Ring-Opening Processes in the 8-Oxabicyclo[3.2.1]octane Ring System

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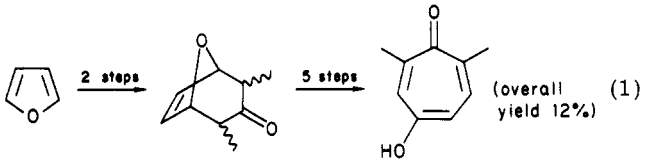
The synthesis of a number of derivatives of 8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) has been carried out in an attempt to generate a short synthesis of 4-tropolone. Lewis acid catalyzed ether cleavage of the saturated analogue of **2** was unsuccessful. The bromine adduct of **2** underwent elimination reactions, leading to all three isomers of hydroxybenzaldehyde, depending upon conditions. An intermediate in one of these processes, an 8-oxatricyclo[3.2.1.$0^{2,7}$]octanone, has been isolated and fully characterized, revealing some mechanistic information concerning these transformations. Preparation of the 6-bromo derivative of **2** was carried out; it was, however, found to be inert to a variety of standard elimination conditions.

Introduction

In connection with a study of new synthetic routes to hydrazulene-based natural products, we sought an efficient synthesis of 4-tropolone (**1**). Previous preparations of this material either required potentially hazardous peroxidation–thermolysis sequences beginning with cycloheptatriene[3] or, beginning with simpler starting materials, were lengthy and proceeded in low yield.[4] The sequence developed by Noyori and co-workers in 1978 for the synthesis of *substituted* derivatives of **1**[5] (e.g., eq 1) appeared

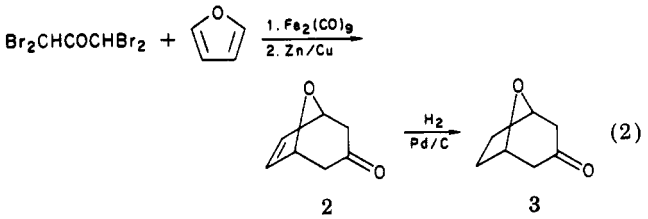


(1)

to offer significant advantages over these other procedures. We report herein our attempts to apply this chemistry to the unsubstituted ring system and the observation of some unusual and novel chemistry associated with the 8-oxabicyclo[3.2.1]octane structure.

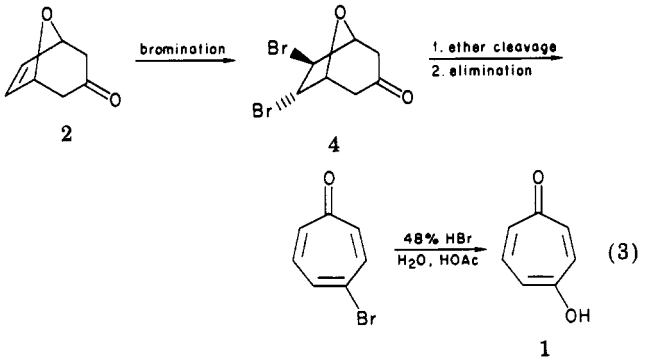
Results

In accord with the literature, 8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) was prepared in two steps from 1,1,3,3-tetrabromoacetone and furan and hydrogenated to saturated ketone **3** in 57% overall yield (eq 2).[6,7] In contrast,



(2)

however, to the results reported for alkyl-substituted derivatives of **3**, several oxygen-bridge ring-opening attempts on **3** using a variety of reagents (BF_3/Ac_2O; FSO_3H; TsOAc; TMSI) were, in our hands, uniformly unsuccessful, resulting generally in decomposition mixtures from which no seven-membered-ring containing products could be isolated. Despite these disappointments, we still viewed the readily accessible ketone **2** as a valuable potential tropolone precursor if a sequence such as that illustrated in eq 3 were to prove possible.



(3)

Attempted bromination of **2** at 0 °C resulted in considerable decomposition; however, dropwise addition of bromine in a dichloromethane–chloroform mixture to **2** in dichloromethane at −78 °C under nitrogen[8] gave the crystalline dibromide **4** in 82% isolated yield. Attempts to open the oxide bridge of **4** under Lewis acid conditions were then undertaken. Reaction of **4** with either boron trifluoride etherate/acetic anhydride[5] or with excess chlorotrimethylsilane/sodium iodide (CH_3CN, 75 °C, 20 h)[9] returned unchanged starting material. Reaction did occur with fluorosulfonic acid; the result, however, was complete decomposition.

Hence, we turned to an alternative sequence of dehydrobromination of **4**, followed by attempted ether cleavage. When compound **4** was treated with 1.6 equiv of diazabicyclononene (DBN) in dry tetrahydrofuran (THF) (at −78 °C, then slowly warmed to room temperature), workup and preparative thin-layer chromatography (silica gel) afforded *o*-hydroxybenzaldehyde and *p*-hydroxybenzaldehyde in approximately a 1:1 ratio (55% combined yield). With different amounts of base and under slightly different reaction and workup conditions, the ratio of ortho isomer to para isomer was found to vary. In fact, we found that if the unreacted excess base was not removed by dilute acid wash immediately during workup, then the product mainly consisted of the ortho isomer.

Dehydrobromination of **4** with the milder reagent diazabicycloundecene (DBU) (1.1–1.2 equiv in dry THF at −78 °C) afforded a pale yellow solid (ca. 73% yield). The

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(3) Yagihara, M.; Kitahara, Y.; Asao, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 236.
(4) Meinwald, J.; Chapman, O. L. *J. Am. Chem. Soc.* **1958**, *80*, 633. Sheehan, J. C.; Bloom, B. M. *J. Am. Chem. Soc.* **1952**, *74*, 3825.
(5) Takaya, H.; Hayakawa, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1778.
(6) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765.
(7) Hill, A. E.; Greenwood, G.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1973**, *95*, 1338; Cowling, A. P.; Mann, J.; Usmani, A. A. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2116.
(8) Paquette, L. A.; Barrett, J. H. *Org. Synth.* **1969**, *49*, 62.
(9) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

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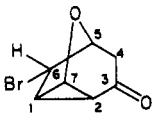
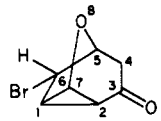
Table I. 360-MHz NMR Data for Compound 5



proton assignment	chem shift, δ	appearance appearance of signal	interpretation from decoupling experiments	coupling constants (J), Hz
H-2	1.92	dd	dd	8.6 5.3
H-4_{exo}	2.38	dd	dd	19.3 3.8
H-1	2.53	m	ddd	8.6 4.3 3.8
H-4_{endo}	2.84	dd	dd	19.3 2.0
H-5	4.44	br m	ddd	5.3 3.8 2.0
H-6_{exo} H-7	4.55	m		

major component of this product mixture, however, appeared to be nonaldehydic (NMR). Indeed, to our surprise the NMR showed signals at δ 1.92 (dd, J = 8.6 and 5.3 Hz, 1 H) and the IR, a band at 3070 cm^{-1} indicative of a *cyclopropyl* C-H. The high-resolution mass spectrum and elemental analysis corresponded to the formula $C_7H_7O_2Br$. On the basis of high-field NMR (360 MHz) (Table I), we assigned the structure for the product as **5**, *endo*-6-bromo-8-oxatricyclo[3.2.1.$0^{2,7}$]octan-3-one. The ^{13}C NMR



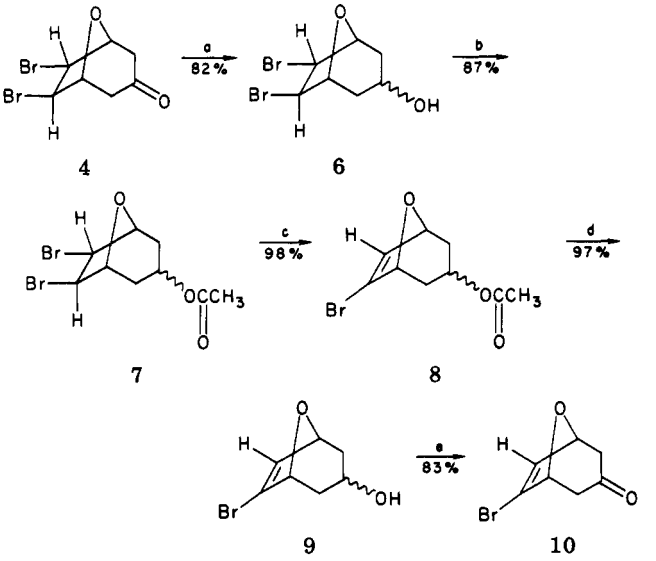
5

spectrum was in agreement with structure **5**, with seven lines in a C-H decoupled spectrum. The above compound was stable in solution for several days when cold (at 0 °C), although the purified solid turned into a black polymeric tar within hours at room temperature. From the black tar, small amounts of *m*-hydroxybenzaldehyde could be extracted as the only characterizable material. The solid could be stored for a few days in the dark at −78 °C under nitrogen or argon.

In order to study the mechanism and also to account for the formation of *m*-hydroxybenzaldehyde from **5**, we treated this material in dry THF with another equivalent of DBU at −78 °C and followed the same workup procedure as was used in the isolation of **5** itself. The NMR of the crude product showed the disappearance of the signals at δ 4.5 corresponding to bridgehead hydrogens. The product after workup (ca. 40% yield) was found to be identical with an authentic sample of *m*-hydroxybenzaldehyde (Aldrich Chemical Co.).

Since the presence of the carbonyl group in compound **4** was clearly leading to undesired chemistry at the α-carbons with the bases DBN and DBU, we attempted to protect the ketone (ethylene glycol, cat. TsOH[10]), but this resulted only in decomposition of the starting material. Alternatively, the dibromide **4** was subjected to reduction with sodium borohydride in ethanol.[11] Both isomeric (exo and endo) alcohols **6** were isolated in the ratio of approximately 1:1, in 82% yield. Attempted dehydrohalogenation on compounds **6** with DBU at low temperature returned the starting material. Upon refluxing with DBU, the mixture showed a weak signal for a vinylic hydrogen in the NMR, but the majority of the product mixture appeared to have decomposed. We observed, however, that when the alcohol **6** was protected as an acetate, the elimination of hydrogen bromide could be achieved in quantitative yield on refluxing with DBU. First, the exo and endo isomers of **7** were separated by fractional recrystallization from dichloromethane–pentane, the exo isomer being the less soluble. Both isomers eliminated hydrogen bromide in approximately 98% yield on refluxing with DBU in THF–Et_2O. The mixture of acetates **8** on treatment with lithium hydride in dry ether at room temperature gave the mixture of alcohols **9**, which was directly oxidized[12] with pyridinium chlorochromate in dichloromethane buffered with sodium acetate at 0 °C. The mixture was stirred at 0 °C for an hour and slowly warmed to room temperature to provide **10** in 82% yield. The sequence to **10** is presented in Scheme I.

Scheme I[a]



[a] a = $NaBH_4$, EtOH, room temperature; b = Ac_2O, Py; c = DBU, Et_2O–THF, reflux; d = LAH, Et_2O; e = PCC, NaOAc, CH_2Cl_2.

The conversion of **10** to γ-bromotropone was attempted by a variety of methods, none of which led to the desired product. These attempts included (1) treatment with excess DBU (−78 °C, then room temperature), (2) reflux with excess DBN (24 h), (3) reflux with Me_3SiCl/NaI/CH_3CN (60 h), (4) treatment with basic alumina (activated), triethylamine, and benzene (room temperature, 17 h; or reflux, 4 h), (5) reflux with pyridine, acetic anhydride, and DMAP (4 days), and (6) treatment with concentrated sulfuric acid. The last resulted in considerable decomposition, showing a mixture of products in the NMR. In the other cases, starting material was recovered unchanged (up to 75%), although small amounts of aldehydic product could also be detected (NMR).

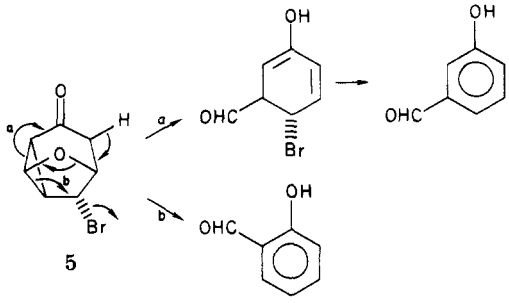
Although further manipulation of functionality might ultimately provide a substrate on which the required eliminations might proceed, the synthetic sequence would by that time have become as long or longer than the lit-

(10) DeLeeuw, J. W.; DeWaard, E. R. *Recl. Trav. Chim. Pays.-Bas.* **1973**, *92*, 1047. Branca, S. J.; Smith III, A. B. *J. Am. Chem. Soc.* **1978**, *100*, 7767.

(11) Mancera, O.; Ringold, H. J.; Djerassi, C; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem .Soc.* **1953**, *75*, 1286.

(12) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

Scheme II

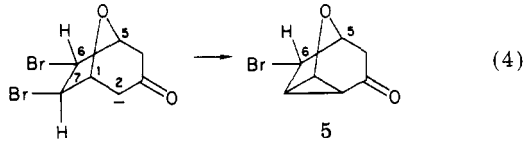


erature procedures it was intended to replace. We have therefore not pursued this line of investigation any further.

Discussion

The 8-oxabicyclo[3.2.1]octane system appears to be a case where seemingly minor changes in structure or reaction conditions have a major effect on the observed behavior. We suspect that our inability to bring about controlled ring opening of saturated ketone **3** in the presence of Lewis acids is a result of sensitivity of the product cycloheptadienone to the reaction conditions. It is known that Lewis acids complex with substituted cycloheptadienones (e.g., eucarvone) to produce cationic species of marginal stability that decompose via ill-defined pathways at or above room temperature.[13] Apparently, the lack of stabilizing substituents in the parent renders the dienone product much less compatible with the reaction conditions that produce it. Thus, throughout an extensive series of experiments (alluded to only briefly above), treatment of **3** with a variety of reagents under several different sets of conditions led, at best, to only traces of incompletely characterized enone-containing materials that were too sensitive to be purified by any chromatographic techniques.

In turning to dibromide **4**, we hoped to eliminate the need for double-bond reduction, followed by subsequent reoxidation, that Noyori followed in eq 1. Lewis acid treatment of the less reactive **4** was also unsuccessful, presumably for the same reasons surmised for **3**: conditions vigorous enough to cleave the ether also destroy the products. Reaction of **4** with bases, although also unsuccessful, presented an interesting spectrum of products, shedding some light on the reactivity preferences in this system. Considering the mildest elimination conditions first, reaction with 1 equiv of DBU at −78 °C leads to loss of HBr and ring closure via internal displacement of an exo bromine from the enolate at C-2 (eq 4). Evidence for



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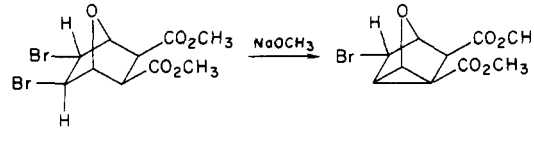
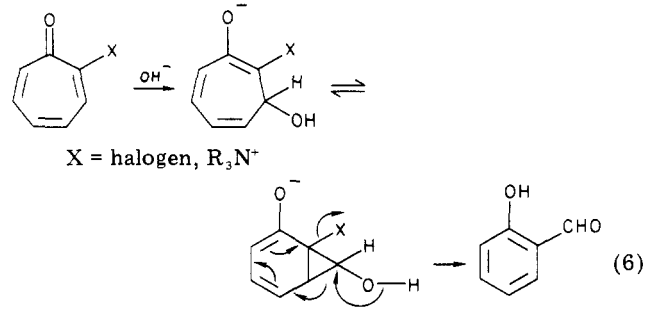
loss of only the exo bromine is quite convincing: both **4** and **5** show $J_{5,6}$ = 5–6 Hz in the NMR at 360 MHz ($J_{1,7} \approx 0$ in the starting material as expected for a near 90° dihedral angle). Similar ring closures have been observed in bicycloheptane systems (e.g., eq 5).[14] Subsequent



(5)

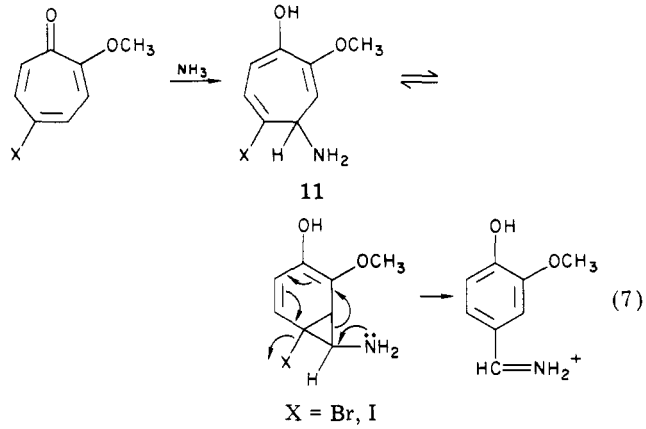
conversion of **5** to *m*-hydroxybenzaldehyde is the expected result of fragmentation of the strained, "push–pull" substituted cyclopropane bond toward the carbonyl carbon (Scheme II, path "a").

The use of DBN, perhaps a more basic, less selective reagent,[15] results in a more complex situation. The formation of *p*-hydroxybenzaldehyde as one product of its reaction with dibromide **4** is almost unprecedented. Several studies, however, have demonstrated facile ring contraction of tropones, substituted with leaving groups in the 2-position, to *o*-hydroxybenzaldehyde, via mechanisms such as the one shown in eq 6.[16] Use of piperidine as the



(6)

base in the presence of a bulky leaving group forces attack at the other β-position, leading to the meta isomer.[17] Although the same authors commented in 1979 that no authenticated ring contractions of 4-substituted tropones were known,[18] they did cite a single report of a low-yield conversion of 2-methoxy-5-halotropone (X = Br or I) to vanillin in liquid NH_3.[19] The likely mechanism, addition to the end of a dienone system, may be applied, in general, to the system under consideration here, as it involves an intermediate, **11**, closely related to the formal product of dehydration of dibromide **4** (eq 7). Thus, *p*-hydroxy-



(7)

benzaldehyde may arise from a species, **12**, where G is either bromine itself or a base-derived nucleophilic group that has displaced bromide or added in a homoconjugate fashion to cyclopropyl derivative **5**. Tautomerism would result in the same type of system as **11** (eq 7), the direct precursor to the para aldehyde (eq 8). Unfortunately, we

(13) Childs, R. F.; Hor, Y.-C. *Can. J. Chem.* **1977**, *55*, 3495 and 3501.

(14) Zefirov, N. S.; Yur'ev, Y. K. *Zh. Obshch. Khim.* **1965**, *35*, 1802. See also Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L.; Majetich, G. *J. Am. Chem. Soc.* **1979**, *99*, 4111.

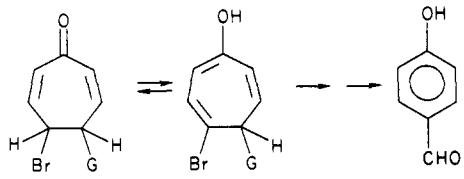
(15) See the following review: Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.

(16) Forbes, E. J.; Warrell, D. C.; Fry, W. J. *J. Chem. Soc.* **1967**, 1693. Biggi, G.; de Hoog, A. J.; Del Cima, F.; Pietra, F. *J. Am. Chem. Soc.* **1973**, *95*, 7108. Biggi, G.; Del Cima, F.; Pietra, F. *Tetrahedron Lett.* **1974**, 3537.

(17) Biggi, G.; Del Cima, F.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1971**, 1627.

(18) Cavazza, M.; Pietra, F. *J. Chem. Soc., Perkin Trans. 2* **1979**, 112.

(19) Kitahara, Y. *Sci. Rep. Tohoku Univ., Ser. 1* **1956**, *39*, 255. Cited in: Nozoe, T.; Mukai, T.; Sakai, T. *Tetrahedron Lett.* **1965**, 1041.



(8)

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have no direct evidence for intermediates associated with this reaction pathway. Reaction of **4** with equimolar DBN at −78 °C disappointingly results in incomplete consumption of starting material, with the final aromatic aldehyde products being the only other detectable species present.

The formation of *o*-hydroxybenzaldehyde, the other major product in the DBN system, can be rationalized as proceeding via an alternate fragmentation of **5** (Scheme II, path "b"). Since this fragmentation involves immediate loss of HBr while the alternative, leading to the meta isomer, does not (at least until after the product-determining step), it may be favored by the presumed greater basicity of DBN over DBU. The odd dependence of the ortho/para isomer ratio to reaction conditions suggests that the formation of the ortho product is slow but irreversible (Scheme II), while initial steps in the pathway to the para isomer are reversible and its isolation dependent on an early quenching of the reaction. Oxygen-bridge cleavage in the 8-oxabicyclo[3.2.1]octane system is well-known to be reversible, given the appropriate functionality and conditions. The ready interconversion of 4-hydroxycycloheptanones with their intramolecular hemiketals attests strikingly to the stability of the oxygen-bridged bicyclic system.[20] It must be emphasized, however, that many of the conversions we have observed here proceed with only modest mass balances, and, therefore, these mechanistic suggestions should be viewed more as starting points for further investigation rather than definitive descriptions of the pathways involved.[21] It is very likely, though, that the resistance of bromovinyl ketone **10** to productive ring opening is directly related to the stability of the [3.2.1]-bridged system, as well as the greater relative stability of **10** as a formal internal Michael adduct, as opposed to the 4-hydroxycycloheptanone hemiketal system.

Experimental Section

General. Solvents. Tetrahydrofuran was dried over neutral alumina grade I and then distilled from lithium aluminum hydride onto sodium benzophenone ketyl from which it was redistilled. For procedures carried out under oxygen-free conditions, ether and dimethoxyethane were distilled from sodium benzophenone ketyl. Acetonitrile was distilled from calcium hydride. Pyridine, dichloromethane, and dimethylformamide were dried over 4Å molecular sieves before use. All other solvents were reagent grade and used as such.

Reagents. Chlorotrimethylsilane (Silar) and boron trifluoride etherate were distilled from calcium hydride. Acetic anhydride was distilled and stored over 4Å molecular sieves. 8-Oxabicyclo[3.2.1]oct-6-en-3-one (**2**)[6] and 8-oxabicyclo[3.2.1]octan-3-one (**3**)[7] were prepared by the literature procedures. Unless otherwise noted, all other materials were obtained from commercial suppliers and were used without further purification.

Alumina grade III (H_2O, 6% by weight) was made from commercially available neutral alumina grade I. For column chromatography, silica gel (Baker) was used as received. Thin-layer chromatography (analytical) was done on commercially available silica gel sheets (Eastman).

Analyses. Boiling points and melting points are uncorrected. Melting points were determined with a Thomas-Hoover capillary melting point apparatus. Analytical samples of products were collected by gas chromatography using the columns and conditions indicated on a Varian 920 instrument. Nuclear magnetic resonance (^1H) spectra were taken on either a Varian EM 360 or EM 390 spectrometer. All high-resolution spectra were taken on a Nicolet NTCFT-1180 360-MHz NMR, and those are indicated. A few spectra were taken on an EC-100 FT (JEOL). Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet), coupling constant(s) (in hertz), number of protons. ^{13}C NMR were measured at 25.14 MHz with the JEOL EC-100-FT. Infrared spectra were recorded on a Beckman IR-8 spectrometer. Only absorptions of special interest on each compound were reported. High-resolution mass spectra were determined by Kei Miyano on a Dupont 21-492 B mass spectrometer. Microanalyses were performed on purified samples by the facility at the University of California at Berkeley.

***trans*-6,7-Dibromo-8-oxabicyclo[3.2.1]octan-3-one (4).** A solution of 0.124 g (1.0 mmol) **2** in 10 mL of dichloromethane was cooled to −78 °C under nitrogen and treated dropwise with a solution of 0.185 g (1.15 mmol) of bromine in 10 mL of 1:1 dichloromethane–chloroform, under conditions of low light. The mixture was stirred at −78 °C for 8 h, diluted with additional dichloromethane, and washed successively with cold saturated aqueous $NaHSO_3$ (twice), cold saturated aqueous $NaHCO_3$ (twice), water, and saturated aqueous NaCl. After the solution was dried ($MgSO_4$) and the solvent was removed, 0.236 g of virtually pure **4** was obtained (83% yield) as a creamy white solid. GC collection yielded analytically pure material (5 ft × $^1/_4$ in. 1.5% OV-101 on Chromosorb G, 130 °C): mp 144–145 °C; IR ($CHCl_3$) 1715 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.58 (d, J = 16.5 Hz, H-2_{endo}), 2.74 (m, H-2_{exo} and H-4_{exo}), 3.02 (d, J = 16.9 Hz, H-4_{endo}), 4.13 (d, J = 4.5 Hz, H-7_{endo}), 4.56 (dd, J = 4.5 and 6.5 Hz, H-6_{exo}), 4.82 (m, H-1 and H-5); ^{13}C NMR ($CDCl_3$) δ 44.3, 47.6, 54.1, 54.6, 77.8, 83.5, 202.5 ppm.

High-resolution mass spectrum calculated for $C_7H_8O_2{}^{81}Br_2$, 285.8850; found, 285.8876. High-resolution mass spectrum calculated for $C_7H_8O_2{}^{79}Br{}^{81}Br$, 283.8870; found, 283.8829. High-resolution mass spectrum calculated for $C_7H_8O_2{}^{79}Br_2$, 281.8891; found, 281.8905. Mass spectrum, m/e (relative intensity), 123.0420 (47.80), $C_7H_7O_2$; 68.9865 (100.00), C_4H_5O.

Anal. Calcd for $C_7H_8O_2Br_2$: C, 29.61; H, 2.84; Br, 56.28. Found: C, 29.57; H, 2.90; Br, 56.36.

Attempted Dehydrobromination of 4 with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). Isolation of 6-Bromo-8-oxatricyclo[3.2.1.$0^{2,7}$]octan-3-one (5). A solution of 0.284 g (1.0 mmol) of **4** in 10 mL of dry tetrahydrofuran was treated dropwise at −78 °C under N_2 with 0.175 mL (1.17 mmol) of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene). The mixture was stirred at −78 °C for 40 h, and the solvent was removed by rotary evaporation, leaving 0.483 g of a yellow solid, which was dissolved in 200 mL of CH_2Cl_2, washed with 3 × 100 mL of 0.015 M aqueous HCl and then saturated aqueous NaCl, and dried for several hours at 0 °C over $MgSO_4$. Removal of the solvent left 0.148 g of virtually pure **5** as a pale yellow solid (73% yield). Although solutions of this compound could be stored at 0 °C for several days, the dry solid decomposed at room temperature within hours, turning into

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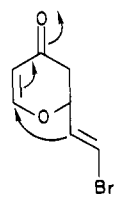
(21) We have also considered another possible route to the ortho and para aldehydes: ring opening of **4** to pyran **13**, which would give the para



13

isomer upon conjugate addition of the vinyl bromide back to the enone as shown. Alternatively, since **13** is an allyl vinyl ether, Claisen rearrangement could take place upon standing, and this would lead to the ortho isomer directly. This mechanism has the virtue of explaining the ortho/para product distributions well. However, its key steps do not appear to be especially favorable thermodynamically.

a black, mostly polymeric tar from which small amounts of *m*-hydroxybenzaldehyde was extracted as the only characterizable material. Solid **5** was stored for several days in the dark at −78 °C under N_2 or Ar, and it was characterized as *endo*-6-bromo-8-oxatricyclo[3.2.1.$0^{2,7}$]octan-3-one (*syn*-8-bromo-6-oxatricyclo-[3.2.1.$0^{2,7}$]octan-3-one): IR ($CHCl_3$) 1715 (C=O), 3070 (cyclopropane CH) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.92 (dd, J = 5.3 and 8.6 Hz, 1 H), 2.38 (dd , J = 3.8 and 19.3 Hz, 1 H), 2.53 (m, 1 H), 2.84 (dd, J = 2.0 and 19.3 Hz, 1 H), 4.44 (br s, 1 H), 4.55 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 28.6, 30.9, 41.5, 45.5, 62.4, 71.6, 201.0.

High-resolution mass spectrum calculated for $C_7H_7O_2{}^{81}Br$, 203.9609; found, 203.9641. High-resolution mass spectrum calculated for $C_7H_7O_2{}^{79}Br$, 201.9629; found, 201.9620.

Anal. Calcd for $C_7H_7O_2Br$: C, 41.41; H, 3.48; Br, 39.35. Found: C, 42.19; H, 3.84; Br, 38.52.

Reaction of 5 with Excess DBU. Compound **5** (0.058 g, 0.287 mmol) was dissolved in 10 mL of dry THF and cooled to −78 °C under N_2. To the stirring solution was added dropwise 70 μL (0.070 g, 0.46 mmol) of DBU, and the mixture was stirred for 40 h. After the removal of solvent, the residue was extracted with dichloromethane (200 mL) and washed with 0.015 M hydrochloric acid (thrice) and then with saturated aqueous NaCl. The organic layer was dried, and then the solvent was evaporated on the rotary evaporator. The 360-MHz NMR of the product (obtained in 40% yield, 0.014 g) was compared with that of a commercial sample of *m*-hydroxybenzaldehyde and found to be identical.

Preparation of *endo*- and *exo*-3-Hydroxy-*trans*-6,7-dibromo-8-oxabicyclo[3.2.1]octanes (6). A solution of 0.284 g (1.0 mmol) of **4** in 20 mL of CH_2Cl_2 was treated with 0.0473 g (1.25 mmol) of solid $NaBH_4$ at room temperature under N_2, followed by sufficient 95% ethanol (ca. 15–20 mL) to just dissolve the solid. The homogeneous mixture was stirred for 21 h, treated with glacial acetic acid dropwise to destroy excess hydride, and stripped. The residue was extracted with dichloromethane, and this solution was washed with saturated aqueous $NaHCO_3$ (three times), water, and saturated aqueous NaCl. After the solution was dried ($MgSO_4$) and the solvent was removed, 0.235 g of a ca. 1:1 mixture of the exo and endo alcohols **6** was obtained as a yellow oil (82% yield). This was used directly in the next step: IR ($CHCl_3$) 3460–3520 (br), 3620 cm^{-1}. For the exo isomer: NMR ($CDCl_3$, 360 MHz) δ 1.56 (ddd, J = 3.7, 11.1, and 12.1 Hz, H-2_{endo}), 1.67 (m, H-4_{endo}), 2.03 (m, H-2_{exo}), 2.26 (br dd, J = 5.9 and 13.5 Hz, H-4_{exo}), 4.05 (m, H-3_{endo}, H-6_{exo}, and H-7_{endo}), 4.40 (m, H-1 and H-5). For the endo isomer: NMR ($CDCl_3$, 360 MHz) δ 1.87 (br d, J = 14.7 Hz, H-2_{endo}), 1.99 (ddd, J = 4.4, 4.4, and 14.7 Hz, H-2_{exo}), 2.07 (d of m, J = 15.9 Hz, H-4_{endo}), 2.15 (ddd, J = 4.5, 4.5, and 15.9 Hz, H-4_{exo}), 4.28 (dd, J = 4.5 and 4.5 Hz, H-3_{exo}), 4.40 (m, H-1, H-5, and H-6_{exo}), 5.03 (d, J = 5.1 Hz, H-7_{endo}). The mixture displayed broad absorptions at δ 1.87 and 2.00, both 1 H, for the hydroxyl protons.

Preparation of *endo*- and *exo*-3-Acetoxy-*trans*-6,7-dibromo-8-oxabicyclo[3.2.1]octanes (7). A solution of 0.286 g (1.0 mmol) of the crude mixture of alcohols **6** in 10 mL of CH_2Cl_2 was treated with 0.4 mL (5.0 mmol) of pyridine, followed by the dropwise addition of 0.47 mL (5.0 mmol) of acetic anhydride. The mixture was heated in a 130 °C bath for 1 h and then poured into ice–water. The mixture was extracted with dichloromethane, and the extracts were washed in turn with dilute aqueous HCl, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. After the solution was dried ($MgSO_4$) and the solvent was removed, 0.286 g of the mixture of *exo*- and *endo*-**7** was obtained as a pale yellow solid (87% yield). This crude mixture was used directly in the following step. Analytical samples of the two isomers were obtained by fractional recrystallization. The less soluble exo isomer was isolated by dissolution of the mixture in a minimum volume of dichloromethane, addition of excess pentane, and slow evaporation of the solvent mixture. The crystals obtained were washed with cold pentane. For *exo*-**7**: mp 155.5–157.5 °C; IR ($CHCl_3$) 1730 (br) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.72 (ddd, J = 3.7, 10.5, and 12.0 Hz, H-2_{endo}), 1.88 (m, H-4_{endo}), 2.04 (s, CH_3), 2.22 (br dd, J = 6.0 and 12.0 Hz, H-4_{exo}), 2.37 (dd, J = 6.0 and 13.0 Hz, H-2_{exo}), 4.27 (d, J = 3.5 Hz, H-7_{endo}), 4.51 (m, H-1, H-5, and H-6_{exo}), 5.17 (m, H-3_{endo}).

Anal. Calcd for $C_9H_{12}O_3Br_2$: C, 32.96; H, 3.69; Br, 48.72. Found: C, 33.20; H, 3.67; Br, 48.44.

The combined mother liquor and washings from the isolation of *exo*-**7** were evaporated and the residue was recrystallized from pentane to yield white crystalline *endo*-**7**: mp 96.0–97.5 °C; IR ($CHCl_3$) 1725 (br) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.94 (br d, J = 15.0 Hz, H-2_{endo}), 2.20 (m, H-2_{exo} and H-4_{exo}), 2.33 (br d, J = 16.0 Hz, H-4_{endo}), 4.35 (dd, J = 5.6 and 5.6 Hz, H-5), 4.51 (m, H-6_{exo} and H-1), 4.82 (d, J = 5.6 Hz, H-7_{endo}), 5.00 (dd, J = 5.4 and 5.4 Hz, H-3_{exo}).

High-resolution mass spectrum calculated for $C_9H_{12}O_3{}^{79}Br_2$, 325.9153; found, 325.9160.

***endo*- and *exo*-3-Acetoxy-6-bromo-8-oxabicyclo[3.2.1]-oct-6-enes (8).** A solution of 0.328 g (1.0 mmol) of **7** (mixture of isomers) in 10 mL of 1:1 ether–tetrahydrofuran was treated dropwise with 0.307 mL (2.05 mmol) of DBU at room temperature under N_2, and the mixture was refluxed for 22 h. After removal of the solvent, the gummy semisolid residue was taken up in dichloromethane, and the solution was washed successively with 0.015 M aqueous HCl (four times), saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. Drying the solution ($MgSO_4$) and removing the solvent left 0.242 g (98% yield) of the mixture of acetates **8** as a viscous yellow oil, which was used without further purification: IR ($CHCl_3$) 1600, 1730 cm^{-1}.

For purposes of NMR spectral assignment, small samples of purified *endo*- and *exo*-**7** were separately converted into *endo*- and *exo*-**8**. For *endo*-**8**: yellow oil; NMR ($CDCl_3$, 360 MHz) δ 1.62 (d of m, J = 15.2 Hz, H-2_{endo}), 1.89 (d of m, J = 15.3 Hz, H-4_{endo}), 2.03 (s, CH_3), 2.12 (ddd, J = 3.6, 5.5, and 15.3 Hz, H-4_{exo}), 2.23 (ddd, J = 3.9, 5.6, and 15.2 Hz, H-2_{exo}), 4.47 (br d, J = 3.6 Hz, H-5), 4.73 (m, H-1), 5.09 (m, H-3_{exo}), 6.29 (d, J = 1.3 Hz, H-7). For *exo*-**8**: a yellow oil; NMR ($CDCl_3$, 360 MHz) δ 1.69 (m, H-2_{endo} and H-4_{endo}), 2.03 (m, CH_3 and H-2_{exo}), 2.14 (dd of m, J = 6.5 and 13.0 Hz, H-4_{exo}), 4.60 (dd, J = 1.8 and 3.6 Hz, H-5), 4.77 (m, H-1), 4.99 (m, H-3_{endo}), 6.24 (d, J = 2.0 Hz, H-7).

High-resolution mass spectrum calculated for $C_9H_{11}O_3{}^{81}Br$, 247.9871; found, 247.9924. High-resolution mass spectrum calculated for $C_9H_{11}O_3{}^{79}Br$, 245.9891; found, 245.9902.

Anal. Calcd for $C_9H_{11}O_3Br$: C, 43.75; H, 4.49; Br, 32.34. Found: C, 45.48; H, 4.86; Br, 30.35.

6-Bromo-8-oxabicyclo[3.2.1]oct-6-en-3-one (10). The mixture of acetates **8** (0.247 g, 1.0 mmol) dissolved in 20 mL of ether was added dropwise to a mixture of 0.076 g of $LiAlH_4$ (2.0 mmol) in 10 mL of ether. After the mixture was stirred for 8 h at room temperature under N_2, the excess hydride was decomposed with 15% aqueous NaOH. The reaction mixture was taken up in dichloromethane and filtered through Celite, and the filtrate was dried ($MgSO_4$) and stripped, leaving 0.199 g of the mixture of the corresponding alcohols **9** as a yellow oil (97% yield). This mixture was converted directly to **10** without further purification: IR ($CHCl_3$) 1600, 3440–3520 (br), 3620 cm^{-1}.

For the endo isomer: NMR ($CDCl_3$, 90 MHz) δ 1.3–1.7 (m, 2 H), 1.7–2.2 (m, 2 H), 3.0 (br s, 1 H), 3.75 (br m, 1 H), 4.50 (m, 1 H), 4.68 (m, 1 H), 6.09 (d, J = 2.0 Hz, 1 H).

For the exo isomer: NMR ($CDCl_3$, 90 MHz) δ 1.3–1.7 (m, 2 H), 1.9–2.4 (m, 3 H), 4.02 (br m, 1 H), 4.40 (m, 1 H), 4.68 (m, 1 H), 6.31 (d, J = 2.0 Hz, 1 H).

A suspension of 0.324 g (1.5 mmol) of pyridinium chlorochromate and 0.0245 g (0.3 mmol) of sodium acetate (anhydrous) in 2 mL of CH_2Cl_2 was treated at 0 °C with a solution of 0.1989 g (0.97 mmol) of alcohol mixture **9** in 2 mL of CH_2Cl_2. After 1 h at 0 °C, the mixture was allowed to stir at room temperature for 3 h. The organic layer was decanted, and the black residue was extracted with 4 × 10 mL of ether. Filtration of the extracts through Florisil, followed by evaporation, left 0.1634 g of a creamy white solid (83% yield): mp 89.0–90.0 °C (from petroleum ether); IR ($CHCl_3$) 1600, 1710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.35 (d, J = 16.6 Hz, H-2_{endo}), 2.58 (d, J = 16.8 Hz, H-4_{endo}), 2.72 (m, H-2_{exo} and H-4_{exo}), 4.83 (dd, J = 0.8 and 4.9 Hz, H-5), 5.03 (ddd, J = 0.8, 1.8, and 4.9 Hz, H-1), 6.33 (d, J = 1.8 Hz, H-7).

High-resolution mass spectrum calculated for $C_7H_7O_2{}^{79}Br$, 201.9629; found: 201.9634.

Anal. Calcd for $C_7H_7O_2Br$: C, 41.41; H, 3.48; Br, 39.35. Found: C, 41.47; H, 3.53; Br, 39.08.

Acknowledgment. We thank Profs. C. Heathcock, M. J. Kurth, R. B. Miller, and G. Zweifel for helpful discussions. The 360-MHz NMR measurements were made by B. LaBelle and M. Knudsen on a Nicolet NT-360 instru-

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Registry No. **2**, 40458-77-3; **4**, 87615-78-9; **5**, 87615-79-0; *endo*-**6**, 87615-80-3; *exo*-**6**, 87679-02-5; *endo*-**7**, 87615-81-4; *exo*-**7**, 87679-03-6; *endo*-**8**, 87615-82-5; *exo*-**8**, 87615-83-6; *endo*-**9**, 87615-84-7; *exo*-**9**, 87615-85-8; **10**, 87615-86-9; *m*-hydroxybenzaldehyde, 100-83-4.

Chiral Acetylenes as Synthetic Intermediates. 4.[1] Synthesis and Chiroptical Properties of Optically Active α,β-Acetylenic Ketones

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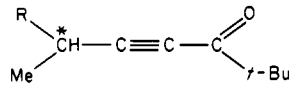
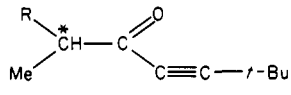
The preparation of some optically active α,β-acetylenic ketones from chiral 1-alkynes or acid chlorides is reported along with the evaluation of the stereospecificity of the synthetic methods adopted. For the compounds prepared, the CD spectra are presented and discussed; Cotton effects are observed in correspondence with the n → π* and π → π* transitions. In agreement with previous hypotheses, another electronic transition at ~250 nm is also measured in the CD spectra of the title compounds.

1-Alkynyl ketones are extremely versatile substrates for several organic syntheses as the acetylenic unit provides a convenient handle which may be converted into a variety of functionalities. Specifically, they are precursors of the corresponding 1-alkynyl carbinols, which are useful intermediate building blocks of various natural products.[2] Thus, numerous methods for carrying out the preparation of α,β-acetylenic ketones have been reported.[3-6] Our interest in this class of compounds derives from the possibility of preparing optically active α,β-acetylenic ketones. The availability of such compounds should permit their use in the synthesis of optically active heterocycles[7] and should offer some information about their chiroptical properties, which to date have received no attention.

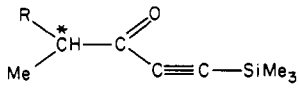
We report here the synthesis and the chiroptical properties of a series of optically active α,β-acetylenic ketones **1–3**.



1a,b



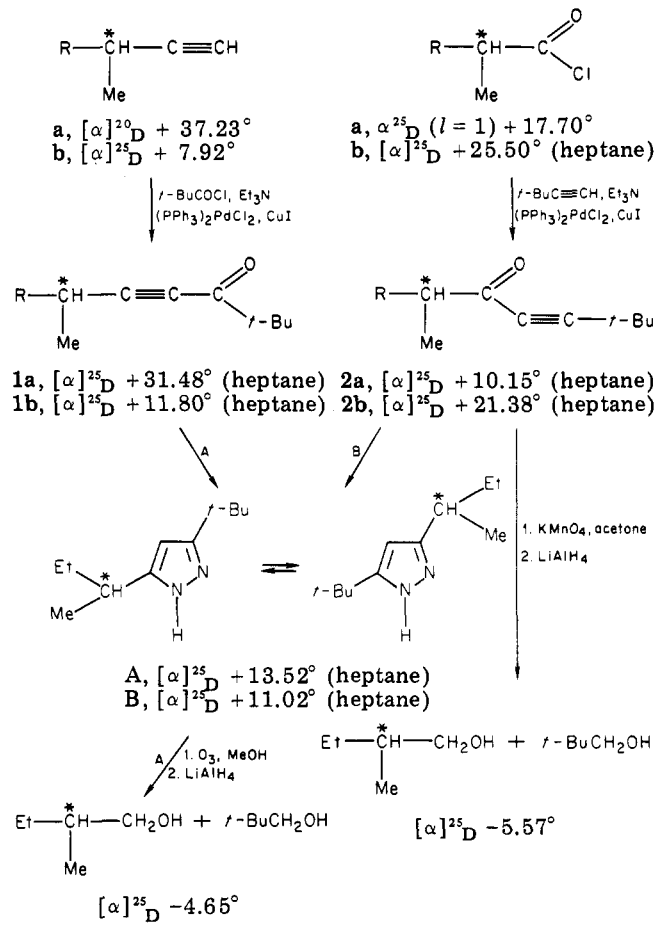
2a,b



3a,b

a, R = Et; b, R = *t*-Bu

Scheme I



Results and Discussion

Synthesis of the Optically Active α,β-Acetylenic Ketones 1–3. Since optically active acyl chlorides and 1-alkynes were readily available,[7,8] we looked for a route

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