C, 64.70; H, 3.95. Found: C, 64.35; H, 3.80.

α-(Z)-(Tetrahydrofuran-2-ylidene)-γ-butyrolactone (23). The reaction of 1 (0.03 mol) and γ-butyrolactone (**21**) (2.58 g, 0.03 mol) in 50 mL of benzene at 150 °C for 8 h in a sealed tube gave 1.42 g (31%) of **23**: mp 81–82 °C (from benzene–hexane) (lit.[16] mp 86.5 °C); IR (Nujol) 1740 (C=O) and 1650 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.85–2.39 (m, 2 H, methylene protons), 2.70–3.30 [m, 4 H, C=C(-O-)CH_2 + C=C(CO)CH_2], and 4.30 (t, 4 H, OCH_2); NMR (C_6D_6) δ 1.05–1.62 (m, 2 H, methylene protons), 2.25–2.66 [m, 2 H, C=C(-O-)CH_2], 2.70–3.05 [m, 2 H, C=C(CO)CH_2], and 3.40–3.80 (m, 4 H, OCH_2); mass spectrum (70 eV) *m/e* 154 (M^+). Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.98; H, 6.29.

The stereochemistry of **23** was determined on the basis of upfield shifts of all protons by a change of solvent from $CDCl_3$ to benzene-d_6 in the NMR spectrum.[2]

Registry No.—**1**, 52217-10-4; **2**, 85-44-9; **3**, 5698-59-9; **4a**, 65652-15-5; **4b**, 65652-16-6; **5**, 65652-17-7; **6**, 703-59-3; **7**, 65652-18-8; **8**, 118-48-9; **9**, 65652-19-9; **10**, 65701-66-8; **11**, 10328-92-4; **12a**, 65701-67-9; **12b**, 65682-25-9; **13**, 65652-20-2; **17a**, 6285-99-0; **17c**, 24186-31-0; **17d**, 21681-63-0; **18a**, 4478-63-1; **18b**, 7570-86-7; **19a**, 65652-21-3; **19b**, 65652-22-4; **20**, 2171-74-6; **21**, 96-48-0; **22**, 65652-23-5; **23**, 65652-24-6; *N*-ethylisatoic anhydride, 50332-68-8; 6,12-diphenyl-1,8-dioxo-2,9-dioxadespiro[4.1.4.1]dodecane, 65652-25-7.

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Chemistry of Carbanions. 32. Formation of the Perhydroazulene System by Intramolecular Alkylation[1]

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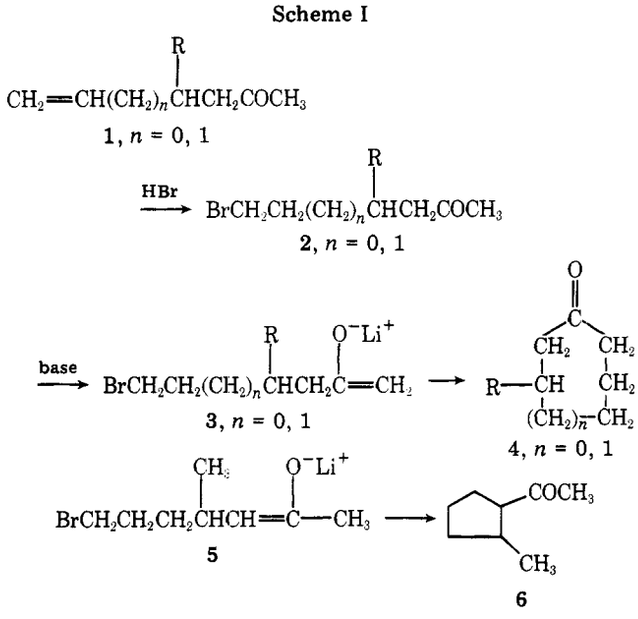
A synthetic route (Schemes II and III) for the formation of the perhydroazulene derivative **10** has been developed based upon the intramolecular cyclization of the bromo enolate **8** formed by the kinetic deprotonation of the bromo ketone **7**. Reaction of this bromo ketone with base under equilibrating conditions (KOBu-*t* in *t*-BuOH) yields the alternative cyclization product **19**. In seeking efficient synthetic routes to the intermediate unsaturated ketone **14**, we attempted to prepare the reagent $Br(CH_2)_3Li$; although this reagent could apparently be generated even at −110 °C in Et_2O–hexane solution, the material decomposed too rapidly to be useful.

In previous papers,[2,3] we have described general procedures for the formation of unsaturated ketones **1** (Scheme I) and the conversion of these intermediates **1**, via the bromo ketones **2** and the enolates **3**, to six- and seven-membered cyclic ketones **4**. In this earlier study, the cyclization of the bromo ketone **2** (R = CH_3, n = 1) to the seven-membered ketone **4** was complicated by the competing formation of the cyclopentyl ketone **6** (40% of the monomeric product). This competing cyclization **2** → **6** was attributed to a combination of three factors: (1) kinetically controlled deprotonation of methyl *n*-alkyl ketones with the hindered base *i*-Pr_2NLi typically forms 80–85% of the terminal enolate (e.g., **3**) accompanied by 15–20% of the internal enolate (e.g., **5**);[4] (2) the reaction of internal enolates (e.g., **5**) with alkyl halides is usually more rapid than the corresponding reaction with terminal enolates (e.g., **3**) that are presumably more highly aggregated;[4,5] (3) intramolecular alkylation to form five-membered rings is more rapid than the analogous reaction to form seven-membered rings.[6] This latter unfavorable rate factor is further enhanced in the present case because the cyclization **3** → **4** (n = 1) requires the additional strain of incorporating a planar enolate system into the cyclic transition state[3] while the cyclization **5** → **6** does not have this unfavorable requirement. The relatively slow rate of cyclization **3** → **4** (n = 1) allowed sufficient time for competing enolate equilbration **3** ⇌ **5** so that a significant amount of the unwanted cyclopentane by-product **6** was produced.

Scheme I



It was apparent that certain of the aforementioned difficulties associated with an intramolecular cyclization to form a cycloheptanone derivative could be mitigated by cyclization of a bromo ketone of the type **7** (Scheme II). In such cases,

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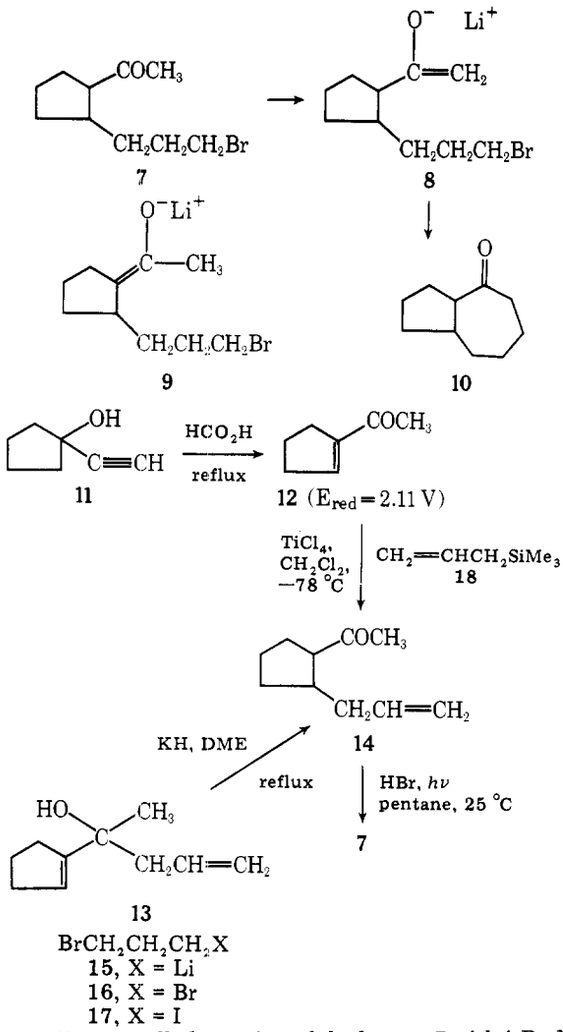
Scheme II



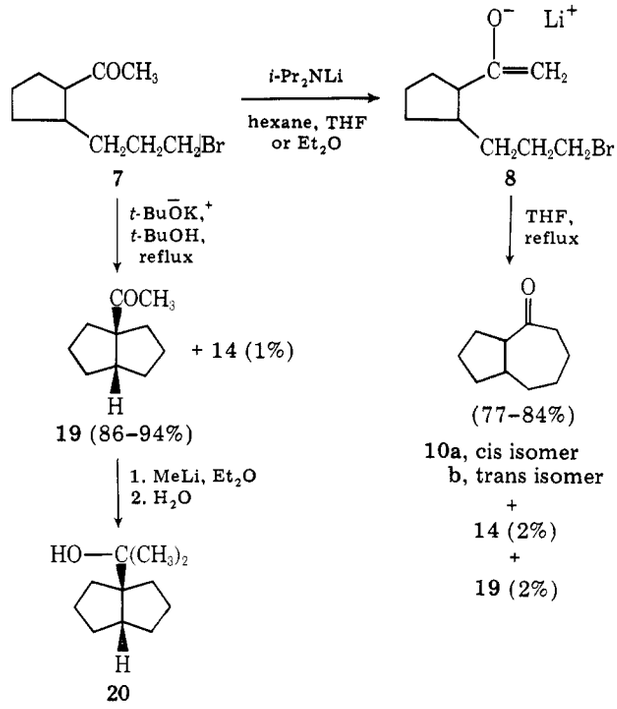
$BrCH_2CH_2CH_2X$
15, X = Li
16, X = Br
17, X = I

kinetically controlled reaction of the ketone **7** with *i*-Pr_2NLi to form a terminal enolate **8** rather than a fully substituted internal enolate **9** is more regiospecific (typically forming >95% of the terminal enolate).[4] Also, attachment of the two reacting functionalities to a preformed ring favors the proximity of the two reacting centers and can be expected[3] to increase the rate of cyclization.

To obtain the desired bromo ketone **7**, the acetylenic carbinol **11** was isomerized with boiling HCO_2H[7] to form the enone **12**. From consideration of the reduction potential (−2.11V vs. SCE in DMF solution) of the enone **12**, conjugate addition of $(allyl)_2CuLi$ to this substrate **12** to form the olefinic ketone **14** would be expected to be only marginally satisfactory.[8] In fact, reaction of $(allyl)_2CuLi$ with this enone **12** produced a mixture of the ketone **14** (29%), the enone **12** (11–24%, from enolate formation), and the alcohol **13** (31%). A more satisfactory synthetic route involved conversion of the enone **12** to the alcohol **13** (83% yield) with the allyl Grignard reagent followed by a base-catalyzed[9] oxy-Cope rearrangement of the alcohol **13** to form the ketone **14** in 78% yield. A still more efficient synthetic route involved direct reaction of the enone **12** with $CH_2{=}CHCH_2SiMe_3$ (**18**) and $TiCl_4$[10] to form the ketone **14** in 83–94% yield. The usual[2] light-induced free-radical addition of HBr to the olefinic ketone **14** (a mixture of stereoisomers) in pentane solution formed the bromo ketone **7** (a mixture of stereoisomers) in 88% yield.

We also examined one other possible procedure for the direct conversion of the enone **12** to the bromo ketone **7**. The reduction potential of the enone **12** is sufficiently positive that the conjugate addition of organocuprates derived from *n*-alkyllithium reagents would be a satisfactory synthetic procedure.[8] (For example, Me_2CuLi readily gives a conjugate addition product with the enone **12**.[3]) Consequently, if the cuprate reagent $(BrCH_2CH_2CH_2)_2CuLi$[11] could be prepared, such a reagent would offer a direct method for the conversion of the enone **12** to the bromo **7**. To explore the possibility of forming the lithium reagent **15**, we examined the behavior of mixtures of *n*-BuLi and the dihalides **16** and **17** in Et_2O–hexane mixtures at low temperatures.[12] Although, as would be expected from earlier work,[13] little if any metal–halogen exchange was observed with the dibromide **16** and *n*-BuLi at −78 °C, the corresponding exchange with *n*-BuLi and the bromoiodide **17** was relatively rapid both at −78 and at −110 °C. Unfortunately, even at −110 °C the decomposition of the lithium reagent **15** (presumably to form cyclopropane) was also rapid. Thus, protonation of the reaction mixtures at −110 °C led to the recovery of *n*-BuI (from lithium–iodine exchange) and a small amount of unchanged dihalide **17** but no *n*-PrBr (the product expected from protonation of **15**).

Scheme III



Conversion of the bromo ketone **7** to its enolate under equilibrating conditions (*t*-BuOK in *t*-BuOH) resulted in a relatively rapid conversion to the methyl ketone **19** (86–94%, Scheme III) with none of the seven-membered cyclic product **10** being detected. This result is, of course, compatible with the idea that the intramolecular reaction **9** → **19** to form a five-membered ring is faster than cyclization **8** → **10** to form a seven-membered ring. The structure and stereochemistry of methyl ketone **19** were confirmed by its conversion to the known alcohol **20**.[14] As we had hoped, kinetic deprotonation of the bromo ketone **7** with *i*-Pr_2NLi exhibited high regiospecificity to form the terminal enolate **8** and, after cyclization, the ketone **10**. Under the best conditions we found (refluxing THF) for cyclization of the enolate, the yields were 77–84% of the desired ketone **10** (a mixture of cis and trans isomers), 2% of the isomeric ketone **19**, and 2% of the dehydrobromination product **14**. When the previously described[3] cyclization conditions (Et_2O–hexane + 4 molar equiv of HMP at 25 °C) were used, the yields of monomeric products were lower (67% **10**, 6% **14**, and 3% **19**) and more high molecular weight by-products (presumably from competing intermolecular alkylation)[3] were formed. When the reaction solvent was either boiling THF or boiling DME, the addition of 4 molar equiv of HMP to coordinate with the Li^+ cation was unnecessary.

In summary, we may conclude that the synthetic route **12** → **14** → **7** → **10** constitutes an efficient and useful route to perhydroazulene derivatives.[15] Furthermore, the high yield obtained in the final intramolecular alkylation step **7** → **10** indicates that, with appropriate substitution to disfavor formation of the isomeric five-membered ring product (e.g., **7** → **19**), this intramolecular alkylation reaction can be a useful method for the formation of cycloheptanone derivatives.

Experimental Section[16]

Preparation of the Enone 12. Our previously described[3] procedure for the HCO_2H-catalyzed isomerization of the acetylenic carbinol **11** to the enone **12** was improved by adding 15.88 g (0.14 mol) of the carbinol **11**, dropwise and with stirring during 50 min, to 150 mL of refluxing 92% HCO_2H. After the addition was complete, the purple reaction mixture was refluxed for an additional 10 min and then partitioned between pentane and aqueous $NaHCO_3$ containing excess solid $NaHCO_3$ to neutralize the HCO_2H. The organic layer was dried, concentrated, and distilled to separate 9.51 g (60%) of the enone **12**, bp 70 °C (18 mm), n^{25}_D 1.4771–1.4781 [lit.[7] bp 67° (16 mm), n^{23}_D 1.4776] with IR absorption corresponding to that previously described.[3] Solutions in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 and 1.2×10^{-3} M enone **12** exhibited a polarographic $E_{1/2}$ value[17] of −2.11 V vs. SCE (n = 1.0, i_d = 51 μA).

Preparation of the Alcohol 13. To a cold (4 °C) solution containing 88.5 mmol of CH_2=$CHCH_2MgBr$ in 200 mL of Et_2O was added, dropwise with stirring and cooling during 30 min, a solution of 8.12 g (73.8 mmol) of the enone **12** in 40 mL of Et_2O. After the addition was complete, the cooling bath was removed and the reaction solution was stirred for 2 h and then poured into an ice–H_2O mixture and extracted with Et_2O. After the ethereal solution had been washed with aqueous $NaHCO_3$, dried, and concentrated, distillation separated 9.29 g (83%) of the alcohol **13** as a colorless liquid: bp 76–78 °C (4.8 mm); n^{25}_D 1.4825–1.4837; IR (CCl_4) 3600, 3570 (OH), 1640 (C=C), and 922 cm^{-1} (CH=CH_2); UV (95% EtOH) end absorption with ε 102 at 210 nm; NMR (CCl_4) δ 4.7–6.0 (4 H, m, vinyl CH), 1.4–2.5 (9 H, m, CH_2 and OH), and 1.25 (3 H, s, CH_3); mass spectrum, m/e (rel intensity) 134 (2), 119 (3), 111 (40), 43 (100), 41 (13), and 39 (10). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.83; H, 10.62.

Preparation of the Olefinic Ketone 14. A. From the Alcohol 13. Following a previously described[9] general procedure, a mixture of 9.00 g (230 mmol) of KH (prewashed with pentane) and 290 mL of DME was treated, dropwise and with stirring during 20 min, with a solution of 11.44 g (75 mmol) of the alcohol **13** in 30 mL of DME. After the resulting mixture had been stirred at 25 °C for 2 h (most of the KH had reacted) it was refluxed for 2.5 h at which time TLC and GLC analysis of an aliquot indicated that the rearrangement was complete. After the reaction mixture had been cautiously siphoned into aqueous NH_4Cl, the combined organic layer and Et_2O extract of the aqueous phase were washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. The residual crude liquid product (11.30 g) was fractionally distilled to separate 508-mg of fractions, bp 80–91 °C (14 mm), n^{25}_D 1.4540–1.4601, containing the ketone **14** and lower boiling impurities. Later distillation fractions contained (GPC) 8.90 g (78%) of the ketone **14** (a mixture of stereoisomers): bp 91–93 °C (14 mm); n^{25}_D 1.4605; IR (CCl_4) 1712 (C=O), 1641 (C=C), and 922 cm^{-1} (CH=CH_2); UV_{max} (95% EtOH) 281 nm (ε 24); NMR (CCl_4) δ 4.7–6.1 (3 H, m, vinyl CH), and 1.0–3.2 (13 H, m, aliphatic CH including a CH_3CO singlet at 2.06); mass spectrum, m/e (rel intensity) 152 (M^+, 1), 137 (3), 109 (17), 94 (12), 79 (14), 71 (19), 67 (29), 43 (100), 41 (18), and 39 (12). The ketone **14** exhibited GPC peaks (UCON 50HB280X on Chromosorb P) for the two stereoisomers at 14.9 and 15.9 min; the corresponding retention time for the enone **12** (a by-product in the rearrangement) was 7.7 min. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.90; H, 10.61.

B. From the Enone 12. Following a literature procedure,[18a] a solution of 73.8 g (0.61 mol) of CH_2=$CHCH_2Br$ and 66.3 g (0.61 mol) of Me_3SiCl in 200 mL of Et_2O was added to 38.61 g (1.59 g-atom) of Mg in 400 mL of refluxing Et_2O during 4 h and the resulting mixture was refluxed for an additional 1 h and then allowed to stand overnight. After the mixture had been filtered and then partitioned between pentane and aqueous NH_4Cl, the organic solution was washed with H_2O, dried, and concentrated. Distillation separated 57.0 g (82%) of the silane **18** as a colorless liquid: bp 85–86 °C; n^{25}_D 1.4052 [lit. bp 86 °C,[18a] n^{20}_D 1.4074[18b]]; IR (CCl_4) 1632 (C=C) and 902 cm^{-1} (CH=CH_2); NMR (CCl_4) δ 4.5–6.1 (3 H, m, vinyl CH), 1.44 (2 H, d, J = 8 Hz, CH_2), and 0.00 (9 H, s, MeSi); mass spectrum, m/e (rel intensity) 114 (M^+, 4), 99 (10), 73 (100), 59 (16), 45 (18), and 43 (10).

Following a previously described[10] procedure, a cold (−78 °C) solution of 4.95 g (45 mmol) of the enone **12** in 100 mL of anhydrous CH_2Cl_2 was treated, dropwise and with stirring, with 8.54 g (45 mmol) of $TiCl_4$. The resulting slurry of a yellow solid was stirred at −78 °C for 5 min and then a solution of 6.3 g (55 mmol) of the silane **18** in 70 mL of CH_2Cl_2 was added, dropwise and with stirring during 30 min at −78 °C. The resulting purple solution was stirred at −78 °C for an additional 30 min and then 50 mL of H_2O was added, dropwise and with striring, to the cold solution. After the resulting colorless mixture had warmed to 25 °C, the organic layer was separated, combined with the Et_2O extract of the aqueous phase, dried, and concentrated. After an aliquot of the crude yellow liquid product (11.55 g) had been mixed with an internal standard (1,3,5-triisopropylbenzene), GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of 1,3,5-triisopropylbenzene (retention time 9.8 min) and the olefinic ketone **14** (13.2 min, 94% yield). The remaining crude product was chromatographed on silica gel with an Et_2O–pentane elutent (1:4 v/v) and the eluted ketone **14** fractions (5.85 g) were distilled to separate 5.65 g (83%) of the olefinic ketone **14**, bp 84.5–85 °C (10 mm), n^{25}_D 1.4609.

Several comparable small-scale experiments were performed at different reaction temperatures and the yield of ketone **14** was determined by GPC analysis. When the reactants were mixed and stirred for 30 min at −78 °C and then allowed to warm to 25 °C and stir overnight, the initial purple solution changed to a deep red colored solution and the yield (GLC) of ketone **14** was 61%. When the reactants were mixed at 25 °C and then stirred for 5 min a deep red solution was obtained immediately and the yield (GLC) of ketone **14** was only 48%.

C. From the Enone 12 and Lithium Diallylcuprate. To a cold (−72 °C) partial solution of 3.94 g (19.1 mmol) of freshly recrystallized[8] Me_2SCuBr in 57 mL of Et_2O and 57 mL of Me_2S was added, dropwise and with stirring at −70 to −72 °C during 20 min, 60 mL of ethereal solution containing 38.4 mmol of CH_2=$CHCH_2Li$ (from CH_2=$CHCH_2OPh$[8]). During this addition the reaction mixture was deep red in color during the first part of the addition and became a pale orange *solution* as the second equivalent of the lithium reagent was added. A solution of 1.057 g (9.6 mmol) of the enone **12** in 20 mL of Et_2O was added, dropwise and with stirring during 20 min, to the cold (−70 to −73 °C) reaction solution with the accompanying reappearance of the red color in the reaction mixture. After the red reaction solution had been warmed to −50 °C during 30 min and then stirred at −40 to −50 °C for 75 min, the mixture was hydrolyzed at −40 °C by the dropwise addition of a solution of 10 mL of HOAc in 100 mL of Et_2O. The resulting mixture was washed successively with an aqueous solution (pH 8) of NH_3 and NH_4Cl, with aqueous 10% NaOH, and with aqueous NaCl and then dried and concentrated. A 223-mg aliquot of the crude liquid product (3.16 g) was mixed with n-$C_{15}H_{32}$ (an internal standard) for GLC analyses [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The product contained (GLC) the enone **12** (retention time 9.2 min, 24% yield), the cis and trans isomers of ketone **14** (15.1 and 16.3 min, total yield 24%), a peak corresponding to the alcohol **13** (or its dehydration product, 22.2 min), and n-$C_{15}H_{32}$ (27.7 min). Collected (GLC) samples of ketones **12** and **14** were identified with authentic samples by comparison of IR and NMR spectra. The remaining crude product was chromatographed on silica gel with Et_2O–hexane mixtures as the eluent to separate, in order of elution, 390 mg (29%) of the ketone **14**, n^{25}_D 1.4616, 142 mg (11%) of the enone **12**, n^{25}_D 1.4793, and 421 mg (31%) of the alcohol **13**, n^{25}_D 1.4823 (identified with the previous sample by comparison of IR and NMR spectra).

Preparation of the Bromo Ketone 7. A solution of 1.00 g (6.6 mmol) of the olefinic ketone **14** in 300 mL of anhydrous, olefin-free pentane was irradiated with the light from a Hanovia 450-W medium-pressure Hg lamp for 6.5 min while a stream of anhydrous HBr gas was passed through the reaction solution. The resulting pentane solution was washed successively with aqueous $Na_2S_2O_3$, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried and concentrated. Distillation afforded 1.37 g of crude product as a brown liquid, bp 82–86 °C (0.05 mm). Redistillation separated 1.34 g (88%) of the pure bromo ketone **7** (presumably a mixture of stereoisomers) as a colorless liquid: bp 76 °C (0.02 nm); n^{25}_D 1.4926–1.4928; IR (CCl_4) 1711 cm^{-1} (C=O); NMR (CCl_4) δ 3.34 (2 H, t, J = 6 Hz, CH_2Br), and 1.0–2.6 (15 H, m, aliphatic CH including a CH_3CO singlet at 2.09); mass spectrum, m/e (rel intensity) 234 (M^+, 0.3), 232 (M^+, 0.3), 153 (9), 111 (33), 109 (20), 71 (30), 67 (28), 43 (100), and 41 (20). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.35; Br, 34.27. Found: C, 51.52; H, 7.39; Br, 34.18.

Cyclization of the Bromo Ketone 7. A With KOBu-*t*. To a solution of KOBu-*t*, from 0.78 g (20 mg-atom) of K and 40 mL of *t*-BuOH, was added, dropwise and with stirring during 10 min, a solution of 4.66 g (20 mmol) of the bromo ketone **7** in 40 mL of pentane.

The resulting mixture was stirred at 25 °C for 30 min and at reflux for an addition 60 min to complete the reaction. After the reaction mixture had been partitioned between Et_2O and H_2O, the organic layer was dried and concentrated. A 50.2-mg aliquot of the crude liquid product (17.75 g) was mixed with 35.0 mg of 1-phenyloctane for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained low-boiling materials, the unsaturated ketone **14** (1% yield, retention time 9.0 min), the ketone **19** (94% yield, 12.0 min), and 1-phenyloctane (17.4 min) but lacked GLC peaks corresponding to the trans ketone **10b** (24.1 min) and the cis ketone **10a** (21.7 min). The remaining crude product was distilled to separate *t*-BuOH and then chromatographed on silica gel with an Et_2O–pentane eluent (1:19 v/v). The colorless fractions (2.62 g) containing the ketone **19** were combined and distilled to separate 2.60 g (86%) of the ketone **19** as a colorless liquid: bp 89–89.5 °C (10 mm); $n^{25}D$ 1.4762; IR (CCl_4) 1699 cm^{-1} (C=O); NMR (CCl_4) δ 2.5–3.0 (1 H, m, CH) and 1.1–2.3 (15 H, m, aliphatic CH including a CH_3CO singlet at 2.07); mass spectrum, *m/e* (rel intensity) 152 (M^+, 3), 137 (35), 111 (25), 109 (100), 67 (90), 55 (24), 43 (46), 41 (23), and 39 (23). Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.87; H, 10.62.

To confirm the structure and stereochemistry of the ketonic product, a solution of 1.52 g (10 mmol) of the ketone **19** in 10 mL of Et_2O was added, dropwise and with stirring during 30 min, to a cold (−78 °C) solution of 10 mmol of MeLi in 17 mL of Et_2O. The resulting solution was allowed to warm to 25 °C with stirring during 30 min and then stirred at 25 °C for 20 min and added to aqueous $NaHCO_3$. After the mixture had been extracted with Et_2O, the ethereal extract was dried and concentrated to leave 1.52 g of crude liquid product that contained (GLC, XE-60 on Chromosorb P) the starting ketone **19** (retention time 13.8 min, ca. 15%) and the alcohol **20** (16.8 min, ca. 85%). Collected (GLC) samples of both products were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. Chromatography of the crude product on silica gel with an Et_2O–hexane eluent (1:9 v/v) separated 0.24 g (14%) of early fractions containing the ketone **19** and 1.22 g (73%) of later fractions containing the alcohol **20.** Distillation afforded 1.19 g (71%) of the pure alcohol **20** as a colorless liquid: bp 90–90.5 °C (4.5 mm); $n^{25}D$ 1.4873; IR (CCl_4) 3610 and 3490 cm^{-1} (OH); NMR (CCl_4) δ 2.1–2.4 (1 H, m, CH) and 1.0–2.1 [19 H, m, OH and aliphatic CH including a $(CH_3)_2C$ singlet at 1.15]; mass spectrum, *m/e* (rel intensity) 153 (2), 135 (17), 108 (31), 82 (26), 79 (27), 67 (46), 59 (100), 58 (28), 43 (42), 41 (44), and 39 (23). Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.53; H, 12.02.

Our product was identified with a previously reported[14] sample of the alcohol **20** by comparison of IR and NMR spectra.

B. With *i*-Pr_2NLi. To a cold (−72 °C) solution, prepared by adding a solution[3] of 33.3 mmol of *i*-Pr_2NLi in 62 mL of hexane to 350 mL of cold THF, was added, dropwise with stirring and cooling during 20 min, a solution of 6.43 g (27.7 mmol) of the bromo ketone **7** in 50 mL of THF. The resulting solution was warmed to boiling during 15 min and then refluxed for 2 h. After the solution had been cooled, it was siphoned into aqueous NH_4Cl and then extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl and then dried and concentrated. An aliquot of the residual liquid (7.08 g) was mixed with a known weight of 1-methylnaphthalene (an internal standard) for GLC analysis [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The crude product contained (GLC) the unsaturated ketone **14** (retention time 6.8 min, 2% yield), the ketone **19** (9.0 min, 1% yield), a mixture of the stereoisomeric ketones **10** (19.6 min for cis isomer **10a** and 22.0 min for trans isomer **10b,** 84% yield), 1-methylnaphthalene (31.8 min), and a series of minor (<2%) unidentified components (3.7, 5.4, 14.1, and 15.9 min). Distillation separated 3.73 g of distillate, bp 100–103 °C (8 mm), containing (GLC) 92% of the ketone **10** (corresponds to an 84% yield) from 0.42 g of higher molecular weight residue (presumably from competing intermolecular alkylation[3]). The distillate was subjected to low-pressure liquid chromatography on silica gel with Et_2O–hexane mixtures as the eluent. Early fractions (278 mg) contained (GLC) mixtures of ketones **14, 19,** and other minor unidentified impurities. Samples of ketones **14** and **19** collected (GLC) from these fractions were identified with authentic samples by comparison of GLC retention times and IR, NMR, and mass spectra. Subsequent chromatographic fractions contained (GLC) 191 mg of a mixture of the cis ketone **10a** and several more rapidly eluted components, 1.94 g of a mixture of cis and trans ketones **10** and 1.32 g of the trans ketone **10b.** The intermediate fractions were rechromatographed twice on silica gel to separate an additional 1.12 g (total yield 2.44 g) of pure trans ketone **10b** and 762 mg of pure cis ketone **10a** as well as fractions containing mixtures of both stereoisomers.

Table I. Cyclization of the Lithium Enolate 8

Solvents	Temp, °C	Time, min	Product yields, % 10	14	19
Hexane, Et_2O, HMP	25	90	67	6	3
Hexane, DME, HMP	84	60	67	4	1
Hexane, DME	84	60	68	4	<1
Hexane, THF, HMP	65	50	79	2	2
Hexane, THF	65	120	77–84	2	1–2

Distillation of the fractions containing the cis isomer afforded 597 mg (14%) of the pure cis ketone **10a** as a colorless liquid: bp 92–97 °C; (6.5 mm); $n^{25}D$ 1.4878–1.4883; IR (CCl_4) 1702 cm^{-1} (C=O); UV_{max} (95% EtOH) 283 nm (ϵ 18); mass spectrum, *m/e* (rel intensity) 152 (M^+, 33), 111 (93), 108 (21), 95 (68), 81 (22), 67 (100), 55 (25), 41 (44), and 39 (25); ^1H NMR (CCl_4) δ 2.8–3.2 (1 H, m, CHCO) and 0.7–2.8 (15 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.8 (s), 54.5 (d), 43.1 (d), 40.3 (t), 35.1 (t), 32.4 (t), 27.7 (t), 26.2 (t), 25.4 (t), and 24.5 (t). Reaction of 0.20 g of the cis ketone **10a** with H_2NOH in boiling H_2O–EtOH for 10 min yielded 0.18 g of the cis oxime as white needles, mp 117–118 °C. Recrystallization from EtOH–H_2O raised the melting point of the cis oxime to 118–119 °C (lit.[19] mp 119 °C); IR (CCl_4) 3580 and 3250 cm^{-1} (OH) with no C=O absorption. Reaction of 31.8 mg of the ketone **10a** with 44.6 mg of 2,4-$(O_2N)_2C_6H_3NHNH_2$ in 5 mL of boiling EtOH containing ca. 0.2 mL of aqueous 12 M (HCl (the minimum required for reaction) for 15 min resulted in extensive epimerization of the cis ketone **10a** so that the major product was 48 mg of the crude 2,4-DNP of the trans ketone **10b,** mp 203–209 °C. Fractional crystallization from EtOH of the more soluble material in the mother liquor separated 2.6 mg of the 2,4-DNP of the cis ketone **10a** as yellow needles: mp 162–163 °C (lit.[20] mp 162–163 °C); UV_{max} (95% EtOH) 234 nm (ϵ 10 000) and 369 nm (ϵ 13 000).

Distillation of the chromatographic fractions containing the trans ketone separated 1.98 g (48%) of the pure trans ketone **10b** as a colorless liquid: bp 96–100 °C (7 mm); $n^{25}D$ 1.4867–1.4872; IR (CCl_4) 1701 cm^{-1} (C=O); UV_{max} (95% EtOH) 285 nm (ϵ 29); mass spectrum, *m/e* (rel intensity) 152 (M^+, 19), 111 (23), 95 (100), 67 (65), 55 (22), 41 (33), and 39 (20); ^1H NMR (CCl_4) δ 0.8–3.1 (m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 212.6 (s), 56.8 (d), 45.3 (d), 43.7 (t), 36.7 (t), 35.7 (t), 29.1 (t), 26.1 (t), 24.1 (t), and 23.5 (t). Reaction of 170 mg of the trans ketone **10b** with NH_2OH in boiling H_2O–EtOH for 10 min yielded 142 mg of the oxime as white needles from EtOH–H_2O: mp 138.5–140 °C (lit.[19] mp 140 °C); IR (CCl_4) 3580 and 3250 cm^{-1} (OH) with no C=O absorption. Reaction of 153 mg of the trans ketone **10b** with 2,4-$(O_2N)_2C_6H_3NHNH_2$ in 27 mL of boiling EtOH containing 0.5 mL of aqueous 12 M HCl for 15 min yielded 252 mg of the 2,4-DNP of the trans ketone **10b,** mp 215–218 °C. Two recrystallizations from EtOH afforded the 2,4-DNP as red-orange needles: mp 219–220 °C (lit.[20] mp 220°); UV_{max} (95% EtOH), 232 nm (ϵ 11 700) and 369 nm (ϵ 14 500). Previous physical constants reported for the ketone **10** (a mixture of stereoisomers) included: bp 92–93 °C (4.5 mm);[21] $n^{25}D$ 1.4862,[20] 1.4870,[21] and 1.4872;[22] IR 1702 cm^{-1};[21] UV_{max} (EtOH) 288 nm (ϵ 27);[21] and mass spectrum, 152 (M^+), 111 (56), 95 (100), and 67 (90).[23] The equilibrium composition of the ketone **10** stereoisomers is reported[24] to be 20% cis ketone **10a** and 80% trans ketone **10b.**

To determine the best conditions for the cyclization **8** → **10,** a series of small scale experiments were performed in which solutions of the enolate **8** were generated by adding the bromo ketone **7** to cold (−70 to −72 °C) solutions containing 1.2 equiv of *i*-Pr_2NLi in a mixture of hexane and Et_2O, THF, or DME. In certain cases, 4 molar equiv of $(Me_2N)_3PO$(HMP) per mol of enolate **8** was then added. The solutions were then stirred for the times and at the temperatures indicated in Table I and then subjected to the previously described isolation procedure. The crude neutral products were mixed with 1-methylnaphthalene (an internal standard) for GLC analysis. The yields of ketones **10, 14,** and **19** are summarized in Table I; the bulk of the remaining material in each reaction was higher molecular weight material (presumably from intermolecular alkylation reactions).

Preparation of the Dihalide 17. To a solution of 20.2 g (100 mmol) of the dibromide **16** in 100 mL of anhydrous acetone was added, dropwise and with stirring during 12 h, a solution of 15.0 g (100 mmol) of NaI in 100 mL of anhydrous acetone. The resulting yellow solution, containing a white precipitate (LiBr), was filtered, concentrated,

washed successively with aqueous $Na_2S_2O_3$ and with H_2O, and dried. Fractional distillation separated 8.6 g of liquid, bp 29–42 °C (1.1 mm) containing (NMR analysis) mainly the dihalide **16**, 14.2 g of liquid, bp 42–50 °C (1.1 mm), containing (NMR) mainly dihalide **17**, and 6.4 g of liquid, bp 55–63 °C (1.1 mm), containing (NMR) mainly 1,3-diiodopropane. Redistillation of the center fraction through a 60-cm Vigreux column separated 12.6 g (51%) of the dihalide **17** as a colorless liquid: bp 46–47 °C (1.1 mm); n^{25}_D 1.5820 [lit.[25] bp 88 °C (17.5 mm); n^{25}_D 1.5810]; NMR (CCl_4 δ 3.1–3.7 [4, m, overlapping triplets, J = 6 Hz, for CH_2I and CH_2Br] and 2.30 (2 H, quintuplet, J = 6 Hz, CH_2); mass spectrum, m/e (rel intensity) 250 (M^+, 100), 248 (M^+, 98), 204 (24), 202 (43), 200 (26), 169 (53), 155 (34), 141 (51), 128 (38), 127 (80), 124 (23), 123 (99), 122 (23), 121 (94), 95 (36), 93 (33), 42 (33), 41 (78), and 39 (49).

Reaction of *n*-BuLi with the Dihalide 17. Following a general halogen–lithium exchange procedure described previously,[13] a cold solution (−110 °C)[26] of 1.25 g (5.0 mmol) of the dihalide **17** in 25 mL of Et_2O was treated, dropwise and with stirring during 1 min, with 3.3 mL of a hexane solution containing 5.0 mmol of *n*-BuLi. The resulting solution was stirred at −110 °C for 2 h and then siphoned into a cold (−110 °C), rapidly stirred solution of 10 mmol of HOAc in 20 mL of Et_2O. The resulting solution was warmed to 0 °C and partitioned between Et_2O and aqueous $NaHCO_3$. After the organic solution had been dried and concentrated, an aliquot of the crude liquid product (3.17 g) was mixed with *n*-$C_{11}H_{24}$ for GLC analysis (silicone XE-60 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained *n*-BuI (retention time 13.4 min, 82% yield) and *n*-$C_{11}H_{24}$ (22.6 min) but no GLC peak was detected corresponding to *n*-PrBr (5.2 min). Analysis on the same GLC column at higher temperature with *n*-$C_8H_{17}Ph$ as the internal standard indicated the presence of the starting dihalide **17** (retention time 6.2 min, 3% recovery) and *n*-$C_8H_{17}Ph$ (21.0 min). Thus, we conclude that the dihalide **17** and *n*-BuLi underwent lithium–iodine exchange but that the organolithium reagent **15** was not stable at −110 °C in Et_2O. From a comparable experiment with *n*-BuLi and the dihalide **17** in Et_2O at −78 °C, the yields were 78% of *n*-BuI and 4% of the dihalide **17** and no GLC peak corresponding to *n*-PrBr was detected. A collected sample of *n*-BuI from this reaction were identified with an authentic sample by comparison of mass spectra. In a similar experiment employing an Et_2O solution of *n*-BuLi and the dibromide **16** at −78 °C, the bulk of the unchanged dibromide **16** was recovered. This result would be expected based on the earlier observation[13] that *n*-BuLi underwent rapid metal–halogen exchange with alkyl iodides but not with alkyl bromides.

Registry No.—*cis*-**7**, 65682-05-5; *trans*-**7**, 65682-06-6; **8**, 65682-07-7; **10a**, 5365-37-7; **10a** oxime, 5365-39-9; **10a** 2,4-DNP, 65682-00-0; **10b**, 5365-38-8; **10b** 2,4-DNP, 65682-01-1; **10b** oxime, 5365-40-2; **11**, 17356-19-3; **12**, 16112-10-0; **13**, 65682-08-8; *cis*-**14**, 65682-09-9; *trans*-**14**, 65682-10-2; **16**, 109-64-8; **17**, 22306-36-1; **18**, 762-72-1; **19**, 65682-11-3; **20**, 62726-63-0; CH_2=$CHCH_2Br$, 106-95-6; 1,3-diiodopropane, 627-31-6.

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