(28) *tert*-Butyl fluoride solvolyses some 10^5 times more slowly than the chloride at 25 °C in 80% aqueous ethanol (see A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, p 82).
(29) C. W. Jefford, J. C. E. Gehret, J. Mareda, nT. Kabengele, W. D. Graham, and U. Burger, *Tetrahedron Lett.*, 823 (1975).
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(31) See Experimental Section for a substantiation of the structural assignments which are based on NMR analyses and comparison of the data of our compounds and those of the authors cited in ref 30.
(32) For related examples of intramolecular cycloadditions, see H. Prinzbach and H. D. Martin, *Helv. Chim. Acta*, **51**, 438 (1968); D. T. Longone and D. M. Stehouwer, *Tetrahedron Lett.*, 1017 (1970); P. G. Gassmann, *Acc. Chem. Res.*, **4**, 128 (1971); L. A. Paquette and L. M. Leichter, *J. Am. Chem. Soc.*, **93**, 5128 (1971); H. D. Martin, *Chimia*, **26**, 16 (1972); W. J. Feast, W. K. R. Musgrave, and W. E. Preston, *J. Chem. Soc., Perkin Trans. 1*, 1830 (1972); R. Bloch, F. Leyendecker, and N. Toshima, *Tetrahedron Lett.*, 1025 (1973); R. D. Miller and D. L. Dolce, *Tetrahedron Lett.*, 4403 (1973); H. D. Martin, *Chem. Ber.*, **107**, 477 (1974).
(33) R. B. Kinnel and P. K. Freeman, *Tetrahedron Lett.*, 4803 (1973).
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β-Epimerization and γ-Hydrogen Abstraction via Homoenolate Ions[1]

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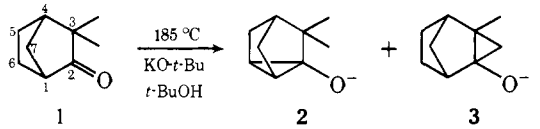
Abstract: Our objective was to study homoenolate ion formation in ketones with enolizable as well as homoenolizable centers, and in other systems having special structural features. Our substrates were camphor, *exo*- and *endo*-isocamphanone, 1-acetoxytricyclane, 2,2,4,4-tetramethylcyclobutanone, norbornan-7-one, cyclodecanone, 2,2,10,10-tetramethylcyclodecanone, cyclododecanone, and 2,2,12-trimethylcyclododecanone. At 185–250 °C in KO-*t*-Bu/*t*-BuOH for prolonged periods camphor, *exo*-isocamphanone, and *endo*-isocamphanone are interconvertible, and the camphor skeleton is favored. The exo ⇌ endo isomerization in the isocamphanones illustrates epimerization at a homoenolic site. The tertiary *exo*-H in *endo*-isocamphanone is abstracted and recaptured more readily than is the *endo*-H in *exo*-isocamphanone. The homoenolate ion liberated from 1-acetoxytricyclane at room temperature partitions differently in proton capture than does the homoenolate generated from the isocamphanones at 185–250 °C. In deuterated medium at high temperature camphor incorporated label at sites other than at C-3 (enolic) and C-6 (homoenolic) as evidenced by species containing d_5 and d_6. Camphor-*10*-d_1 was synthesized and was shown to lose some of its deuterium when homoenolized in nondeuterated medium, thus establishing that hydrogens at C-10 are exchangeable. After an exchange of camphor in *t*-BuOD ^{1}H NMR studies showed that label is incorporated at C-8 and C-10 to comparable extents. Exchange at C-8 reveals that rigid C–H orientation is not a requirement for γ-hydrogen abstraction. D assay of mass spectral fragment ions confirmed that camphor exchanges at C-6, C-8, and C-10 in addition to the enolic site C-3. Exchange at C-6 in camphor proved more difficult than at C-6 in camphenilone, probably because camphor has competitive enolization as well as steric hindrance by methyl groups. At 185 °C in KO-*t*-Bu/*t*-BuOD, 2,2,4,4-tetramethylcyclobutanone exchanges at the methylene and at the methyl positions, but much of the ketone is cleaved to 2,2,4-trimethylpentanoic acid. When similarly treated, norbornan-7-one undergoes α-bridgehead exchange but no homoenolic exchange; most of the ketone is cleaved to cyclohexanecarboxylic acid. Cyclodecanone and cyclododecanone undergo enolic exchange (and some loss, probably by aldol condensations) but there is no homoenolic exchange or product that would indicate transannular interactions in these medium-ring ketones. Cyclodecanone was tetramethylated by repeated alkylations with $NaNH_2/CH_3I$, but cyclododecanone could only be trimethylated. These methylated ketones incorporated deuterium slightly at homoenolic sites.

Ever since generation of homoenolate ions by vigorous alkaline treatment was demonstrated with camphenilone (**1** → **2** + **3**)[2] additional examples have been found in other



1 **2** **3**

polycyclic ketones.[3] Homoenolic species have also been recognized as intermediates in a variety of reactions, including those of open-chain systems.[4] Hydrogens α to carbonyl groups are ordinarily much more acidic than more distant ones, and invariably homoenolizations have been explored with substrates that either lacked α protons or whose α protons were at bridgeheads and could not enolize readily because of Bredt's rule.[5] For studies of the reverse process (homoketonization), the homoenolate species are conveniently generated from cyclopropyl alcohols or cyclopropyl acetates and allowed to protonate under irreversible conditions.[6] The scope of homoenolization would be broadened considerably if remote proton abstractions could occur in substrates that also possess enolic hydrogens. One of our present objectives was to examine ketones that had α and β hydrogens to learn if enolate formation could lastingly prevent generation of homoenolate ions. We also wanted to learn whether remote chiral centers could be epimerized via homoenolate ions and, via deuterium exchange, to explore homoenolization in a variety of ring structures.

Our ketonic substrates were camphor (**4**), *endo*-isocamphanone (**7**),[7] and *exo*-isocamphanone (**8**),[7] each of which has enolizable α hydrogens as well as potentially homoenolic hydrogens. We hoped that the enolates would be sufficiently hindered by the methyl groups to prevent excessive loss by aldol condensations and other side reactions. Abstraction from C-6 in camphor produces the delocalized homoenolate ion depicted by the single resonance structure **6**. Proton recapture can either revert it to camphor or can produce the isocamphanones **7** and **8** by exo and endo protonation, respectively. Therefore alkali-induced isomerization of camphor to the isocamphanones or vice versa would establish homoenolate intermediates, and exo–endo interconversion of the two isocamphanones would demonstrate remote epimerization. Our study also included homoketonization of

Table I. Homoenolization and Homoketonization in the Camphor-Isocamphanone Series with KO-*t*-Bu in *tert*-Butyl Alcohol[a]

Run	Substrate[b]	Temp, °C	Time, h	Rel % ketones after reaction: Camphor **4**	*endo*-Iso **7**	*exo*-Iso **8**
1	Camphor (**4**)	185	667[c]	97.5	1	1.5
		220	142			
2	Product of run 1	250	168	98	0.5	1.5
3	*endo*-Iso (**7**)	185	507	45	55	
4	*endo*-Iso (**7**)	250	32	58	40.5	1.5
5	*exo*-Iso (**8**)[d]	185	507	4.5	18.5	77
6	*exo*-Iso (**8**)[e]	250	52	22	36	42
7	*exo*-Iso (**8**)[e]	240	245	87	11	2
8	1-Acetoxytricyclane (**5**)[f]	20	16	100		
9	1-Acetoxytricyclane (**5**)[f,g]	20	20	100		
10	1-Acetoxytricyclane (**5**)[f,h]	20	20	99.7	0.2	0.1

[a] The KO-*t*-Bu concentrations were 1-1.5 *m* in runs 1-8. [b] The camphor concentrations were 0.18-0.28 *m*; the *endo*-isocamphanone 0.02-0.05 *m*; the *exo*-isocamphanone 0.04-0.17 *m*; the 1-acetoxytricyclane 0.25-0.5 *m* (run 8). [c] After treatment at 185 °C, the temperature was raised to 220 °C for 142 h. [d] The starting exo isomer contained 11% of the endo epimer. The numbers are corrected for this component. [e] The starting exo isomer had 14.5% of the endo epimer. The percentages in run 6 are corrected by use of the data in run 4. Run 7 has no comparable run and is not corrected. Nevertheless, based on run 4 most of the endo component should rearrange to camphor and the resulting corrections would be minor. [f] Duplicate runs that gave identical results. [g] These runs were conducted in methanol containing sodium methoxide (1.2-1.8 *m*) and substrate (0.6-0.8 *m*). [h] These runs were conducted in methanol containing sulfuric acid (3.4-4.5 *m*) and substrate (0.4-0.5 *m*).

1-acetoxytricyclane (**5**)[8] at room temperature to learn the preferred direction for irreversible opening of homoion **6**.

Each of the three ketones **4**, **7**, and **8** was heated (185-250 °C) in *tert*-butyl alcohol containing a large excess of potassium *tert*-butyl alcoholate, and the recovered product was analyzed by analytical gas chromatography sensitive enough to detect 0.1% of any of these isomers. Even at these elevated temperatures the ketones largely survived, and our recoveries were of the order of 80%. Runs 1-7 in Table I summarize results for the three ketones, and runs 8-10 describe room-temperature homoketonizations of the homoenol acetate **5** in three different media.

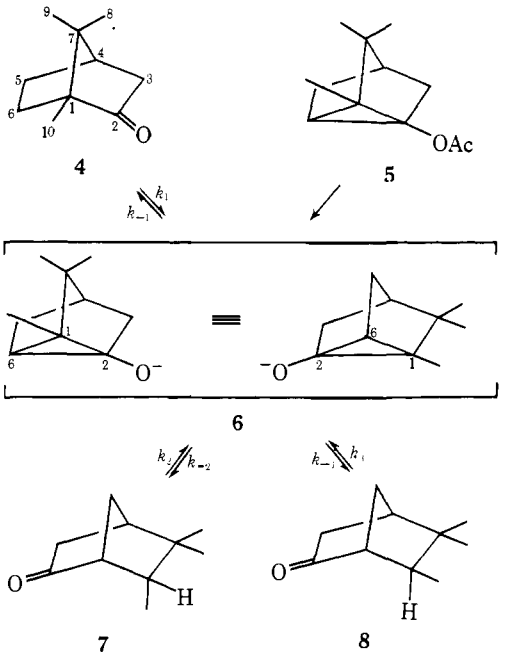
Results

Camphor (**4**) rearranges only slightly (2.5%) to the two isocamphanones even on prolonged alkaline treatment (runs 1 and 2). As will be evident later from our deuterium studies, this reluctance to isomerize is partly due to relative difficulty of homoion formation at C-6 but also reflects the greater thermodynamic stability of the camphor skeleton. Although we have no evidence that equilibrium has been reached in any of the isomerizations in Table I, we can safely conclude from runs 1 and 2 that camphor would persist almost entirely were it produced under homoenolization conditions. Some qualitative information about the relative rate constants shown in Scheme I is extractable from Table I.

Runs 3 and 4 show that *endo*-isocamphanone (**7**, hereafter abbreviated *endo*-iso) homoenolizes and rearranges preferentially to camphor rather than to its epimer *exo*-isocamphanone (**8**, hereafter abbreviated *exo*-iso), i.e., $k_{-1} > k_{-3}$. We know that this behavior is not due to instability of *exo*-iso because runs 5 and 6 reveal that the bulk of it would have remained after comparable treatment.

Runs 5-7 with *exo*-iso (**8**) show substantial conversion to its endo epimer **7** and to camphor (**4**). Importantly, run 5 (23% total isomerization) and run 6 (58% total isomerization) produced more *endo*-iso (**7**) than camphor (**4**). In these runs the percentages of *endo*-iso are minimum values because much of this isomer would have subsequently gone on to camphor (see runs 3 and 4). Therefore the homoion derived from *exo*-iso (**8**) protonates from the exo direction to produce *endo*-isocamphanone (**7**) faster than it protonates at the alternative carbon to give camphor; i.e., $k_{-2} >$

Scheme I



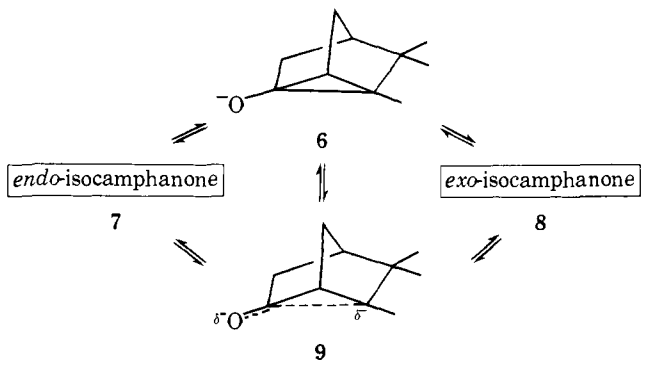
k_{-1}. If we accept that a single homoenolate ion (**6**) is a common intermediate in these transformations, its relative proton capture rates at 185-250 °C fall in the order $k_{-2} > k_{-1} > k_{-3}$.

In the case of proton abstraction, comparison of run 4 with run 6 allows us to conclude that $k_2 > k_3$ because in these two runs the alkali concentrations were virtually identical (1.20 *m*) but run 6 had a 3.4-fold higher ketone concentration and was conducted 20 h longer than run 4. Despite the higher concentration, longer reaction time, and lower reversibility (i.e., $k_{-3} < k_{-2}$ from above), all of which should favor faster disappearance of **8** over **7**, both ketones rearranged to comparable extents (cf. 58 + 1.5 = 59.5% for run 4 with 36 + 22 = 58% for run 6). Consequently *endo*-iso (**7**) must have the greater specific rate constant for this homoenolic proton abstraction (i.e., $k_2 > k_3$). Taken along with our earlier conclusion that $k_{-2} > k_{-3}$, it is clear that both the loss and the gain of the tertiary exo hydrogen in **7** are faster than the loss and gain of the

tertiary endo hydrogen in **8**. This *exo*-H preference in KO-*t*-Bu/*t*-BuOH agrees with earlier findings with other bicyclo[2.2.1]heptan-2-one systems such as norcamphor[6b] and fenchone.[1b,3i] Exo protonation corresponds to inversion of configuration at the electrofugal carbon (termed Semi-W in generalized stereochemical notation[9]) and this preference for inversion in alkaline media is also observed in noradamantan-2-one,[10] adamantanone,[3h] brexan-2-one,[10] and brendan-2-one.[10] However, several cases of high retention of configuration (Semi-U) in KO-*t*-Bu/*t*-BuOH have also been reported (see ref 6i for complete references).

Further information emerged from irreversible cleavage of 1-acetoxytricyclane (**5**) in KO-*t*-Bu/*t*-BuOH at room temperature (run 8). The product was camphor (**4**) exclusively. This result is interesting because the same (presumably) homoion **6** generated from *exo*-isocamphanone (**8**) at high temperature (e.g., runs 5 and 6) initially produced more of **7** than of camphor (**4**). Therefore the homoion liberated at room temperature partitions differently than does the homoion generated at 185–250 °C. If only one homoenolate ion is really involved, we may have identified nothing more than a temperature effect on the relative rate constants, a finding that should be kept in mind for deuterium labeling via homoenolizations and homoketonizations. However, more complex situations could prevail. For example, if the initial intermediate from the isocamphanones differs geometrically and electronically from the homoion **6** from 1-acetoxytricyclane, then **7** and **8** may be able to interconvert by a path distinct from that involving homoion **6**. We illustrate such a possibility in Scheme II where homoe-

Scheme II



nolate ion **9** symbolizes a geometrically distorted form of **6**. The existence of more than one homoenolate ion would implicate additional equilibria, whose relative rate constants could account for the partitioning behavior we described earlier. Although sets of interconverting homoenolate ions[2] may ultimately prove to be a more accurate description, we adopt the simpler interpretation in Scheme I until conclusive evidence demands otherwise.

For additional comparison we also homoketonized **5** in $NaOCH_3/CH_3OH$ (run 9) and in one acid medium, H_2SO_4/CH_3OH (run 10). The alkaline methanol run gave results identical with that in KO-*t*-Bu/*t*-BuOH, and the acid opening was similar except that it produced tiny amounts of the isocamphanones **7** and **8**. Although their relative percentages are subject to large errors, epimer **7** consistently predominated over **8**. Therefore in acid, the bond between C-1 and C-2 prefers to cleave by inversion at the electrofugal site (i.e., Semi-W geometry[9]). This stereochemical pathway is uncommon in acid homoketonizations, and only two other examples are known.[6i,j]

The results in Table I establish that homoenolate ions can be generated in ketones with enolic protons, and also that chiral centers β to a carbonyl can be epimerized via

Table II. Mass Spectral Deuterium Distribution in the M, M − 15, and M − 57 Ions from Camphor after Treatment with KO-*t*-Bu/*t*-BuOD at 185 °C for 797 h[a,b]

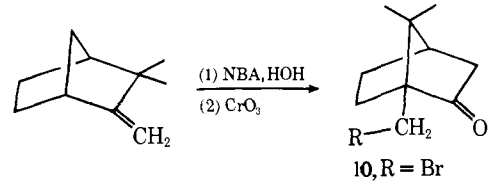
	Rel % deuterated species[c]							Total D/
m/e (ion)	d_0	d_1	d_2	d_3	d_4	d_5	d_6	molecule
152 (M)	1	5	15	41	31	6	1	3.18
137 (M − 15)	4	14	23	32	22	4	1	2.70
95 (M − 57)	11	40	43	6	0	0	0	1.44

[a] Camphor (0.2 *m*) in *t*-BuOD containing KO-*t*-Bu (1.3 *m*) was heated at 185 °C for 307 h, was recovered, and was heated similarly in fresh *t*-BuOD an additional 490 h. [b] By comparison, camphenilone (**1**; 0.25 *m*) in *t*-BuOD containing KO-*t*-Bu (0.86 *m*) heated at 185 °C for 48 h showed 13% d_0, 55% d_1, 29% d_2, 3% d_3, 0% d_4 (total D/molecule is 1.22), virtually all of which enters via abstraction at C-6.[2b] [c] Rounded to the nearer whole number.

such ions. Because camphor (**4**) has β hydrogens also at C-4 and C-10 and has γ hydrogens at C-5, C-8, and C-9, we examined deuterium incorporation to identify other homoenolic sites. At the outset we may confidently exclude C-9 because it is geometrically incapable of bonding with the carbonyl. Likewise, from strain considerations C-4 and C-5 are unlikely sites, and in fact these positions have been shown to undergo no detectable hydrogen–deuterium exchange in the related ketone camphenilone (**1**).[2c] To get information about C-8 and C-10, we conducted several prolonged exchanges with camphor in KO-*t*-Bu/*t*-BuOD at 185–250 °C and analyzed the recovered camphor mass spectrally for deuterium content.

Table II summarizes the details from a typical experiment and displays the deuterium distribution in the molecular ion M (*m/e* 152), in the M − 15 ion (*m/e* 137), which represents loss of a methyl group, and in the M − 57 ion (*m/e* 95), which corresponds to loss of ketene plus a methyl group. The presence of d_3–d_6 species in the molecular ion proves that camphor has incorporated deuterium extensively at sites other than the C-3 enolic one.[11] The following considerations show that C-10 is one of these sites.

We synthesized[12] camphor-*10*-d_1 (**11**; 94% d_1) from camphene. The final step was reduction of the known 10-bromocamphor (**10**)[13] with Zn in acetic acid-d_4. In KO-*t*-Bu/*t*-BuOH at 250 °C for 212 h the camphor-*10*-d_1 lost 4% of its deuterium, and therefore C-10 is a homoenolizable site. The loss is modest because the statistical factor as well as a primary isotope effect would favor proton, rather than deuteron, removal from C-10.



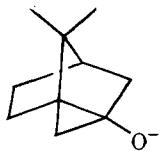
10, R = Br
11, R = D

Weinberg and Djerassi[14] and also Dimmel and Wolinsky[15] studied mass spectral fragmentations in camphor and established that the *m/e* 137 ion (i.e., M − 15) is produced by statistical loss of one of the three methyl groups. Table II shows that this M − 15 fragment has 0.48 D/mol *less* total deuterium than does the molecular ion *m/e* 152. Clearly there is substantial deuterium on the C-8 and/or C-10 methyl groups, because the C-9 methyl is not homoenolizable. Furthermore, Dimmel and Wolinsky[15] showed that the M − 57 (i.e., *m/e* 95) fragment, which is the base peak, arises by loss of C-2 and C-3 (as $CH_2{=}C{=}O$) along

with loss of one of the three methyl groups (the C-10 methyl 45% of the time, the C-9 methyl 34% of the time, and the C-8 methyl 21% of the time). Because the M − 57 fragment ion lacks the original enolic site, C-3, any deuterium remaining in this ion must necessarily have entered by homoenolic exchanges. In fact (Table II), this M − 57 ion still had 1.44 D/molecule, which included some d_3 species. These d_3 species must involve methyl hydrogens because the C-6 site in camphor could only account for species up to d_2. We were able to demonstrate by the following ^{1}H NMR studies that *both* C-8 and C-10 undergo exchange.

Camphor in chloroform gives three well-resolved singlets for the methyl protons, which have been assigned by several research groups as follows: C-9, 0.97 δ; C-10, 0.91 δ; C-8, 0.83 δ.[17] In a separate, prolonged *d* exchange with camphor (250 °C, 168 h) and with the nonhomoenolizable C-9 methyl as an internal integration standard, we found that the C-8 proton signal was less intense than in the natural abundance precursor by ca. 10.5%, and the C-10 proton signal was less intense by ca. 8.5%. As expected, both of these diminished signals were also slightly broadened by the small splitting caused by deuterium. Because these intensity changes are small, they reflect, approximately, the competitive initial abstraction rates from C-8 compared to C-10 (i.e., k_8/k_{10} = 1.24), and are applicable to other runs that do not involve heavy deuteration at these sites.[16]

Our results establish that camphor homoenolates **12** and **13** are formed comparably under the vigorous alkaline treatment in addition to homoenolate **6,** which is formed by abstraction at C-6. The 1,3-homoenolate **12** is noteworthy because the cyclopropyl ring at the bridgehead of this bicyclo[2.2.1]heptane ring system has some of the strain character found in anti-Bredt olefins.[5] Similar bridgehead methyl exchange has been observed in fenchone.[1b,3i] The 1,4-homoion **13** is of interest not only as the first reported



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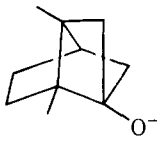
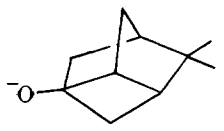


13

case of γ-hydrogen abstraction[1a,2b] but also because these γ C–H bonds are not rigidly oriented. Therefore fixed orientation in space is not a requirement for γ-H abstraction, although it may facilitate it.[3d,e,j] Finally, it appears that homoenolic exchange at C-6 is more difficult in camphor than in camphenilone (**1**), which contains no enolic hydrogens. For example, under similar treatment (see footnote *b* in Table II for details) camphenilone picked up much more deuterium at C-6 in 48 h (1.22 D/molecule) than camphor did in 797 h (0.53 D/molecule). In camphor, steric hindrance by the methyl groups as well as competitive enolization probably contribute to this ketone's greater reluctance to undergo exchange at C-6.

Two questions about our deuterium incorporation in camphor should be dealt with. First, is the carbonyl group needed to activate β and γ hydrogens or could exchange occur in its absence? As a check, we subjected the parent hydrocarbon, camphane, to KO-*t*-Bu/*t*-BuOD at 250 °C for 215 h and found no detectable deuterium incorporation.[18] Second, since camphor and the isocamphanones are interconvertible, could C-8 and/or C-10 in camphor undergo exchange while these groups are part of the isocamphanone structure? Such a situation would implicate the 1,4-homoion **14** and the 1,5-homoion **15** and would require that they be generated considerably more readily than **12** and **13** to compensate for the low concentrations of the isocamphanones (see runs 1 and 2, Table I). These possibilities do not detract from our findings because ion **14** represents γ-hydrogen loss from a nonrigid C–H and would prove the same point as did homoion **13,** and ion **15** requires δ-hydrogen abstraction, which would be of even greater interest but to date is unprecedented. Therefore, although ions like **14** and **15** are not truly excluded by our camphor work (or by work on fenchone[1b,3i]), we defer them until warranted by explicit evidence.



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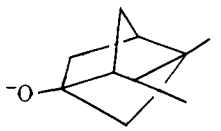
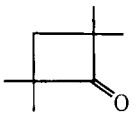


15

To probe for homoenolization in other skeletons, we prepared and examined deuterium exchange in ketones **16** and **17,** because their homoenolates would be highly strained, and also in systems **18–21,** because transannular homoenolization in these medium rings could possibly produce alkoxides of five- or six-membered alcohols, which might be isolable.



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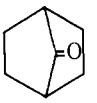

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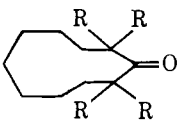
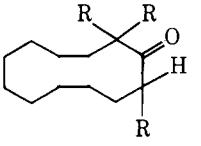


18, R = H
19, R = CH_3



20, R = H
21, R = CH_3

2,2,4,4-Tetramethylcyclobutanone (**16**) was prepared as reported,[19] and norbornan-7-one (**17**) was obtained from 2-*exo*-bromo-7-*syn*-hydroxynorbornane[20] by zinc–acetic acid reduction followed by oxidation. Cyclodecanone (**18**) was converted to 2,2,10,10-tetramethylcyclodecanone (**19**) by repeated alkylations with sodium amide and methyl iodide. Similar treatment of cyclododecanone (**20**), however, gave only 2,2,12-trimethylcyclododecanone (**21**), and our attempts to introduce the fourth methyl group were unsuccessful. Molecular models (and also deuterium exchange experiments) suggest that the tertiary H in **21** is strongly hindered sterically, and thereby difficult to abstract.

Base-induced homoenolizations of **16** and **17** were complicated by Haller–Bauer type[21] ring cleavage to give 2,2,4-trimethylpentanoic acid and cyclohexanecarboxylic acid, respectively. Therefore conditions had to be chosen under which some **16** and **17** would survive. Thus, treatment of **16** with KO-*t*-Bu/*t*-BuOD at 185 °C for 210 h gave a mixture of **16** and the ring-cleaved product. The recovered ketone **16** had only 5% d_1 and 1% d_2. In the mass spectrum the molecular ion and a fragment ion revealed that a little over half of this deuterium was located on the methyl groups. Because of the 12/2 statistical ratio of methyl/methylene hydrogens, we conclude that in **16** a single methylene hydrogen was exchanged about five times more readily than a single methyl hydrogen.

Haller–Bauer cleavage of **17** prevailed even more than it did with **16.** After 100 h at 185 °C in KO-*t*-Bu/*t*-BuOD ketone **17** was largely (>80%) converted to cyclohexanecarboxylic acid. The small amount of **17** recovered contained only mono- and dideuterated species (12% d_1, 3% d_2, and <0.5% d_3). Our results parallel those of Gassman and

Zalar[20] who found that norbornan-7-one (**17**) exchanges at the two bridgeheads (apparently because of hybridization and inductive effects) but not elsewhere. Clearly, homoenolization is not significant in this skeleton. This finding is in line with a report that C-7 hydrogens in camphenilone (**1**) are nonexchangeable at 185 °C.[2c] Apparently, homoenolate interaction between C-7 and C-2 would strain a bicyclo[2.2.1]heptane skeleton too much when the carbonyl group is at either location.

In the medium ring ketones **18** and **20,** we found no evidence for deuterium exchange other than at the α-enolic positions. Nor were any isomeric ketones produced that would have implicated decalols or hydrindanols as intermediates. As a control, we checked the behavior of *trans*-9-decalol,[22] which is a possible product of transannular homoenolization of **18.** The alcohol was unchanged after 80 h at 185 °C in KO-*t*-Bu/*t*-BuOD. At 250 °C (24 h) it decomposed to a 1:4 mixture of 9-octalin and (presumably) an isomeric olefin. Neither of these products was detected after similar homoenolization attempts on cyclodecanone **18.**

We examined the alkylated analogues **19** and **21** to learn whether the lack of homoenolization of **18** and **20** had been caused by preferential enolization. Both **19** and **21** could be recovered even after extended treatment with KO-*t*-Bu/*t*-BuOD at 250 °C, but relatively little deuterium was incorporated. For, e.g., after 97 h, **19** had 71% d_0, 22% d_1, 6% d_2, 1% d_3. We presume the deuterium is on the methyl groups but did not rigorously prove it. In none of these methyl-substituted ketones **16, 19, 21,** or in those discussed earlier (**4, 7, 8**) did we find any skeletal isomerizations involving the homoenolizable methyl groups, and to date there seems to be no authentic example of that type of homoenolate rearrangement.

An interesting result in our medium-ring work was the resistance to exchange of the single α hydrogen in **21.** After 103 h at 250 °C in KO-*t*-Bu/*t*-BuOD, the recovered ketone still had appreciable α-H as indicated by ^{1}H NMR and by mass analysis (29% d_0, 48% d_1, 17% d_2, 3% d_3, 1% d_4, 1% d_5, 1% d_6), which reveals that at least 23% of the molecules had undergone one homoenolic exchange, and at least 6% had undergone two or more homoenolic exchanges. These are minimum values and presume that the 48% d_1 is entirely at the α position. Therefore enolization and homoenolization appear comparably difficult in this ketone.

Experimental Section

General. See previous papers for general information about exchange in deuterium solvents and mass spectral assays of deuterium.[2b,c] Unless stated otherwise the following information applies. Melting points are corrected, infrared spectra were taken on a Perkin-Elmer Model 337 grating spectrophotometer, and ^{1}H NMR spectra were recorded on a Varian 60 MHz spectrometer, with tetramethylsilane as the internal standard for chemical shifts. Analytical gas chromatography was conducted with a Perkin-Elmer Model 226 instrument and a hydrogen flame ionization detector. Preparative GLC was done on an Aerograph Autoprep Model A-700 with a thermal conductivity detector. Mass spectra were obtained at Johns Hopkins with a Consolidated Electrodynamics Corporation Spectrometer, type 2103C, or with a Hitachi Perkin-Elmer RMU-6D spectrometer operated by the Morgan-Schaffer Corporation, Montreal, Canada. Natural abundance spectra were recorded for comparison with spectra of deuterated samples. Microanalysis were performed by Mr. Joe Walter, and combustion deuterium analyses by the falling-drop method were carried out by Mr. Josef Nemeth, Urbana, Ill. Deuterated solvents were from Merck Co. Ltd. of Canada or Columbia Organic Chemicals Co., Inc., and were >95% isotopically pure. Solvents were either "reagent" quality or were purified before use. Pentane, hexane, and petroleum ether were purified by treatment with fuming sulfuric acid followed by several washings with water and finally by distillation from sodium. *tert*-Butyl alcohol was distilled twice from sodium, and potassium *tert*-butyl alcoholate was sublimed in vacuo at 250 °C before use. Camphenilone (**1**) was available from earlier work.[2b]

(+)-Camphor (4). Commercial material (Eastman Organic Chemicals) was sublimed; mp 177.5–178 °C, αD +43° (chloroform); reported[23] 178.6 °C, αD +43.6°. GLC indicated one symmetrical peak 99.2%, plus 0.8% of borneol.

***endo*-Methylisocamphanone (7).** This racemic ketone, mp 108 °C (reported mp 109 °C), was kindly supplied by Dr. E. Demole.[7] It was 100% pure by GLC.

exo-Methylisocamphanone (8). Two samples of this racemic ketone were provided by Dr. E. Demole.[7] Both had mp 74 °C (reported mp 74 °C). GLC showed that one sample contained 11%, and the other had 14.5%, of the endo epimer.

Homoenolizations in KO-*t*-Bu/*t*-BuOH. After alkaline treatment of the ketone in sealed Pyrex tubes, as recorded in Table I, the crude product was obtained by addition of pentane, which was washed by extractions with water. The pentane solutions were analyzed directly on a $\frac{1}{8}$ in. column (9 ft) packed with 15% diethylene glycol succinate polyester on SS. Products were identified by peak enhancement with a standard mixture of the three authentic ketones.

Deuterium Exchange in Camphor (4). (a) After the deuterium exchange reported in Table II (footnote *a*) pentane was added and the alkali was washed out by extraction with water. To replace enolic deuterium lost in this work-up, we treated ca. 0.04 g of the recovered ketone in CH_3OD (0.85 g) containing KOD (0.11 g) at 65 °C for a prolonged period (1 month) and worked it up similarly except that D_2O was used to wash the pentane solutions. The mass spectral analysis of the recovered camphor is summarized in Table II.

(b) For ^{1}H NMR studies a separate deuterium exchange was conducted for 168 h at 250 °C in *t*-BuOD (4.2 g) containing camphor (0.11 g) and KO-*t*-Bu (0.75 g). The camphor-*d* recovered from this treatment was dissolved in methyl alcohol (25 ml) and water (6 ml) containing potassium hydroxide (1.0 g), and the solution was stirred at room temperature under nitrogen for 70 h to wash out enolizable α deuterium. Workup gave 0.06 g of crystalline camphor-*d*, which was purified for ^{1}H NMR analysis by chromatography over alumina. Mass spectrum: 13% d_0, 39% d_1, 37% d_2, 10% d_3, 1% d_4 (total 1.47 D/molecule). The ^{1}H NMR spectrum of this sample (in alcohol-free chloroform) was repeatedly scanned along with that of natural abundance camphor under standardized operating conditions. The intensity of the C-9 methyl signal at 0.97 δ (3.00 H) was used as an integration standard, and the intensities of the C-8 signal at 0.83 δ and the C-10 signal at 0.91 δ were compared to those in the natural abundance material. The C-8 methyl had diminished by 10.5 ± 0.2% and the C-10 methyl by 8.5 ± 0.2%.

Homoketonization of 1-Acetoxytricyclane (5). This homoenol acetate was prepared as reported[8] and was homoketonized in KO-*t*-Bu/*t*-BuOH, in $NaOCH_3/CH_3OH$, and in H_2SO_4/CH_3OH as described in Table I. Duplicates were run in each medium, and workup in all cases involved addition of water, extraction with pentane, and GLC analysis of the pentane as described above for homoenolizations. We could detect as little as 0.1% of the isomers as established with authentic ketones.

10-Bromocamphor (10). A mixture of (±)-camphene (50 g, 0.37 mol), *N*-bromoacetamide (51 g, 0.37 mol), water (500 ml), *tert*-butyl alcohol (50 ml), and concentrated sulfuric acid (10 ml) was stirred in the dark at room temperature for 90 h. The mixture was extracted with ether, which was washed with 5% bicarbonate, dried ($MgSO_4$), and evaporated. The residual bromoalcohol (ν 3600–3300 cm^{-1}), which still contained some camphene (880 cm^{-1}), was dissolved in acetone (500 ml, distilled from potassium permanganate) and oxidized with 100 ml of the Jones reagent[24] (17.5 g of CrO_3, 15 ml of H_2SO_4, 125 ml of H_2O). Methanol was added and the solution was concentrated at aspirator pressure. The residue was extracted (ether), washed (bicarbonate), and dried ($MgSO_4$). The bromoketone had mp 73–74.5 °C (12 g) after several recrystallization from methanol, and was raised to 74–76.5 °C by passage through alumina (reported[17] mp 77 °C for optically active 10-bromocamphor prepared differently). The ^{1}H NMR showed methyl singlets at 0.96 and 1.13 and an AB quartet at 3.47 δ (CH_2Br). Reduction with Zn/HOAc produced (±)-camphor, identical (via GLC and ir) with authentic (±)-camphor.

Camphor-*10*-d_1 (11). A sublimed sample of 10-bromocamphor (6 g, mp 74.5–76 °C), zinc dust (15 g), and acetic acid-d_4 (30 g) was refluxed 1.5 h and kept at 45 °C an additional 5 h. Water was added followed by 6 N sodium hydroxide to neutralize the mixture. Ether workup and vacuum sublimation of the product gave camphor-*d*, mp 172–175 °C (3.7 g). To remove any enolic deuterium, a solution of the ketone (3.2 g), sodium methoxide (0.76 g), and methanol (10 ml) was refluxed 17 h. The ketone was recovered and recycled through another $NaOCH_3/CH_3OH$ wash for 44 h. Workup with ether left 2.5 g: mp 178–179 °C (sealed capillary); 99.5% pure by GLC; ir 2170 cm^{-1} (C–D). After chromatography over alumina (ligroin) the camphor-*10*-d_1 was 99.9% pure and had 6% d_0 and 94% d_1. That the deuterium is at C-10 is clear from the ^1H NMR ($CHCl_3$), which showed normal methyl singlets at 0.98 δ (C-9) and 0.84 δ (C-8), and a slightly split multiplet of lower intensity centered at 0.92 δ, as expected for a CH_2D unit at C-10.[15] Camphor-*10*-d_1 has also been synthesized by other workers.[15,17]

Homoenolization of Camphor-*10*-d_1 (11). The ketone (0.5 g) dissolved in 5 ml of a solution of KO-*t*-Bu in *tert*-butyl alcohol (prepared from 0.42 g of potassium and 11 ml of *t*-BuOH) was heated in a sealed Pyrex tube at 250 °C for 212 h. The recovered ketone had 10% d_0 and 90% d_1. A duplicate experiment gave the same result. (Mass analysis of the starting camphor-*10*-*d* under identical spectrometer conditions gave 6% d_0 and 94% d_1, which corroborated the assay obtained earlier on a different instrument.)

Camphane Control. This hydrocarbon (mp 154–155 °C, reported[25] 158–159 °C) was prepared by Wolff-Kishner reduction of (+)-camphor according to the Huang-Minlon modification.[26] After treatment with KO-*t*-Bu/*t*-BuOD for 336 h at 185 °C, the recovered camphane was purified by sublimation and showed no detectable deuterium incorporation ($d_1 < 0.5\%$) by mass spectroscopy. A second experiment at 250 °C for 215 h gave the same result.

Synthesis and D Exchange in Ketones 16–21. (see J.E.O. in ref 1a for complete details).

2,2,4,4-Tetramethylcyclobutanone (16). The ketone (0.48 *m*), prepared as reported,[19] was heated with KO-*t*-Bu (1.2 *m*) in *tert*-butyl alcohol-*O*-*d* in a sealed tube for 210 h at 185 °C. The recovered material was worked up to give an acidic and a neutral fraction.

The acid (2,2,4-trimethylpentanoic acid) in ether was esterified with diazomethane. The methyl ester (ν 1740, 2140; 99% pure by GLC) had a molecular ion too weak for accurate *d* analysis. Three fragment ions (M − 15; M − 31, M − 56) gave good agreement on total deuterium content (1.01, 1.01, 1.02 D/molecule) despite inherent inaccuracies in this type of analysis.

The neutral fraction was treated with semicarbazide hydrochloride, and after purification, the semicarbazone was hydrolyzed with aqueous oxalic acid. The derived tetramethylcyclobutanone (**16**) was 98.5% pure by GLC and had 94% d_0, 5% d_1, and 1% d_2 by mass analysis of its molecular ion. The base peak (*m/e* 70) corresponds to a dimethylketene fragment and had 98% d_0, 1.5% d_1, and 0.5% d_2.

Norbornan-7-one (17). We prepared 2-*exo*-bromo-7-*syn*-hydroxynorbornane as reported.[20] This crude bromoalcohol (5.0 g) was stirred at reflux overnight with zinc dust (12 g) in glacial acetic acid (65 ml). Water was added and the mixture was steam distilled. The two-phased distillate was made alkaline with potassium hydroxide and was stirred 1 day at room temperature to saponify acetates. The mixture containing precipitated alcohol was extracted with ether, which was worked up to leave crude norbornan-7-ol (96%): mp 151–155 °C (softens at 144 °C), reported 149–150 °C.[20] This product was oxidized with the Jones reagent,[24] in acetone. The norbornan-7-one (ca. 25%; 98% pure) was separated from starting alcohol and norbornan-2-one by preparative GLC (Carbowax 100 on Chromosorb W).

In an attempted homoenolization norbornan-7-one (0.052 g) was heated at 185 °C for 97 h in *tert*-butyl alcohol-*O*-*d* (2.1 ml) containing potassium *tert*-butyl alcoholate (0.2 g; 1.1 *m*). The products were separated into acid and neutral fractions. The acid fraction was treated with ethereal diazomethane, and the derived ester (0.035 g; 99.9% pure; ν 2280, 2150 cm^{-1}) was identified as methyl cyclohexanecarboxylate by ir comparison (of a sample obtained from a run in nondeuterated medium) with an authentic specimen.

The neutral fraction was rectified by distillation through a spinning band column and finally by preparative gas chromatography (Carbowax 1500 on Chromosorb W). Norbornan-7-one was collected and sublimed for mass analysis: 84% d_0, 12% d_1, 4% d_2. An unknown compound with longer retention time was also obtained (ν 1745, 1735 (shoulder), 1120, plus weak C–D absorption at 2360 and 2330 cm^{-1}). Authentic *tert*-butyl ester of cyclohexanecarboxylic acid had a different retention time than this unknown. From several experiments we estimate that 80–85% of the norbornan-7-one was cleaved by the alkaline treatment.

Attempted Homoenolization of Cyclodecanone (18). Cyclodecanone (purified to 99.5% via its semicarbazone) was converted to the *2,2,10,10-d_4* analogue by repeated exchange cycles with Na_2CO_3 in D_2O–CH_3OD–dioxane. The ketone (98% pure after sublimation; a solid slightly below room temperature) on duplicate combustion analysis gave 22.10 and 22.10 atom % excess D, which corresponds to 3.93 D/molecule. Cyclodecanone-*2,2,10,10-d_4* (0.11 g) was heated at 185 °C for 107 h in a sealed Pyrex tube with KO-*t*-Bu (0.60 g) and *t*-BuOD (9.8 g). Acetic acid-*O*-*d* (0.7 ml) was added and the mixture was partitioned between pentane and water. The pentane gave an oil from which the ketone was sublimed in vacuo to a clear liquid (0.07 g, >99% pure by GLC), which solidified slightly below room temperature. The ir spectrum (CCl_4) was identical with that of starting deuterated ketone, and duplicate combustion analyses gave 21.25 and 21.20 atom % excess D (3.83 D/molecule).

***trans*-9-Decalol Stability Control.** This alcohol[22] (0.02 g; mp 45–50 °C, lit. mp 52 °C) was heated at 185 °C for 80 h with KO-*t*-Bu (0.20 g) and *tert*-butyl alcohol (5 ml). Workup gave a white solid (0.015 g) whose ir was identical with that of starting alcohol.

Attempted Interconversion of Cyclodecanone (18) and *trans*-9-Decalol. Two similar mixtures were prepared and heated at 250 °C for 24 h, viz.: mixture A (cyclodecanone, KO-*t*-Bu, *t*-BuOH) and mixture B (*trans*-9-decalol, KO-*t*-Bu, *t*-BuOH). After the usual workup, gas chromatography of the product from A showed cyclodecanone (97%) and four small peaks none of which amounted to more than 1%. The product from B showed no OH or carbonyl bands in the ir, and had two principal GLC peaks (ratio 1:4), the first of which was identified as 9-octalin by peak enhancement. The second peak may be an isomeric olefin. There were no components common to the two product mixtures, and so the starting ketone and alcohol do not interconvert or form any common intermediates.

2,2,10,10-Tetramethylcyclodecanone (19). A solution of cyclodecanone (1.0 g) in anhydrous ether (25 ml) was stirred under N_2 with sodium amide (1.2 g) for 6 h at room temperature, then methyl iodide (2 ml) was added and stirring was continued several hours. Volatile components were removed on a rotary evaporator and the residue was again treated with fresh ether, sodium amide, and methyl iodide, as before. The process was continued through six such cycles, then the solvent was evaporated, and the residue was treated with ice and dilute sulfuric acid. The mixture was extracted with ether, and the ether solution was washed with aqueous sodium sulfite, water, and brine, then was dried and evaporated. The residue (1.2 g of a light-brown oil) was purified by preparative gas chromatography (Carbowax, 200 °C). Two fractions were collected: first, a liquid (0.44 g, presumably 2,2,10-trimethylcyclodecanone), and then, a solid, **19**, mp 43–47 °C (0.35 g). The solid was purified by recrystallization from methanol–water followed by vacuum sublimation, mp 49–49.5 °C. Anal. ($C_{14}H_{26}O$) C, H.

The infrared and NMR spectra of **19** agree with the assigned structure: ν (CCl_4) 1680 (highly substituted carbonyl) and 1495, 1470 cm^{-1} (geminal dimethyl); δ (CCl_4) 1.17, singlet (CH_3).

Homoenolization of 2,2,10,10-Tetramethylcyclodecanone (19). A solution of this ketone (0.80 g, mp 46–47.5°) in *tert*-butyl alcohol-*O*-*d* (5 ml) containing KO-*t*-Bu (0.45 g) was divided into two equal portions and heated at 250 °C in sealed tubes (sample no. 1 for 49 h; sample no. 2 for 97 h). Conventional pentane–water workup gave from each sample 0.030 g of solid, mp 46–47 °C after vacuum sublimation from barium oxide. Sample no. 1 had 87% d_0, 10% d_1, 2% d_2, and 1% d_3. Sample no. 2 had 71% d_0, 22% d_1, 6% d_2, and 1% d_3.

Attempted Homoenolization of Cyclododecanone (20). The enolizable hydrogens in cyclododecanone were first replaced with deuterium by four exchange cycles with Na_2CO_3 in D_2O–CH_3OD at reflux. This ketone (0.10 g, mp 60–61°; 4% d_3, 96% d_4 (18.05 atom % excess minimum, because this *d* level decreased with time

in the mass spectrometer[11]) was heated in a sealed tube with KO-*t*-Bu (0.60 g) and *tert*-butyl alcohol-*O*-*d* (10 g) at 185 °C for 100 h. Acetic acid-*O*-*d* (0.4 ml) was added and the mixture was partitioned between pentane and water. The pentane extracts gave a residue, which was sublimed in vacuo to white, crystalline ketone, mp 55–58 °C (0.07 g, single peak on GLC). Duplicate combustion analyses gave 17.80 and 17.85 atom % excess D (calculated for $C_{12}H_{18}D_4O$: 18.18 atom % excess D). As a control to show there was no *d* loss during workup, the starting ketone-d_4 was let stand 5 min in a solution of KO-*t*-Bu/*t*-BuOH that had been treated with a slight excess of acetic acid. Conventional processing with pentane–water gave the ketone with 17.85 and 17.90 atom % excess D.

2,2,12-Trimethylcyclododecanone (21). This ketone was prepared by methylation of cyclododecanone with sodium amide and methyl iodide (seven cycles) in ether as described for the synthesis of **19.** The crude, solid product was recrystallized from methanol–water and then was sublimed, mp 55.5–56 °C. Anal. ($C_{15}H_{28}O$) C, H.

The ir and ^{1}H NMR agree with the assigned structure; ν (CCl_4) 1695 (highly substituted ketone), 1490, 1475, 1470 cm^{-1} (geminal dimethyl plus methyl bending); singlets at 1.00 and 1.23 δ (C-2 methyls) and a doublet (J = 6.7 Hz) at 1.02 (C-12 methyl). Attempts to methylate **21** further with sodium hydride and methyl iodide in dimethoxyethane resulted only in recovery of **21.**

Homoenolization of 2,2,12-Trimethylcyclododecanone (21). The ketone (0.098 g, mp 56–57 °C), KO-*t*-Bu (0.45 g), and *t*-BuOD (4.0 ml) were heated at 250 °C for 103 h. Pentane–water workup gave 0.085 g of a solid, mp 50–52 °C, raised to 56–57 °C by two recrystallizations from methanol. In the ^{1}H NMR spectrum the methyl doublet was partially, but not completely, collapsed, indicating only partial replacement of the α hydrogen by deuterium. Its mass analysis gave 29% d_0, 48% d_1, 17% d_2, 3% d_3, 1% d_4, 1% d_5, and 1% d_6.

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(16) This information along with the data in Table II allow us to estimate the deuterium distribution in the ketone. We accept the premise of zero incorporation at C-9, C-4, and C-5, and let the total D at each of the four exchangeable sites (C-3, C-6, C-8, C-10) be represented by a subscript denoting its location. The following equations interrelate these four unknowns, and simultaneous solution gives 1.27 D/molecule at C-3 (40% of the total);[11] 0.45 D at C-6 (14%); 0.81 D at C-8 (26%); and 0.65 D at C-10 (20%).

$$D_3 + D_6 + D_8 + D_{10} = 3.18$$

$$D_3 + D_6 + 0.33(D_8 + D_{10}) + 0.33D_8 + 0.33D_{10} = 2.70$$

$$D_8 + 0.34(D_8 + D_{10}) + 0.21D_{10} + 0.45D_8 = 1.44$$

$$D_8 = 1.24D_{10}$$

Therefore of the total 3.18 D/molecule assayed mass spectrally in camphor 1.91 D/molecule (60%) entered by homoenolic exchange. We wish to emphasize that because D assays in fragment ions are often inherently inaccurate these estimates are crude at best, and only qualitative conclusions should be drawn from them.

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(18) We recognize that at 250 °C in a Pyrex tube the KO-*t*-Bu/*t*-BuOD solution could gradually undergo decomposition to destroy the base. Therefore homoenolizations run for prolonged periods at very high temperatures may not necessarily be more effective than those run for shorter periods. Our qualitative conclusions are not affected by these considerations.

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