**. NMR (300 MHz, $CDCl_3$) δ5.20 (dt, J = 7.5, 1.8 Hz, 1H), 4.80 (brt, J = 2.7Hz, 1H), 2.74-1.12 (series of m, 13H), 0.86 (s, 9H).

(*E*)-5-*tert*-Butyl-2-*n*-propylidenecyclohexanone (7b). NMR (300 MHz, $CDCl_3$) δ6.60 (t, J = 7.2 Hz, 1H), 2.74 (m, 1H), 2.59 (m, 1H), 2.20-0.9 (series of m, 5H), 2.10 (q, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H).

(*E*)-5-*tert*-Butyl-2-n-pentylidenecyclohexanol. (*E*)-**4c**. NMR (300 MHz, $CDCl_3$) δ 5.32 (dt, J = 7.2, 1.8 Hz, 1H), 4.25 (t, J = 2.8 Hz, 1H), 2.71 (m, 1H), 2.48 (m, 1H), 2.10-1.12 (series of m, 12H), 0.91 (t, 3H, J = 7.5 Hz), 0.87 (s, 9H); (*Z*)-**4c**. NMR (300 MHz, $CDCl_3$)δ5.38 (tq, 1H, J = 6.6, 1.7 Hz), 4.00 (dd, J = 11.5, 3.6 Hz, 1H), 2.71-1.12 (series of m, 14H), 0.92 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H); (*E*)-**5c**. NMR (300 MHz, $CDCl_3$) δ5.20 (dt, J = 7.5, 1.8 Hz, 1H), 4.79 (brt, J = 2.7Hz, 1H), 2.74-0.91 (series of m, 17H), 0.86 (s, 9H).

(*E*)-5-*tert*-Butyl-2-*n*-pentylidenecyclohexanone (7c). NMR (300 MHz, $CDCl_3$) δ6.63 (t, J = 7.3 Hz, 1H), 2.73 (m, 1H), 2.57 (m, 1H), 2.20-0.9 (series of m, 11H), 0.90 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H).

5-*tert*-Butyl-2-benzylidenecyclohexanol. (*E*)-**4d**. NMR (300 MHz, $CDCl_3$) δ 7.39-7.10 (m, 5H), 6.43 (s, 1H), 4.43 (t, J = 2.8 Hz, 1H), 2.82 (m, 1H), 1.93-1.11 (series of m, 7H), 0.87 (s, 9H). (*Z*)-**4d**. NMR (300 MHz, $CDCl_3$) δ 7.39-7.10 (m, 5H), 6.56 (s, 1H), 4.89 (t, J = 2.7Hz, 1H), 2.98 (m, 1H), 2.35-1.11 (series of m, 7H), 0.89 (s, 9H). (*E*)-**5d**. NMR (300 MHz, $CDCl_3$) δ 7.39-7.10 (m, 5H), 6.35 (s, 1H), 4.89 (t, J = 2.8 Hz, 1H), 2.82 (m, 1H), 1.93-1.11 (series of m, 7H), 0.87 (s, 9H).

(*E*)-5-*tert*-Butyl-2-benzylidenecyclohexanone (7d). δ 7.36-7.20 (series of m, 6H), 3.40 (m, 2H), 2.20-1.17 (series of m, 5H), 0.90 (s, 9H).

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12. The calculated activation energy for **TS1** corresponding to a terminal approach (**c**) in Scheme 2 appears to be > 8.3 kcal/mol for compound **3a**, much higher than those of two internal approaches (**a**, **b**) and the routes *via* approach (**c**) are ruled out for further consideration.
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