Synthesis of Tricyclo[3.2.0.0^{2,7}]heptan-6-ones and Their Reaction with Nucleophiles[1]

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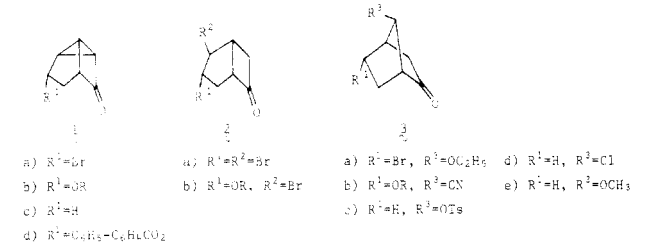
The synthesis of the title ring system from bicyclo[3.2.0]heptan-6-ones is described. Reactions of the tricyclic ketones with various nucleophiles are discussed. Generally, nucleophilic attack results in clean homoconjugate addition to give anti 7-substituted bicyclo[2.2.1]heptan-5-ones. An exception to this rule is seen with phenyllithium, with which 1,2-addition to the carbonyl occurs to give an alcohol in which the tricyclic skeleton is retained.

Introduction

The synthesis and chemical reactions of tricyclo[3.2.0.0^{2,7}]heptan-6-ones, **1**, have recently attracted interest, in particular as part of programs involving the eventual synthesis of prostanoids.[4] This paper provides full details of our previously reported work in this area[1] as well as results of some of our subsequent studies on this tricyclic system.



This type of ketone appears first to have been proposed as a reactive intermediate to rationalize phenomena associated with both bicyclo[3.2.0]heptan-6-ones (**2**) and bicyclo[2.2.1]heptan-2-ones (**3**). Thus, Dreiding and Mitch proposed that the course of the ethoxide-promoted conversion of *exo*-2-*endo*-3-dibromobicyclo[3.2.0]heptan-2-one (**2a**) to *anti*-7-ethoxy-*endo*-5-bromobicyclo[2.2.1]heptan-2-one (**3a**) involved formation of **1a**, which suffered stereoselective nucleophilic attack at C-1 to afford **3a**.[5] A similar sequence of events was subsequently postulated by Roberts for the conversion of **2b** to **3b** in methanolic sodium methoxide saturated with potassium cyanide, **1b** therein being the key intermediate.[6]

The bicyclo[2.2.1] system as a source of **1** was first considered by Gassman et al., who proposed that formation of the oxonium ion derived by protonation of **1** could explain the significantly enhanced rate of acetolysis of *anti*-7-(tosyloxy)bicyclo[2.2.1]heptan-2-one (**3c**) relative to the syn isomer,[7a] although they subsequently expressed favor for the nonclassical form of this ion as the critical intermediate.[7b] Simultaneously with Gassman's first report,[7a] Lumb and Whitham postulated production of the parent tricyclic ketone, **1c**, in order to rationalize the observation that treatment of the anti 7-chloro isomer, **3d**, with methoxide afforded *anti*-7-methoxybicyclo[2.2.1]-heptan-2-one (**3e**), whereas the syn isomer of **3d** failed to undergo this net nucleophilic substitution at all.[8] These authors proposed that **3d** first was transformed to its enolate, which then closed to **1c** by internal displacement of chloride. Methoxide subsequently converted **1c** to **3e** by nucleophilic attack at C-1. The analogous route is blocked in the syn isomer of **3d** owing to the failure of the internal nucleophilic substitution because of stereoelectronic factors.

Paquette et al. appear to be the first to have reported the actual isolation of a tricyclo[3.2.0.0^{2,7}]heptan-6-one.[9] They noted that reduction of the tetracyclic epoxide **4** with lithium in liquid ammonia gave **5**, which could be oxidized to the tricyclic ketone **6** with ruthenium oxide. Confirmation of the previously suspected susceptibility of such ketones to nucleophilic attack at C-1 was provided by the observation of these workers that treatment of **6** with lithium aluminum hydride provided the ring-opened alcohol **7** in over 60% yield.

The isolation of **6** encouraged us to undertake a rational synthesis and characterization of a less substituted example. Success in this venture was envisioned to have considerable synthetic potential given the facility and high regio- and stereoselectivity with which the tricyclic ketones, **1**, apparently underwent homoconjugate reaction with nucleophiles to yield anti 7-substituted bicyclo[2.2.1]heptan-2-ones (**3**).[10] Analogues of the latter ketones had already been shown to be useful in the synthesis of prostaglandins, among other natural products.[11] However, preparation of these analogues was based on a Diels–Alder reaction between α-chloroacrylonitrile and a 5-substituted cyclopentadiene,[10c-e] and the requirement of the latter limits the general utility of the method as a source of **3**.

(1) A portion of this work has been previously communicated: Gilbert, J. C.; Luo, T.; Davis, R. E. *Tetrahedron Lett.* **1975**, 2545.

(2) Taken in part from the dissertation of T.L. (Ph.D., 1975) and the thesis of U.P. (M.S., 1979), both submitted in partial fulfillment of the requirements of the respective degrees.

(3) Partial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

(4) Reviews: (a) Newton, R. F.; Roberts, S. M. *Chem. Biochem. Pharmacol. Act. Prostanoids Incl. Proc. Symp.* **1978**, 61, Roberts, S. M.; Scheinmann, F. Ed. (b) Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163.

(5) Mitch, E. L.; Dreiding, A. S. *Chimia* **1960**, *14*, 424.

(6) Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1974**, 948.

(7) (a) Gassman, P. G.; Marshall, J. L. *J. Am. Chem. Soc.* **1966**, *88*, 2599. (b) Gassman, P. G.; Marshall, J. L.; Hornback, J. M. *J. Am. Chem. Soc.* **1969**, *91*, 5811.

(8) Lumb, J. T.; Whitman, G. H. *J. Chem. Soc., Chem. Commun.* **1966**, 400.

(9) Paquette, L. A.; Fuhr, K. H.; Porter, S.; Clardy, J. *J. Org. Chem.* **1974**, *39*, 467.

(10) For other approaches to anti 7-substituted bicyclo[2.2.1]heptyl derivatives, see, for example (a) Roberts, J. D.; Johnson, F. O.; Carboni, R. A. *J. Am. Chem. Soc.* **1954**, *76*, 5692. (b) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *Ibid.* **1955**, *71*, 4193. (c) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *Ibid.* **1969**, *91*, 5675. (d) Corey, E. J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, *93*, 1489. (e) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varman, R. K. *Ibid.* **1971**, *93*, 1491.

(11) Review: Garcia, G. A.; Maldonado, L. A.; Crabbé, P. *J. Org. Chem.* **1977**, *36*, 121.

0022-3263/81/1946-4042$01.25/0

Table I. Selected Molecular Parameters of 1a

bond distances, (Å)		bond angles, deg	
C_1-C_2	1.484	C_1-C_2-C_7	61.9
C_1-C_5	1.528	C_2-C_1-C_7	60.9
C_1-C_6	2.072	C_1-C_7-C_2	57.2
C_1-C_7	1.557	C_1-C_2-C_3	110.1
C_2-C_3	1.494	C_2-C_1-C_5	100.8
C_2-C_6	2.465	C_2-C_3-C_4	105.7
C_2-C_7	1.542	C_3-C_4-C_5	103.9
C_3-Br	1.969	C_4-C_5-C_6	112.3
C_3-C_4	1.517	C_1-C_5-C_4	105.2
C_4-C_5	1.526	C_5-C_6-C_7	94.0
C_5-C_6	1.523	C_6-C_7-C_2	110.9
C_6-O	1.203	C_7-C_6-O	132.1
C_6-C_7	1.450	C_5-C_6-O	132.0
		C_2-C_3-Br	111.0
		C_4-C_3-Br	112.0
		C_2-C_7-C_6	110.9
		C_1-C_7-C_6	87.0
		C_5-C_1-C_7	89.6

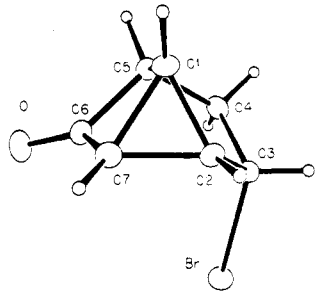
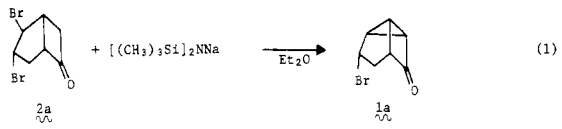


Figure 1. ORTEP plot of **1a**.

The target molecule chosen for the attempted synthesis of a tricyclo[3.2.2.2^{2,7}]heptan-6-one was **1a**. This choice was made not only because this is the intermediate proposed by Mitch and Dreiding[5] but also because ring opening of **1a** could provide a bicyclo[2.2.1]heptan-2-one suitably substituted for application to prostanoid synthesis.

Results and Discussion

It was our belief that reaction of the known[5] dibromide **2a** with a nonnucleophilic base, which could deprotonate **2a** but ideally would not promote ring opening of the desired tricyclic ketone, would permit successful isolation of **1a**. In the event, reaction of **2a** with sodium hexamethyldisilazide[12] in anhydrous ether afforded a 95% crude yield of **1a** (eq 1). Recrystallization and sublimation



(1)

of this yellow solid afforded pure, colorless **1a** in 81% yield.

The spectral data that support the assignment of the structure as **1a** are provided in the Experimental Section, and chemical observations consistent with this structure are discussed below. Moreover, a single-crystal X-ray structural determination confirmed the assignment and provided the molecular parameters summarized in Table I.[13] An ORTEP reproduction of the molecule is presented in Figure 1.

Several aspects of the detailed structure of **1a** are of interest. (1) The five-membered ring of the molecule is in the envelope conformation and contains carbon–carbon bond angles that range from 112.3° (C_4–C_5–C_6) to 100.8° (C_2–C_1–C_5). (2) The four-membered ring is folded by 21° about the C_5–C_7 line, a relatively modest flattening of the ring relative to cyclobutane itself.[14] (3) A significant difference in bond length exists between C_1–C_2 as compared to C_2–C_7, the latter bond being longer by some 0.06 Å. (4) The dihedral angle C_1–C_7–C_6–O is 150.7°, whereas the corresponding angle C_2–C_7–C_6–O is 156.2°, a fact that suggests that the C_1–C_7 bond, as compared to that between C_2–C_7, is slightly better oriented stereoelectronically to interact with the π-system of the carbonyl group; the potential significance of this is discussed below. (5) The hydrogen atom at C_3 is essentially trans periplanar with the carbon atom, C_7, and is pointing toward the line defined by extension of the C_2–C_7 bond (Figure 2); possible ramifications of this are also discussed below.

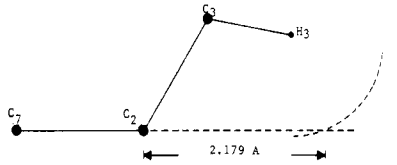
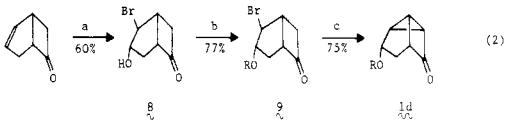


Figure 2. Steric interactions for attack at C_2.

A second derivative of **1**, specifically **1d**, has also been synthesized by us with the intent that it would prove to be more readily purifiable and more stable than **1a**. The 4-phenylbenzoyloxy group was selected as the protecting group for the hydroxyl group owing to the anticipated crystallinity of substrates containing this moiety and to the availability of a method for its ready removal.[15] The scheme for preparing **1d** follows directly from that for generating **1a**, and is shown in eq 2. The intermediate



(2)

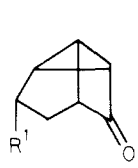
a) $CH_3CONHBr/KOH/CH_3COCH_3$; b) 4-$C_6H_5$-$C_6H_4COCl$/Pyridine; c) $[(CH_3)_3Si]_2NNa$/THF/Et_2O.

bromohydrin, **8**, which had previously been synthesized and characterized by Roberts and Grudzinski,[16] was converted to the bromo ester, **9**, which was readily purified by column chromatography. Reaction of **9** with sodium hexamethyldisilazide smoothly converted it to the desired tricyclic ketone, **1d**, a solid which was easily purified by recrystallization.[17] This ketone, which was characterized spectroscopically (see Experimental Section), proved to be more stable upon storage (at 0 °C) than **1a**. Consequently, our hopes for the 4-phenylbenzoyloxy group were fully realized.

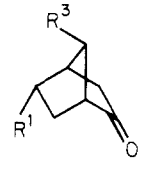
The availability of the ketones **1a** and **1d** made it possible to study the reactions of this tricyclic system with a variety of nucleophiles. As shown in Table II, both uncharged (entries 1, 2) and charged nucleophiles (entries 3–5) effect homoconjugate addition to the ketone in good to excellent yields. The evidence for the regio- and stereochemical outcome of such reactions has been presented elsewhere[5,18] and will not be detailed here. It is noteworthy,

(12) Wannagut, U.; Niederprum, H. *Chem. Ber.* **1961**, *94*, 1450.
(13) We thank Professor R. E. Davis for obtaining these data.
(14) Schulman, J. M.; Fisanick, G. J. *J. Am. Chem. Soc.* **1970**, *92*, 6653.
(15) Gassman, P.; Scheak, W. N. *J. Org. Chem.* **1977**, *42*, 918.
(16) Roberts, S. M.; Grudzinski, Z. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1767.
(17) The ease of purification would appear to make this derivative more desirable for use than the corresponding tetrahydropyranyl and acetoxy derivatives reported by the groups of Roberts and Newton.[18] However, their success in preparing the *tert*-butyldimethylsilyl analogue of **1d**, i.e., **1b** with R = *t*-Bu $(CH_3)_2Si$,[19] would seem to make this the derivative of choice for synthesis of prostaglandins from the tricyclic ketones **1**.
(18) Lee, T. V.; Roberts, S. M.; Newton, R. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1179.

Table II. Products of Reaction of 1 with Various Nucleophiles



1



3

entry	1, R^1	Nu	3, R^3	% yield
1	Br	CH_3OH	CH_3O	90
2	4-$C_6H_5C_6H_4CO_2$	$C_6H_5CH_2SH$	$C_6H_5CH_2S$	72
3	Br	NC^-/CH_3OH	NC and CH_3O [a]	95
4	4-$C_6H_5C_6H_4CO_2$	$(CH_3OCO)_2CH^-/CH_3OH$	$(CH_3OCO)_2CH$	78
5	4-$C_6H_5C_6H_4CO_2$	$(C_6H_5)_2CuLi$	C_6H_5	80

[a] Produced in a ratio of 1.5:1 (see Experimental Section).

however, that the observation of such homoconjugate addition to 1 is in complete agreement with the proposition discussed above; namely, that 1 is the key intermediate in the transformation of bicyclo[3.2.0]heptan-6-ones (2) to bicyclo[2.2.1]heptan-2-ones (3).

The carbon–carbon bond forming reactions exemplified by entries 3–5 are perhaps of greater interest, owing to their central role in the eleaboration of 1 into prostanoids, sequences for which have been developed by the groups of Newton and Roberts.[4b] The key step in their approach involves homoconjugate addition of organocuprates with 1. As noted by these workers, the success of this critical reaction can be ascribed to the additional strain anticipated to be present in 1 as compared to analogues such as 10 and 11; both of the latter cyclopropyl ketones are inert toward

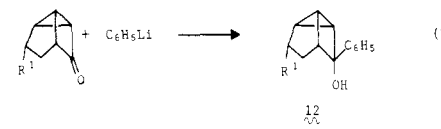
10

11

lithium dimethylcuprate.[20,21] Thus, the reaction of organocuprates with 1 undoubtedly does not occur via initial electron transfer to the ketone but rather involves simple nucleophilic attack facilitated by release of the strain of the tricyclic system.[22] This same effect accounts for the success of the homoconjugate addition involving dimethyl malonate (entry 4), a process that normally requires diactivated cyclopropyl compounds.[23]

The susceptibility of 1 to ring opening also extends to much weaker uncharged nucleophiles such as methanol and benzyl mercaptan (entries 1 and 2). Anti 7-heteroatom-substituted bicyclo[2.2.1]heptan-2-ones are therefore readily available from 1 under extremely mild reaction conditions[24] and may be useful in the synthesis of analogues of prostaglandins.[25]

The chemistry of 1 with nucleophiles is thus clearly dominated by a preference for homoconjugate addition. The sole exception to this mode of addition that we have uncovered is the reaction of this tricyclic system with an organolithium. Specifically, treatment of **1d** with 1 equiv of phenyllithium afforded the tertiary alcohol **12** (eq 3) in

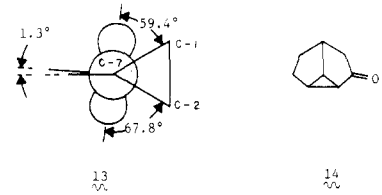


(3)

12

about 60% yield. All spectral data are in accord with the proposition that 1,2-addition has occurred in this instance (see Experimental Section). This same mode of reaction has also recently been noted by Newton et al., who used 1-lithio-1-alkynes as the nucleophilic species.[26] The overall conversion of the bicyclic ketones 2 to tricyclic alcohols such as 12 by 1,2-addition to the ketones 1 represents a facile construction of the system and appears to have greater flexibility in terms of substituents than the methods of synthesis devised previously.[27]

The aforementioned proclivity of the tricyclic ketone 1 to undergo homoconjugate addition regioselectively at C_1 rather than at C_2 merits comment. Consideration of probable differences in bond energies and of stereoelectronic factors gives clues to the potential sources that contribute to this regioselectivity. For example, that the C_1–C_7 bond is presumably weaker than the C_2–C_7 bond, and thus more susceptible to cleavage, is implied by the slightly greater length of the former. In addition, the more favorable stereoelectronic disposition of the C_1–C_7 bond relative to the π-system of the carbonyl group should enhance its lability. The dihedral angle between the π-orbital and the C_1–C_7 bond is some 8° less than the analogous angle involving the C_2–C_7 bond, as shown in **13**. Therefore,



13

14

the σ-orbital between C_1 and C_7 should be better situated for development of orbital overlap with the π-orbital as the carbon-carbon bond is broken by nucleophilic attack. The importance of continuous orbital overlap in defining the regioselectivity of ring opening of cyclopropyl ketones has been proposed previously in connection with cleavage

(19) Lee, T. V.; Roberts, S. M.; Dimsdale, M. J.; Newton, R. F.; Rainey, D. K.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1176.
(20) House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102.
(21) Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* **1972**, 997.
(22) For a discussion of the mechanisms of ring opening of cyclopropylcarbonyl compounds by organocuprates, see: House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.
(23) Review: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.
(24) Thiophenoxide has been reported to effect an analogous reaction of the tricyclic system, but no experimental details are given.[4b] This ion also is effective in promoting the conversion of bicyclo[3.2.0]heptan-6-ones (2) to anti 7-substituted bicyclo[2.2.1]heptan-2-ones (3), undoubtedly by way of 1.
(25) Cf. Crabbe, P.; Greene, A. E.; Padilla, A. *J. Org. Chem.* **1978**, *43*, 4377.
(26) Newton, R. F.; Reynolds, D. P.; Greenwood, J.; Scheinmann, F. *J. Chem., Soc., Perkin Trans. 1* **1980**, 2346.
(27) For other approaches to analogues of **12**, see ref 9 and also Tufariello, J. J.; Mich, T. F.; Lorence, R. J. *J. Chem. Soc., Chem. Commun.* **1967**, 1202.

reactions of the tricyclic ketone **14**.[28]

Another factor that may be of importance in assessing the stereoelectronic features of the cyclopropyl bonds in **1** relative to the carbonyl group can be derived from consideration of the relative distances from C_1 and C_2 to the carbonyl carbon atom, C_6. The former is some 0.4 Å shorter than the latter, which requires that the C_2–C_7 bond is at a greater average distance from C_6 than is the C_1–C_7 bond; this again suggests more effective interaction of the latter with the π-system.

A final consideration regarding the regioselectivity of nucleophilic homoconjugate attack on **1** has to do with the geometrical relationships given in Figure 2. If it is assumed that the lowest energy pathway for attack of a nucleophile on the carbon–carbon bond of a cyclopropane is colinear with that bond,[29] then a nucleophile approaching C_2 will enter the van der Waals radius of the hydrogen atom at C_3 at a distance of some 2.2 Å from C_2. No analogous destabilizing factor is associated with the approach of a nucleophile to C_1. Molecular mechanics calculations are claimed also to support the contention that H_3 impedes homoconjugate addition at C_2.[31]

The successful synthesis of tricyclo[3.2.0.0^{2,7}]heptan-6-ones (**1**) appears essentially to depend only upon the availability of the appropriately substituted bicyclic ketones **2**. Given the high regio- and stereoselectivity of reaction of **1** with a range of nucleophiles, these tricyclic ketones may have potential value in synthesis beyond that demonstrated to this point.

Experimental Section

Proton magnetic resonance (^{1}H NMR) spectra were obtained by using either a Varian A-60 or a Varian HA-100 spectrometer. Chemical shifts are reported in parts per million downfield from Me_4Si as internal reference at 0.00 ppm. Coupling constants (J) are reported in hertz. Ratios of areas of absorptions were obtained by averaging at least two successive integrations. Unless otherwise noted, ^{1}H NMR data are reported in the following manner: parts per million downfield from Me_4Si, multiplicity, coupling constant if applicable, number of protons, and the carbon atom(s) to which the hydrogen atom(s) are attached (if known).

All infrared (IR) spectra were recorded on a Beckman IR-5A spectrophotometer. All absorptions are reported in units of cm^{-1} and are calibrated to the absorption at 1601 cm^{-1} in polystyrene. IR analyses of liquids were performed on neat samples held as films between salt plates and those of solids as KBr pellets or as solutions.

Determination of accurate mass was made on a Du Pont (CEC) 21-210 high-resolution mass spectrometer, operating at 70 eV.

Elemental analyses were performed by Chemalytics Inc., Tempe, AZ.

Melting points (mp) were taken on samples contained in unsealed capillary tubes, using a Mel-Temp apparatus. Both melting points and boiling points (bp) are uncorrected.

A Varian Aerograph 90-P gas-liquid partition chromatography (GLC), equipped with a thermal conductivity detector and with 0.25 in. columns, was employed for preparative purposes. Helium was used as the carrier gas at a flow rate of 60 mL/min unless otherwise noted. Retention times (t_R) are reported relative to the time of injection.

***endo*-3-Bromotricyclo[3.2.0.0^{2,7}]heptan-6-one (1a).** Approximately 40 mL of dry diethyl ether and 4.0 g (15 mmol) of *exo*-2-*endo*-3-dibromobicyclo[3.2.0]heptan-6-one (**2a**)[5] were combined in a 250-mL one-necked, round-bottomed flask equipped with a stir bar and an addition funnel fitted with a nitrogen inlet. The resulting solution was cooled to −10 °C with the aid of an ice–salt water bath. A solution of 80 mL of diethyl ether and 3.0 g (16 mmol) of sodium hexamethyldisilazide[12] was then added at a rate such that the temperature of the reaction mixture never exceeded −5 °C. Upon completion of addition, the reaction mixture was stirred for an additional 2 h at 0 °C. After vacuum filtration, solvents were removed by rotary evaporation. Hexamethyldisilazane was distilled from the resulting heterogeneous residue at room temperature by application of vacuum line techniques. The nontransferable yellow residue, crude **1a**, weighed 2.7 g. Yield was 95% based on **2a**. The crude product mixture was first washed with 5 mL of hexane, which removed a minor impurity, and was then dissolved in 100 mL of dry diethyl ether; a second minor contaminant failed to dissolve. Removal of ethereal solvent by rotary evaporation yielded 2.3 g (81%) of yellow residue. The yellow residue could be further purified by sublimation (room temperature/0.1 mmHg), which afforded colorless triclinic crystals of **1a**, mp 62.5–64.0 °C.

Spectral data: ^{1}H NMR ($CDCl_3$) δ 2.1–2.3 (1 H, dm, large J = 14.5 Hz, H_4-endo), 2.6–3.0 (1 H, ddd, J = 14.5, 8.2, 4.5 Hz, H_4-exo), 2.9–3.1 (2 H, m, H_2 and H_7), 3.2–3.4 (1 H, m, H_5), 3.5–3.7 (1 H, dt, J = 2.5, 1.5 Hz, H_1), 4.7–4.9 (1 H, m, H_3); ^{13}C NMR ($CDCl_3$) δ 34.04 (C-4), 42.95 (C-2, tentative assignment), 44.35 (C-1, tentative assignment), 49.33 (C-7), 51.28 (C-5), 58.27 (C-3), 187.69 (C-6); IR 1745 cm^{-1} (C=O); exact mass 185.9676 calcd for $C_7H_7{}^{79}BrO$, 185.9681). Satisfactory elemental analysis of **1a** could not be obtained owing to its lability.

Anal. Calcd for C_7H_7BrO: C, 44.95; H, 3.77; Br, 42.72. Found: C, 42.78; H, 3.83; Br, 40.22.

***exo*-2-Bromo-*endo*-3-((4-phenylbenzoyl)oxy)bicyclo[3.2.0]heptan-6-one (9).** To a 25-mL one-necked, round-bottomed flask containing a stir bar and 2.0 g (9.8 mmol) of the bicyclic ketone 8[16] were added 2.1 g (9.7 mmol) of 4-phenylbenzoyl chloride and 25 mL of dry pyridine. The reaction mixture was stirred under dry nitrogen at room temperature for 24 h. The reaction was monitored by TLC (silica gel/CH_2Cl_2) and after 24 h only a single spot corresponding to the product was observed. The reaction mixture was then treated with 50 mL of ice-cold 1 N sulfuric acid and 50 mL of diethyl ether. The organic layer was separated and washed 4 times with cold dilute sulfuric acid and then 4 times each with saturated sodium bicarbonate solution and water. The aqueous washed were back-extracted twice with dietyl ether. The combined organic fractions were dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The yellow residue weighed 3.5 g and was purified by column chromatography (silica gel/CH_2Cl_2). The white solid so obtained weighed 3.0 g (77%), mp 114–115 °C.

Spectral data: ^{1}H NMR ($CDCl_3$) δ 2.5–2.7 (1 H, m, H_4-endo), 3.0–3.3 (1 H, m, H_4-exo), 3.4–3.6 (3 H, m, H_1, H_7-endo, H_7-exo), 3.9–4.2 (1 H, m, H_5), 4.6 (1 H, s, H_2), 5.7–5.9 (1 H, m, H_3), 7.3–8.0 (9 H, m, aromatic protons); IR ($CHCl_3$) 1775 (C=O, ketone), 1725 cm^{-1} (C=O, ester); exact mass 384.0350 (calcd for $C_{20}H_{17}{}^{79}BrO_3$, 384.0361).

Anal. Calcd for $C_{20}H_{17}BrO_3$: C, 62.35; H, 4.45; Br, 20.74. Found: C, 62.48; H, 4.41; Br, 20.60.

***endo*-3-((4-Phenylbenzoyl)oxy)tricyclo[3.2.0.0^{2,7}]heptan-6-one (1d).** The cyclization was accomplished in a manner analogous to that used for the preparation of **1a**. Purification could be achieved by vacuum filtration of the reaction mixture, removal of solvent by rotary evaporation and of hexamethyldisilazane by vacuum line techniques, and recrystallization of the resulting pale yellow residue from dry diethyl ether. A yield of 1.2 g (75%) of colorless **1d**, mp 69–70 °C, was obtained.

Spectral data: ^{1}H NMR ($CDCl_3$) δ 2.1–2.4 (1 H, m, H_4-endo), 2.5–2.6 (1 H, m, (H_4-exo), 2.7–2.9 (2 H, m, H_2, H_7), 3.5–3.8 (1 H, m, H_1), 4.1–4.2 (1 H, m, H_5), 5.6–5.9 (1 H, m, H_3), 7.4–8.3 (9 H, m, aromatic protons); IR (CCl_4) 1745 (C=O, ketone), 1725 cm^{-1} (C=O, aryl ester); exact mass 304.1105 (calcd for $C_{20}H_{16}O_3$, 304.1099).

(28) Monti, S. A.; Bucheck, D. J.; Shepard, J. C. *J. Org. Chem.* **1969**, *34*, 3080.

(29) It is difficult to assess the validity of such an assumption if the σ (and σ^*) molecular orbitals that constitute the skeletal bonds of the ring are accepted as being bent.[30] If such is the case, a nonlinear trajectory of attack of a nucleophile on **1** might be expected, and the steric effect of H_3 would be correspondingly lessened. No thorough analysis of the trajectory of nucleophilic attack on cyclopropane rings seems to have appeared in the literature.

(30) (a) Hoffmann, R.; Davidson, R. B. *J. Am. Chem. Soc.* **1971**, *93*, 5699. (b) Coulson, C. A.; Goodwin, T. H. *J. Chem. Soc.* **1962**, 2851. (c) *Ibid.* **1963**, 3161. (d) Walsh, A. D. *Nature (London)* **1947**, *159*, 167, 712. (e) Walsh, A. D. *Trans. Faraday Soc.* **1949**, *45*, 179.

(31) Tute, M. J.; Roberts, S. M., unpublished results cited in footnote 22 of 4b.

Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.85; H, 5.18.

***endo*-2-Bromo-*anti*-7-methoxybicyclo[2.2.1]heptan-5-one (3, R^1 = Br, R^3 = OCH_3).** In a 50-mL one-necked, round-bottomed flask equipped with a stir bar were combined 0.19 g (10 mmol) of **1a** and 20 mL of anhydrous methanol. After being stirred at room temperature for 2 h, the reaction mixture turned a bright yellow color. Following addition of 20-mL of water, the aqueous layer was extracted 5 times with diethyl ether. The combined ethereal extracts were sequentially washed with water and saturated sodium chloride and were then dried (Na_2SO_4). Removal of solvents by rotary evaporation followed by purification by GLC (0.33 m, 15% FFAP column, 190 °C, t_R 2 min) afforded pure product in 90% yield.

Spectral data: ^1H NMR (CCl_4) δ 1.6–1.8 (1 H, ddd, J = 14.0, 4.0, and 1.5 Hz, H_6-endo), 1.9–2.2 (1 H, ddd, J = 18.0, 4.5, and 1.5 Hz, H_3-exo), 2.5–2.9 (4 H, m, H_1, H_3-endo, H_4, H_6-exo), 3.35 (3 H, s, OCH_3), 3.7–3.9 (1 H, m, H_7), 4.5–4.7 (1 H, ddt, J = 10.0, 4.0, 4.0, and 1.5 Hz, H_5-exo); IR (neat) 1750 (C=O), 1110 cm^{-1} (COC); exact mass 217.9942 (calcd for $C_8H_{11}{}^{79}BrO$, 217.9942).

Anal. Calcd for $C_8H_{11}BrO$: C, 47.32; H, 5.46. Found: C, 47.41; H, 5.63.

Reaction of *endo*-3-Bromotricyclo[3.2.0.$0^{2,7}$]heptan-6-one (1a) with $NaOCH_3$/KCN/CH_3OH. To a 100-mL one-necked, round-bottomed flask, equipped with a stir bar and an addition funnel, was added 0.19 g (10 mmol) of **1a**. To this was added dropwise, and at room temperature, 60 mL of methanol saturated with potassium cyanide and containing a catalytic amount of sodium methoxide. After being stirred for 2 h at room temperature, the reaction mixture was subjected to a workup procedure identical with that described in the previous experiment and gave, in 95% yield, a 1.5:1 (GLC) ratio of **3** (R^1 = Br, R^3 = OCH_3) and **3** (R^1 = Br, R^3 = CN). The latter, a white solid, mp 97.5–99 °C, had a retention time of 8.8 min under the GLC conditions used above and was characterized as follows.

Spectral data: ^1H NMR ($CDCl_3$) δ 1.7–1.9 (1 H, ddd, J = 16.0, 4.5, 1.0 Hz, H_6-endo), 2.2–2.5 (1 H, ddd, J = 19.0, 4.5, 1.0 Hz, H_3-exo), 2.8–3.3 (5 H, m, H_1, H_3-endo, H_4, H_6-exo, H_7), 4.6–4.9 (1 H, ddt, J = 10.0, 4.0, 4.0, 2.0 Hz, H_5); IR ($CHCl_3$) 2250 (C≡N), 1750 cm^{-1} (C=O); exact mass 214.9772 (calcd for $C_8H_8{}^{81}BrNO$, 214.9770).

Anal. Calcd for C_8H_8BrNO: C, 44.89; H, 3.77; N, 6.54. Found: C, 44.81; H, 3.67; N, 6.37.

***anti*-7-Phenyl-*endo*-5-((4-phenylbenzoyl)oxy)bicyclo[2.2.1]heptan-2-one (3, R^1 = 4-$C_6H_5C_6H_4CO_2$, R^3 = C_6H_5).** A 100-mL three-necked, round-bottomed flask was equipped with a dropping funnel, nitrogen inlet, stir bar, and rubber septum, and 0.20 g (1.6 mmol) of anhydrous cuprous bromide and 25 mL of dry diethyl ether were introduced. The contents were cooled to 0 °C, and 0.20 g (3.3 mmol) of phenyllithium in benzene/ether was added via syringe to the vigorously stirred slurry. Following this addition, stirring was continued at 0 °C for 5 min during which the solution turned grey. Ketone **1d** (0.50 g, 1.7 mmol) in 15 mL of dry diethyl ether was then added dropwise to the organocuprate at 0 °C. The resulting mixture was stirred at 0 °C for an additional 2 h. It was then poured into 50 mL of ice-cold hydrochloric acid (1 N) and extracted 3 times with 25-mL portions of diethyl ether. The organic fractions were combined, washed sequentially with saturated sodium bicarbonate solution, and water and then dried (Na_2SO_4). Removal of solvent by rotary evaporation left a yellow solid weighing 0.6 g. Purification of this material by column chromatography (silica gel/CCl_4) afforded colorless product in 80% yield, mp 80–82 °C.

Spectral data: ^1H NMR ($CDCl_3$) δ 1.6–1.8 (1 H, m, H_6-endo), 2.2–2.6 (1 H, m, H_3-exo), 2.7–3.0 (3 H, m, H_3-endo, H_6-exo, H_1), 3.4–3.6 (1 H, m, H_7), 5.7–5.9 (1 H, m, H_5), 7.3–8.0 (14 H, m, aromatic protons); IR (CCl_4) 1750 (C=O, ketone), 1725 cm^{-1} (C=O, aryl ester); exact mass 382.1571 (calcd for $C_{26}H_{22}O_3$, 382.1569).

Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.88; H, 5.72.

***anti*-7-((Dicarbomethoxy)methyl)-*endo*-5-((4-phenylbenzoyl)oxy)bicyclo[2.2.1]heptan-2-one (3, R^1 = 4-$C_6H_5C_6H_4CO_2$, R^3 = $[CH_3OCO]_2CH$).** To a dry 50-mL round-bottomed flask equipped with a stir bar, drying tube, nitrogen inlet, and rubber septum were added 0.10 g (2.6 mmol) of sodium methoxide and 10 mL of dry methanol. To this mixture was added 0.30 g (2.6 mmol) of dimethyl malonate via a syringe. The reaction mixture was maintained at 50 °C for 5 min and allowed to cool to room temperature. Ketone **1d** (0.80 g, 2.6 mmol) in 15 mL of dry tetrahydrofuran was added, and the mixture was stirred at room temperature for 2 h. It was then poured into 50 mL of ice water and extracted 3 times with 50-mL portions of diethyl ether. The organic fractions were combined, washed with water, and dried ($MgSO_4$). Removal of solvent by rotary evaporation gave 1.1 g of a solid consisting of two components (TLC). Purification of column chromatography (silica gel/CCl_4) gave 0.9 g (78%) of colorless low-melting product.

Spectral data: partial ^1H NMR ($CDCl_3$) δ 3.8 (6 H, s, C(O)-OCH_3), 7.3–8.3 (9 H, m, aromatic protons); IR 1750 (C=O, ketone), 1740 (C=O, aliphatic ester), 1725 cm^{-1} (C=O, aryl ester); exact mass 436.1515 (calcd for $C_{25}H_{24}O_7$, 436.1522).

Anal. Calcd for $C_{25}H_{24}O_7$: C, 68.80; H, 5.54. Found: C, 68.73; H, 5.67.

***endo*-2-((4-Phenylbenzoyl)oxy)-*anti*-7-(thiobenzyl)bicyclo[2.2.1]heptan-5-one (3, R^1 = 4-$C_6H_5C_6H_4CO_2$, R^3 = $C_6H_5CH_2S$).** To a dry 25-mL round-bottomed flask containing 0.40 g (1.3 mmol) of **1d** in 10 mL of dry tetrahydrofuran was added 0.15 mL (1.3 mmol) of benzyl mercaptan. The reaction mixture was stirred at rt for 2 h, treated with 25 mL of water, and extracted 3 times with 25-mL portions of diethyl ether. The combined organic fractions were washed with water and dried ($MgSO_4$). Solvent was removed by rotary evaporation, and the yellowish residue was purified by column chromatography (silica gel/CH_2Cl_2). The resulting colorless product, 0.40 g (72% yield), had mp 80–82 °C.

Spectral data: partial ^1H NMR ($CDCl_3$) δ 3.8 (2 H, s, SCH_2), 7.2–8.0 (14 H, m, aromatic protons); IR 1750 (C=O, ketone), 1725 cm^{-1} (C=O, aryl ester); exact mass 428.1452 (calcd for $C_{27}H_{24}O_3S$, 428.1446).

Anal. Calcd for $C_{27}H_{24}O_3S$: C, 75.67; H, 5.65. Found: C, 75.80; H, 5.83.

***endo*-6-Hydroxy-6-phenyl-*endo*-3-((4-phenylbenzoyl)oxy)tricyclo[3.2.0.$0^{2,7}$]heptane (12).** To a dry 25-mL three-necked, round-bottomed flask equipped with a stir bar, nitrogen inlet, and rubber septum was added 0.50 g (1.7 mmol) of **1d** in 15 mL of dry diethyl ether. This solution was cooled to 0 °C. To this was added a solution of 0.10 g (1.6 mmol) of phenyllithium in benzene/ether via syringe. The reaction mixture was stirred at 0 °C for an additional 2 h. It was then poured over 50 mL of ice-cold 1 N sulfuric acid and extracted 3 times with 30-mL portions of diethyl ether. The organic fractions were combined, washed sequentially with saturated sodium bicarbonate solution, and water and then dried ($MgSO_4$). Removal of solvent by rotary evaporation left a semisolid residue that was purified by column chromatography (silica gel/CH_2Cl_2). The colorless alcohol, obtained in 63% yield, was a very low-melting solid.

Spectral data: ^1H NMR ($CDCl_3$) δ 1.9–2.0 (1 H, m H_4-endo), 2.1–2.3 (1 H, m, H_4-exo), 2.7–2.9 (2 H, m, H_2, H_7), 3.8–4.6 (3 H, m, H_1, H_5, OH), 5.7–5.9 (1 H, m, H_3), 7.3–8.2 (14 H, m, aromatic protons); IR (CCl_4) 3350 (OH), 1725 cm^{-1} (C=O, ester); exact mass 382.1573 (calcd for $C_{26}H_{22}O_3$, 382.1569).

Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.45; H, 6.05.

Registry No. **1a**, 57260-95-4; **1d**, 78592-00-4; **2a**, 57260-94-3; **3** (R^1 = Br; R^3 = OCH_3), 78592-01-5; **3** (R^1 = Br; R^3 = CN), 68821-05-6; **3** (R^1 = 4-$C_6H_5C_6H_4CO_2$; R^3 = C_6H_5), 78592-02-6; **3** (R^1 = 4-$C_6H_5C_6H_4CO_2$; R^3 = $[CH_3OCO]_2CH$), 78592-03-7; **3** (R^1 = 4-$C_6H_5C_6H_4CO_2$; R^3 = $C_6H_5CH_2S$), 78592-04-8; **8**, 56011-39-3; **9**, 78592-05-9; **12**, 78592-06-0; 4-phenylbenzoyl chloride, 14002-51-8; dimethyl malonate, 108-59-8; benzyl mercaptan, 100-53-8.