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Analysis of the Stereochemical Integrity at C_α in Sequences Employing Ketone Tosylhydrazones

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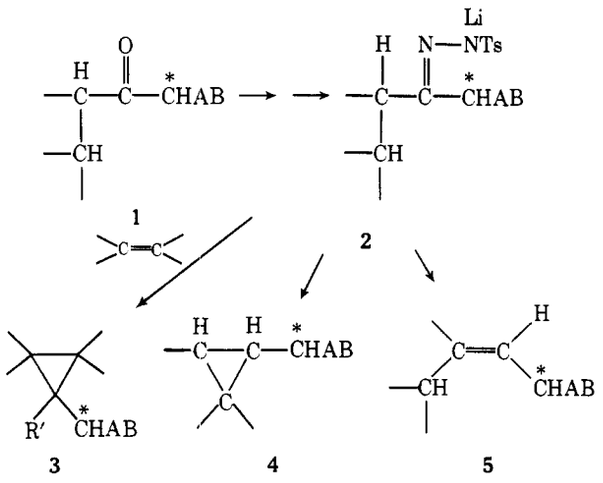
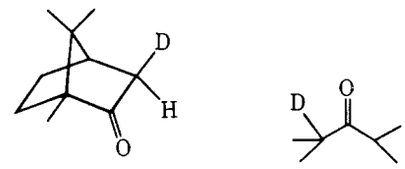
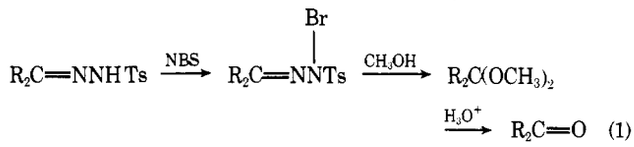
The tosylhydrazones of ketones and their alkali metal salts are most useful synthetic intermediates. Ketones generally may be readily converted in high yields to alkali metal salts of tosylhydrazones (**2**). Pyrolysis or photolysis may be used to create either an alkene (**5**) or cyclopropane (**4**) species in an intramolecular process or a cyclopropane adduct (**3**) as a consequence of an intermolecular reaction with an olefin.[1] In mechanistic studies of carbene intermediates ketone tosylhydrazones and their alkali metal salts usually represent the most readily available precursors for the generation of dialkyl carbenes. In either a synthetic or mechanistic application the preservation of stereochemical integrity at the α position may be of paramount importance. Conversion of a ketone to tosylhydrazone (H_2NNHTs, H^+) and then to lithium salt (CH_3Li) might very well alter the stereochemical environment at C_α through enolization. One convenient method to check on this might involve the reconversion of ketone tosylhydrazone salt **2** to ketone **1**, using a procedure which is mild enough not to cause additional enolization.



We chose to consider *exo*-3-deuteriocamphor[2] (**6**) and 4-deuterio-2,4-dimethyl-3-pentanone (**7**) as representative ketone substrates and cleavage using pyruvic acid catalysis[3] or the method of Rosini (*N*-bromosuccinimide)[4] (eq 1). Since





the *exo*-3-deuterium should be lost in preference to *endo*-3-hydrogen in the case of *exo*-3-deuteriocamphor,[2,5] deuterium loss from either **6** or **7** should be a sensitive measure of enolate formation.

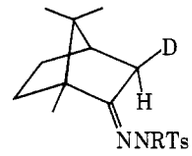
The deuterium content of ketones **6** and **7** was determined and both were converted to tosylhydrazone (**8a** and **9**). Analysis of cleavage back to ketone from tosylhydrazone (**8a**, **9**) or lithium salt of tosylhydrazone (**8b**) (Table I) clearly demonstrates that the *N*-bromosuccinimide method is an eminently suitable method to check the stereochemical integrity at C_α in tosylhydrazone intermediates.

Experimental Section

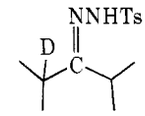
Melting points were obtained using either a Buchi melting point apparatus or a Mel-Temp device and are uncorrected. NMR spectra were recorded at 100 MHz with a Varian HA-100 or at 60 MHz with a Varian Anaspect EM-360. Infrared spectra were obtained with either a Beckman IR-8 or a Perkin-Elmer Model 621. Vapor-phase chromatographic analyses were carried out using a Varian Aerograph A-90-P, an 18 ft × ¼ in. 5% OV-17 on 60/80 chromosorb G column; yields were determined using *p*-cymene as an internal standard.

Deuterium analyses were accomplished by a low-voltage, mass-spectral technique using a Varium MAT CH-7 spectrometer, inter-

Table I. Reconversion of Ketone Tosylhydrazones to Parent Ketone



8a, R = H
b, R = Li



9

Cleavage method		Pyruvic acid	NBS	NBS
% yield		75	70	93
D content of initial ketone	D_0	7.0 ± 0.4[a]	7.0 ± 0.4	27.4 ± 0.6
	D_1	79.3 ± 0.4	79.3 ± 0.4	49.1 ± 0.6
	D_2	13.7 ± 0.3	13.7 ± 0.3	23.5 ± 0.5
D content of final ketone from reconversion of **8a** or **9**	D_0	63.1 ± 1.0	7.1 ± 0.4	27.7 ± 1.1
	D_1	32.8 ± 1.0	79.2 ± 0.4	49.8 ± 1.1
	D_2	4.1 ± 0.5	13.7 ± 0.2	22.5 ± 0.9
D content of ketone from reconversion of **8b**	D_0		7.4 ± 0.4	
	D_1		78.8 ± 0.6	
	D_2		13.8 ± 0.8	

[a] Standard deviation.

faced with a pdp-8/m computer. Before analyzing a deuterated sample, the nondeuterated sample was run to determine the exact intensities of P, P + 1, and P + 2 at a voltage which eliminated the P − 1 peak (usually 18–20 eV). The molecular ion region was scanned 10–20 times; the mean and standard deviation are reported.

Spectral grade $CDCl_3$ was supplied by Merck, Sharp, and Dohme, CCl_4 by Mallinckrodt, D_2O by Stohler Isotope Chemicals. Pyruvic acid was purified by distillation in vacuo using a Kugelrohr distillation apparatus.

4-Deuterio-2,4-dimethyl-3-pentanone. CH_3OD was prepared by the general method of Streitwieser.[6] Using carefully dried apparatus, a solution prepared from 15 mL of CH_3OD, 3.0 g (0.026 mol) of ketone, and 0.08 g of Na was stirred for 9 h at room temperature. The solution was then quenched with D_2O, extracted with ether, washed with H_2O, and dried over $MgSO_4$; NMR (CCl_4) δ 2.7 (heptet, 0.9 H, J = 7 Hz), 1.06 (m, 12 H); mass spectrum % D_0 = 27.4 ± 0.6, % D_1 = 49.1 ± 0.6, % D_2 23.5 ± 0.5.

4-Deuterio-2,4-dimethyl-3-pentanone Tosylhydrazone. Ketone (2.2 g, 0.019 mol), tosylhydrazine (3.59 g, 0.019 mol), 40 mL of ethanol (95%), and 1 drop of concentrated HCl were combined and the resulting solution placed on a steam bath for 4 h. The solvent was largely removed by evaporation. Refrigeration produced 3.5 g (65%) of a white crystalline solid which was used without further purification, mp 95–99 °C. An analytical sample of undeuteriated tosylhydrazone had mp 106.9–108.7 °C.

Anal. Calcd for $C_{14}H_{22}N_2O_2S$: C, 59.54; H, 7.85. Found: C, 59.66; H, 7.87.

3-Deuteriocamphor. An adaptation of the procedure of Tidwell[5d] was used. In a dry 250-mL round-bottom flask, 60 mL of reagent grade dioxane and 30 mL of D_2O were combined. The flask was cooled to 0 °C, and 0.08 g of Na was added in three portions. The ice bath was removed and the solution was allowed to come to room temperature. Camphor (2.0 g.) was dissolved in 5 mL of dioxane and then added to the above solution. After 30 h of stirring, the solution was extracted with ether, washed with H_2O, and dried over $MgSO_4$: mass spectrum % D_0 = 7.0 ± 0.4, % D_1 = 79.3 ± 0.4, % D_2 = 13.7 ± 0.3.

The Tosylhydrazone (8a) and the Lithium Salt of the Tosylhydrazone (8b) of *exo*-3-Deuteriocamphor. Tosylhydrazone **8a** was prepared as described above for 2,4-dimethyl-3-pentanone, giving a 75% yield, mp 157–159 °C.[7] The lithium salt of tosylhydrazone **8a** (**8b**) was prepared by treating **8a** (0.2916 g, 0.908 mmol) in 10 mL of THF with 1 equiv of methyllithium (2 M solution in THF). The lithium salt **8b** was then reconverted to tosylhydrazone by neutralization with 0.1 N acetic acid. This mixture was extracted with ether, washed with water, and dried ($MgSO_4$); evaporation of solvent gave an 80% recovery of **8a**.

The Tosylhydrazone to Ketone Conversion Using *N*-Bromosuccinimide. This procedure is an adaptation of the method of Rosini.[4] Tosylhydrazone (10^{-4} mol) and internal standards, if desired, were dissolved in a mixture of 14 mL of acetone and 4 mL of water. When dissolution was complete, the mixture was cooled to 0 °C using an ice/water bath. *N*-Bromosuccinimide (4×10^{-4} mol) was then added. Stirring, using a magnetic stirring bar, was continued for 2 min. (Evolution of N_2 was apparent after 10–15 s, and the resulting solution was yellow.) The reaction was quenched with 1–2 mL of saturated sodium bisulfite. The ice bath was removed and the stirring continued while adding ca. 10 mL of water. The ketone was extracted with ether and the combined organic extracts were washed with water, 10% Na_2CO_3, water, and then dried over $MgSO_4$.

The Tosylhydrazone to Ketone Conversion Using Pyruvic Acid. Tosylhydrazone (10^{-4} mol) was combined with 10^{-4} mol of *p*-cymene (internal standard), 4 mL of glacial acetic acid, 1 mL of water, and 0.5 g of purified pyruvic acid. The solution was heated at reflux for 2 h. After cooling, it was extracted with ether, washed with water, 10% Na_2CO_3, water, and finally dried over $MgSO_4$. Yields were typically ca. 75%.

Registry No.—**6**, 27808-88-4; **7**, 60877-43-2; **8a**, 62930-36-3; **8b**, 62930-37-4; **9**, 62930-38-5; CH_3OD, 1455-13-6; 2,4-dimethyl-3-pentanone, 565-80-0; tosylhydrazine, 1576-35-8; camphor, 76-22-2.

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Gas Chromatographic Analysis of Ortho Esters as a Convenient New General Method for Determining the Enantiomeric Purities of Chiral δ-Lactones

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The rapid developments being made in the area of asymmetric synthesis have increased the demand for methods of measuring enantiomeric purities. The traditional dependence on optical rotation comparisons for this purpose is well recognized to be unreliable at times and techniques permitting enantiomeric excesses to be measured directly are much to be preferred. Determination of optical purities by NMR analysis, either of appropriate diastereomeric derivatives[1] or in the presence of chiral shift reagents,[2] has proven to be the most powerful of the generally applicable approaches to the problem. However, at the present time there are many compounds whose enantiomeric purities cannot be readily evaluated by the NMR techniques because the preferred structural features or functionalities are absent. Lactones of the type **1a,d,e**,[4a]

Scheme I