Synthesis of 7-Carboxytricyclo[3.3.1.0^{3,7}]nonan-3-ol

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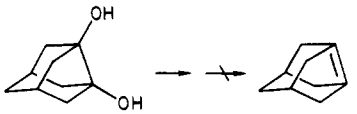
The title compound (**5a**) has been synthesized in three steps from diol **6**, which can be prepared in two steps from commercially available adamantanone. Jones oxidation of the diol gave, in addition to the desired endo keto acid (**3a**), diketone **11**. The mechanism for formation of the diketone in this reaction is discussed in light of conformational studies carried out on the methyl ester **3b**. These studies show that **3** and the C-7 epimer **4**, which has also been prepared starting from adamantanone, both prefer chair–chair conformations. The synthesis of **5** was completed by base-catalyzed closure of **3b**. Because equilibration of **3b** and **5b** is faster than hydrolysis, acid **5a** can be prepared in one step from ester **3b**. The rapidity of the ring closure reaction may be due to assistance by the proximate carbonyl group in the enolization process, since in methanol-*d* **3b** gives **5b** faster than it captures deuterium from the solvent. The epimeric bicyclic keto ester **4b** does not close to **5b**. Although **4b** equilibrates slowly with **3b** and **5b**, it was found to be thermodynamically more stable than either of them.

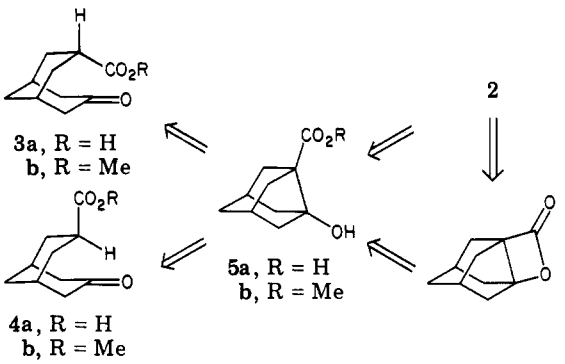
Attempts to form the highly strained olefin **2** by treatment of the (dimethylamino)dioxolane derivative of diol **1** with Lewis acids in refluxing tetraglyme have met with



1 **2**

failure,[1] despite the success of this reaction in the synthesis of a less strained homologue of **2**.[2] A number of reactions involving different derivatives of **1** proved similarly unsuccessful in generating **2**.[1] Consequently, we turned our attention to the preparation of other possible olefin precursors.

β-Hydroxy acid **5a** appeared an attractive target for investigation, since hydroxyl-group activation and carboxyl-group deprotonation would provide a derivative that might undergo decarboxylative fragmentation to **2**.



3a, R = H
b, R = Me

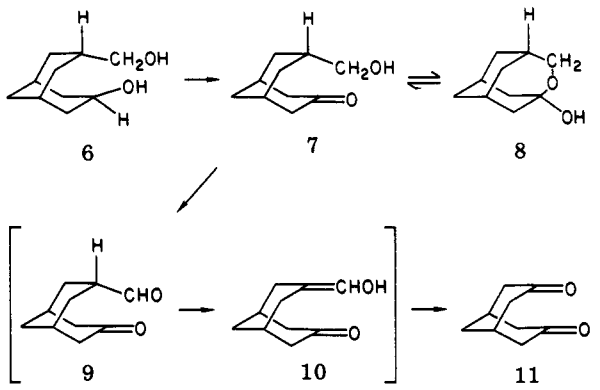
4a, R = H
b, R = Me

5a, R = H
b, R = Me

Conversion of β-hydroxy acids to olefins can be effected under mild conditions by this method,[3] and β-hydroxy acids have previously been used for the synthesis of bridgehead olefins.[4] Moreover, dehydration of **5a** to the β-lactone would furnish another possible precursor of **2**, since β-lactones undergo loss of CO_2 on thermolysis at relatively low temperatures.[5]

Retrosynthetic analysis suggests that an ester of the tricyclic β-hydroxy acid **5a** might be formed by base-catalyzed ring closure from one or both of the bicyclic keto esters **3b** and **4b**. In this paper we report the preparation of **3–5**. Experimental and computational results are presented that bear on the preferred conformations of **3** and **4**, and some interesting aspects of the reactions that lead to **5a** are discussed.

Scheme I. Proposed Pathway for Formation of 11 in the PDC Oxidation of 6



6 **7** **8**

9 **10** **11**

Results and Discussion

Diol **6**, which is readily prepared from commercially available adamantanone by Baeyer–Villiger oxidation,[6] followed by $LiAlH_4$ reduction,[7] is a promising precursor of **3a**. However, oxidation of **6** with pyridinium dichromate (PDC)[8] does not yield **3a**. Instead, this reaction affords essentially pure **11** in 75% yield,[9] thus providing a convenient alternate route to the previously published synthesis of this diketone.[10] The PDC oxidation (Scheme I) has been shown to proceed via keto alcohol **7**, which is in equilibrium with lactol **8**.

A related result has been reported by Peters et al.[11] They found that *endo*-7-alkyl-*endo*-3-(hydroxymethyl)bicyclo[3.3.1]nonanes (**12a**) also undergo oxidative loss of the hydroxymethyl group to give *endo*-7-alkylbicyclo[3.3.1]nonan-3-ones **13**. In contrast, Jones oxidation of alcohols that lack an endo substituent at C-7 (**12b,c**) affords the expected carboxylic acids **14**.

It seems likely that oxidation of the aldehyde enol is responsible for C–C bond cleavage in **6** and **12a**, since enols have been implicated in the chromic acid cleavage of ke-

(1) Greenhouse, R.; Borden, W. T., unpublished results.
(2) Greenhouse, R.; Borden, W. T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 1664.
(3) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545. Mulzer, J.; Bentrop, G. *Chem. Ber.* **1982**, *115*, 2057.
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(5) Adam, W.; Baeza, J.; Jiu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.
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(7) Wynberg, H.; Udding, A. C.; Strating, J. *Tetrahedron Lett.* **1968**, 5719.
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(10) Gagneux, A. R.; Meier, R. *Tetrahedron Lett.* **1969**, 1365.
(11) Peters, J. A.; Van Der Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1975**, *31*, 2273.

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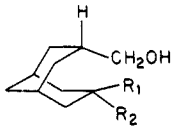
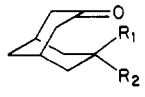
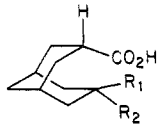




12a, R_1 = alkyl; R_2 = H
b, R_1 = H; R_2 = alkyl
c, R_1 = R_2 = H

13, R_1 = alkyl; R_2 = H

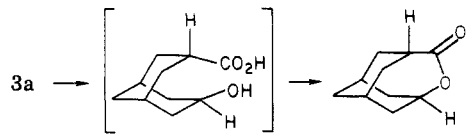


14a, R_1 = H; R_2 = alkyl
b, R_1 = R_2 = H

tones.[12] Enol formation should be especially favorable in the aldehydes formed from both **6** and **12a**, because enol formation would relieve steric crowding.

The production of the acids **14** in "almost quantitative yield"[11] from the Jones oxidation of the exo-7-alkyl alcohols **12b** suggested that under the same set of conditions **3a** might be formed from **6**. In the event, an approximately 1:1 mixture of acid **3a** and neutral products, including **11**, was isolated from the reaction of **6** with Jones reagent. It is possible that **3a** is formed in this oxidation but not in that with PDC because, under the aqueous conditions of the Jones oxidation, hydration prevents at least some of the aldehyde **9** from forming enol **10**. Keto acid **3a** was found to be stable to the reaction conditions, thus providing additional evidence that it is at the aldehyde stage of oxidation that formation of diketone **11** occurs.

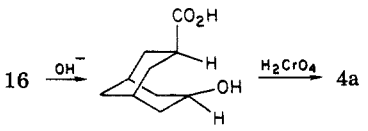
In order to prove chemically that epimerization had not taken place during the oxidation reaction, keto acid **3a** was



15 16

reduced with L-Selectride (Aldrich) to the endo,endo hydroxy acid **15**. The product actually isolated was not **15** but lactone **16**. The lactone was identical with a sample prepared by Baeyer–Villiger oxidation of adamantanone.[6]

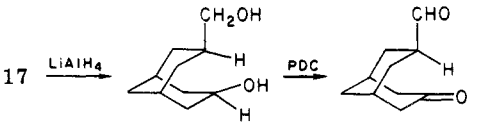
Starting from **16**, which serves as an intermediate in the synthesis of **3a** from adamantanone, the epimeric keto acid



17

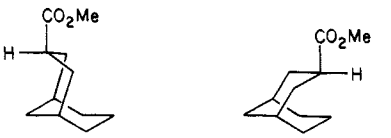
4a was also prepared. Heating a solution of **16** in aqueous sodium hydroxide at reflux for 3 days gave a mixture of epimerized hydroxy acid **17** and unreacted lactone. The two were readily separated, and **17** was isolated in 30% yield. The synthesis of **4a** was completed by Jones oxidation of **17**, which gave the desired keto acid cleanly in 75% yield.

In order to test the hypothesis that steric crowding is responsible for the formation of diketone **11** on PDC oxidation of diol **6**, the C-7 epimeric diol **18** was prepared by $LiAlH_4$ reduction of **17**. Since the hydroxymethyl group is exo in **18**, the steric driving force for enol formation in the aldehyde oxidation product **19** should be greatly reduced from that in **9**, where the aldehyde group is endo. Therefore, it was not surprising that unlike the epimeric diol **6**, **18** underwent smooth PDC oxidation to keto aldehyde **19**, with no evidence of the formation of diketone **11**.



18 19

The synthesis described above made the two epimeric keto acids **3a** and **4a** readily available. The conformations of bicyclo[3.3.1]nonanes are of some interest,[11,13] so we decided to determine the preferred conformation of **3** and **4**. From the work of Peters on the methyl ester of bicyclo[3.3.1]nonane-*exo*-3-carboxylic acid (**21**),[11] one would



20 21

expect **4** to exist in a flattened chair–chair conformation. In contrast, the C-7 endo substituent in **3** might be anticipated to force the ring containing C-7 to adopt a flattened boat conformation in order to relieve nonbonded repulsions between the substituent and the carbonyl group at C-3. Indeed, Peters et al. have found that in the methyl ester of the endo acid **20**, which differs from **3** only by absence of the ketone group, the ring bearing the ester group is in a boat conformation.[11] By analogy, a chair–boat conformation for **3** would also be predicted.

^1H NMR spectra were obtained on the methyl esters **3b** and **4b** at 500 MHz. Even at this high field strength the spectra of **3b** and **4b** were poorly resolved with chloroform-*d* as the solvent. However, in benzene-d_6 each unique proton resonance in both isomers was well separated from all the others. The observed chemical shifts and coupling constants are contained in Table I.

The assignments in Table I of the resonances in **3b** and **4b** were made by proton decoupling studies. In addition, treatment with dilute base in the presence of D_2O resulted in exchange of only two protons in both isomers. The protons that are exchanged can therefore be assigned as being on carbons α to the ketone carbonyl and conformationally fixed so that they are acidified by this group.

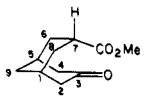
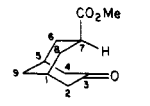
As anticipated, the coupling constants for the exo ester **4b** are in good agreement with those reported by Peters et al. for exo ester **21**, to which a flattened chair–chair conformation has been assigned.[11] However, the coupling constants for **3b** are quite different from those for the endo ester that lacks the carbonyl (**20**), to which a chair–boat conformation has been attributed by Peters. In particular, $J_{1,8x}$ and $J_{6(8)n,7}$ in **3b** are significantly smaller than the values of 10.2 and 12.5 Hz, respectively, reported by Peters et al. for the comparable coupling constants in **20**. In **3b**, $J_{6(8)n,7}$ is so small that the splitting due to this coupling is not detectable in the 500-MHz spectrum.

The coupling constants in **3b** are consistent with a chair–chair conformation for this molecule. In both **3b** and **4b** the coupling of H_1 with H_{2n} and H_{8n} is so small as to be unobserved, as expected for flattened chair cyclohexane rings. The coupling constants $J_{1,2x}$ and $J_{1,8x}$ in **3b**, which

(12) Rocek, J.; Riehl, S. A. *J. Am. Chem. Soc.* **1967**, *89*, 6691.

(13) Peters, J. A.; Baas, J. M. A.; Van De Graaf, B.; Van Der Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1978**, *34*, 3313.

Table I. ^{1}H NMR Data and Assignments for 3b and 4b[a]

assignment[b]	δ[c]	multiplicity, J (Hz)[d]
		
	3b	
9	1.28	1 H, d, J_g = 13.0
9	1.33	1 H, d, J_g = 13.0
exo-6,8	1.46	2 H, p, J_g = 13.9, J_1 = 7.2, J_7 = 6.5
1,5	1.89	2 H, br s
exo-2,4	2.00	2 H, d of d, J_g = 16.7, J_1 = 6.5
7	2.25	1 H, t, $J_{6(8)x}$ = 6.5
endo-6,8	2.38	2 H, d, J_g = 13.9
endo-2,4	2.48	2 H, d, J_g = 16.7
methyl ester	3.60	3 H, s
		
	4b	
9	1.30	2 H, br s
exo-6,8	1.64	2 H, t of d, J_7 = 13.0, J_g = 13.0, J_1 = 3.7
endo-6,8	1.79	2 H, br d, J_g = 13.0
1,5	1.89	2 H, br s
exo-2,4	2.03	2 H, d of d, J_g = 15.7, J_1 = 5.6
endo-2,4	2.27	2 H, d, J_g = 15.7
7	2.60	1 H, t of t, $J_{6(8)x}$ = 13.0, $J_{6(8)n}$ = 4.6
methyl ester	3.38	3 H, s

[a] ^{1}H NMR spectra recorded as benzene-d_6 solutions at 500 MHz. [b] Protons are numbered by the carbon to which each is attached. [c] Chemical shifts relative to benzene at δ 7.25. [d] J_g, J_x, and J_n denote, respectively, coupling constants to geminal, exo, and endo protons.

are respectively, 6.5 and 7.2 Hz, are larger than those, 5.6 and 3.7 Hz, in **4b**. This observation suggests a greater amount of flattening in both rings of **3b** than in **4b**, consistent with the change that would be expected for replacement of the endo proton at C-7 in **4b** by the more sterically demanding ester group in **3b**. The difference in configuration at C-7 also reduces the large $J_{6(8)x,7}$ transdiaxial coupling constant of 13.0 Hz in **4b** to $J_{6(8)x,7}$ = 6.5 Hz for the axial–equatorial coupling constant in **3b**.

The coupling constants observed in the ^{1}H NMR spectrum of **3b** and **4b** are in reasonable agreement with those predicted for the chair–chair conformations. The geometries were optimized by molecular mechanics calculations with the MM2 force field,[14] and the coupling constants were computed by using the relationships developed by Altona et al.[15] The boat–chair conformation of **3b** was also calculated; but the relevant coupling constants that were obtained, although close to those measured by Peters et al. for **20**, were quite different from those observed for **3b**. The optimized geometries and the coupling constants computed at them are contained in the supplementary material.

The calculated strain energies lead to the prediction of a preferred chair–chair conformation for **3b**, with the boat–chair computed to be 1.3 kcal/mol were strained. The chair–chair conformation of the epimeric exo keto ester **4b** was calculated to possess 3.9 kcal/mol less strain

(14) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(15) Haasnoot, E. A. G.; de Leeuw F. A. A. N.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

Table II. ^{13}C NMR Data (δ) for 3b and 4b[a]

3b	4b
200.34 (s)	200.83 (s)
175.21 (s)	175.66 (s)
52.32 (q)	51.62 (q)
46.95 (t)	47.28 (t)
35.15 (d)	35.22 (d)
32.25 (t)	34.52 (t)
31.11 (t)	32.13 (t)
29.08 (d)	30.04 (d)

[a] Spectra were recorded as chloroform-*d* solutions. Chemical shifts are reported relative to internal tetramethylsilane.

than the more stable of the two conformations of **3b**.

The ^{13}C NMR spectrum of **3b** is also indicative of a preferred chair–chair conformation for the endo keto ester. Peters has found that several of the ^{13}C chemical shifts in bicyclo[3.3.1]nonanes differ by 5–6 ppm between chair–chair and chair–boat conformations.[16] The nearly identical ^{13}C chemical shifts observed for **3b** and **4b** (Table II) thus argue for similar conformations.

The difference in preferred conformation between **3b** (chair–chair) and **20** (chair–boat) may reasonably be ascribed to the sp^2 hybridization of C-3 in **3**. The absence of an endo hydrogen at C-3 in **3** allows the cyclohexane ring bearing the ester group to assume a chair conformation without engendering the severe transannular crowding between the endo hydrogen and ester group that disfavors the chair–chair conformation in **20**.

A similar difference in preferred conformation is likely to exist between the aldehyde precursors of **3** and **20**. Thus, a chair–chair conformation is anticipated for **9**, whereas the aldehydes formed as intermediates in the oxidations of **12b** and **12c** are expected to exist predominantly in chair–boat conformations. This conformational difference could influence both the amount and rate of enol formation from the two types of aldehydes under the conditions of the Jones oxidation. Such a difference between the conformations preferred by the aldehydes may therefore be responsible for the observation that **6** gives, in addition to keto acid **3a**, substantial amounts of diketone **11** on Jones oxidation, whereas **12b** and **12c** give the corresponding acids **14a,b** cleanly.

The fact that **3a** can be obtained from the oxidation of **6** proved crucial to the synthesis of **5**. On treatment of the endo keto ester **3b** with dilute (0.04 M) sodium methoxide in methanol at room temperature, **5b** was formed; but under the same conditions, the exo keto ester **4b** failed to undergo cyclization. The exo-keto aldehyde **19** similarly failed to undergo transannular ring closure on treatment with base.[17]

Treatment of **3b** with base under the above conditions provided a 3:7 equilibrium mixture favoring **5b**. The two compounds could be separated by chromatography, and resubmission of **5b** to the reaction conditions gave the same 3:7 mixture, confirming that equilibrium had indeed been reached. Under these conditions the exo keto ester **4b** was not formed. However, in refluxing methanol after 2.0 h, **4b** was the only one of these three esters detected.

The rapid equilibrium of **3b** with **5b** and the much slower transformation of these compounds to the more

(16) Peters, J. A.; Van Der Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1977**, *33*, 349.
(17) *exo*-7-Acetylbicyclo[3.3.1]nonan-2-one, which was prepared by reaction of lactone **16** with 1 equiv of methyllithium, followed by base-catalyzed epimerization and Jones oxidation of the adduct, also failed to undergo transannular ring closure: Gilbert, K. E.; Borden, W. T., unpublished results.

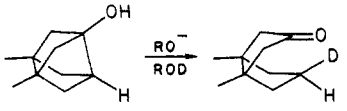
stable **4b** suggest that protonation of the putative ester enolate intermediate from the sterically shielded endo face, although thermodynamically favorable, is kinetically difficult. Consistent with this postulate, the reverse reaction, deprotonation of **4b** at C-7, was found to be very slow. Under the conditions where **3b** was equilibrated with **5b** in less than 5 min, no detectable exchange at C-7 of **4b** occurred after 1 h in methanol-*d*. After 24 h, deuterium incorporation at C-7 in **4b** was detectable but far from complete.

We also examined the equilibration of the endo keto ester **3b** with the tricyclic hydroxy ester **5b** in methanol-d_4. Since this experiment was carried out in order to probe whether exchange of the C-7 proton in **3b** is competitive with transannular ring closure to **5b**, it was necessary to examine unreacted **3b** before back-reaction of **5b** became important. This necessitated decreasing the methoxide base concentration to 0.01 M in order to slow the equilibrium sufficiently that the reaction could be conveniently interrupted at an early stage. The equilibration was quenched after 5 min, during which time 30% of **3b** had been transformed into **5b**. From solution of the kinetic equations for simultaneous reactions, it can be calculated that at this level of conversion back-reaction from **5b** accounts for less than 3% of the **3b** reisolated.

The mass spectrum of the **3b** recovered showed the incorporation of only two deuterium atoms. The 500-MHz ^{1}H NMR spectrum confirmed that the incorporation had occurred at the axial positions adjacent to the ketone carbonyl. No deuterium incorporation was detected at C-7. However, at longer reaction times deuterium was, as expected, incorporated at this position via the reaction of **5b** back to **3b**. No deuterium was incorporated at the equatorial positions adjacent to the ketone carbonyl, even under conditions where these protons were rapidly exchanged in **4b**.

The lack of deuterium incorporation at C-7 in **3b** may indicate that closure of a putative ester enolate ion to **5b** is faster than capture of deuterium from the solvent. Alternatively, proton loss from C-7 may be assisted by bond formation to C-3 of the proximate ketone carbonyl, so that deprotonation and its reverse are best viewed as concerted S_E2 reactions.

Evidence for an S_E2 reaction has been obtained in the base-catalyzed ketonization of dinoradamantanol **22**.[18] However, the transformation of **22** to **23** has been shown



22 23

to proceed with retention of configuration rather than the inversion observed in the equilibration of **3b** with **5b**. It seems possible, however, that the steric bulk and electron delocalization provided by the ester group might serve to overcome the intrinsic stereochemical preference of the S_E2 reaction for retention of configuration that is manifested in the transformation of **22** to **23**.

As interesting as the deuterium exchange reaction of **3b** proved, the most important synthetic aspect of the chemistry of this compound was the fact that unlike its stereoisomer **4b**, **3b** could be equilibrated with **5b**. The mixture of **3b** and **5b** could be separated by chromatography, albeit with some difficulty, and **5b** hydrolyzed in methanolic sodium hydroxide to the acid **5a**.

As expected from the rapidity with which **3b** and **5b** are equilibrated, reequilibration occurs faster than hydrolysis, so that **3a**, as well as **5a**, is formed in the hydrolysis of **5b**. Consequently, for synthetic purposes there is no reason to equilibrate the esters and then separate them. Instead, **3b** can be subjected to the basic hydrolysis reaction under which conditions it equilibrates rapidly with **5b**, to provide a 1:3 mixture of the acids **3a** and **5a**. The two acids can be separated by chromatography much more readily than their methyl esters.

The synthesis described in this paper makes hydroxy acid **5a** available in three steps from diol **6** in an overall yield of 18%. The overall yield suffers from the oxidation of **6**, which gives **3a** in only 29% yield. Nevertheless, the neutral products of the oxidation are readily removed by extraction from **3a**, its esterification to **3b** is quantitative, and after simultaneous equilibration and hydrolysis, **5a** is easily separated chromatographically from the 25% of **3a** that accompanies it. Since **6** can be prepared in two steps and 94% yield from commercially available adamantanone,[9] the synthesis of **5a** described here represents a convenient route to this hydroxyacid. The chemistry of **5a** is under active investigation.

Experimental Section

General Procedures. All ^{1}H NMR spectra were obtained on either a Varian EM-360L (60 MHz), CFT-20 (80 MHz), or a Brucker WM-500 (500 MHz) spectrometer; ^{13}C NMR spectra were obtained on a Brucker CXP-200 (50 MHz) spectrometer. The NMR spectra were recorded as chloroform-*d* solutions with chemical shifts reported in ppm downfield from internal reference tetramethylsilane, unless otherwise stated. The infrared spectra were obtained on a Beckman Acculab 4 and were recorded as methylene chloride solutions vs. a solvent reference cell. The mass spectra were obtained on a Hewlett-Packard 5985A GC/MS system, equipped with a fused silica capillary column and operating in the electron-impact mode with an ionizing energy of 70 eV. Exact masses were determined on a VG 7070 GC/MS and associated VG 2035 F/B data system operating in either electron-impact (70 eV) or chemical-ionization (methane) mode. Gas chromatographic analyses were performed on a Hewlett-Packard 5880A chromatograph, equipped with a fused silica capillary column (J & W, DB-5, 20 m) and a flame ionization detector. Solvents were dried over and distilled from appropriate reagents. Melting points are uncorrected.

***7-endo*-Carboxybicyclo[3.3.1]nonan-3-one (3a).** A solution of 1.0 g (5.9 mmol) of diol **6**[9] in 200 mL of acetone was cooled to 0 °C, and 13.0 mL of Jones reagent was added dropwise with stirring. After stirring for 4 h at 0 °C, 1 mL of isopropyl alcohol was added. The solution was diluted with 100 mL of methylene chloride and washed with three 20-mL protons of saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, and removal of solvent gave 320 mg of a white solid consisting of lactone **16** (39%), bicyclo[3.3.1]nonane-3,7-dione (**11**) (31%), hydroxy ketone **7** (18%), and several other minor products (12%). These compounds were identified by GLC and mass spectral comparisons with authentic samples. The aqueous phase was acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with 5–50-mL portions of methylene chloride. Drying and removal of solvent gave 310 mg (29%) of **3a** as a crystalline solid: mp 138.0–139.0 °C; ^{1}H NMR δ 1.7–2.2 (m, 4 H), 2.5–2.8 (m, 9 H), 9.10 (br s, 1 H); IR 3550–3000, 2940, 1720 cm^{-1}; MS, *m/e* (relative intensity) 182 (M^+, 32.1), 164 (19.5), 136 (16.8), 95 (100.0); exact mass calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0946.

Stability of 3a. A solution of 35 mg (0.19 mmol) of **3a** and 100 mg (0.27 mmol) of pyridinium dichromate in 5 mL of methylene chloride was stirred at room temperature for 20 h. The solution was filtered and concentrated to give recovered **3a** quantitatively.

L-Selectride Reduction of 3a. A solution of 50 mg (0.28 mmol) of **3a** in 5 mL of THF was cooled to −78 °C under nitrogen.

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A solution of L-Selectride (0.69 mmol) in hexane was added dropwise, and the resulting solution was stirred at −78 °C for 2 h. After being warmed to room temperature and addition of 5 mL of water, the solution was acidified with 6 N hydrochloric acid and extracted with three 20-mL portions of methylene chloride. Drying and removal of solvent gave 30 mg (71%) of **16** as a crystalline solid, identical with an authentic sample.

7-*endo*-Carbomethoxybicyclo[3.3.1]nonan-3-one (3b). A solution of 235 mg (1.29 mmol) of **3a** in 50 mL of diethyl ether was treated with diazomethane, prepared by the addition of 1.0 g of *N*-nitrosomethylurea to a stirred solution of 10 mL of 40% aqueous sodium hydroxide and 20 mL of diethyl ether of 0 °C. After 5 min the ether layer was separated and dried over potassium hydroxide pellets. The ethereal diazomethane solution was added dropwise to the solution of **3a** until the yellow color of the diazomethane persisted. After gas evolution had ceased, the excess diazomethane was quenched with a drop of glacial acetic acid. The ether layer was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and dried. Removal of solvent gave 252 mg (100%) of **3b** as a crystalline solid; after sublimation mp 49.0–50.5 °C; the ^{1}H NMR spectrum is given in Table I and the ^{13}C NMR spectrum in Table II; IR 2940, 1730, 1700 cm^{-1}; MS, *m/e* (relative intensity) 196 (M$^+$, 55.6), 164 (47.7), 136 (61.1), 108 (81.6), 95 (100.0); exact mass calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1100.

7-*exo*-Carboxybicyclo[3.3.1]nonan-3-*endo*-ol (17). A solution of 5.0 g (30.0 mmol) of **16** and 4.0 g of sodium hydroxide in 50 mL of water was heated at reflux for 3 days. After cooling, the basic solution was washed with three 30-mL portions of methylene chloride. Drying and removal of the methylene chloride gave 120 mg (2%) of **16**. The aqueous phase was acidified with concentrated hydrochloric acid and extracted with five 20-mL portions of chloroform. Drying and removal of solvent gave 1.5 g (30%) of **17** as a crystalline solid: mp 149.5–150.5 °C after recrystallization from acetone; ^{1}H NMR (acetone-d_6) δ 1.3–1.6 (m, 8 H), 1.8–2.0 (m, 4 H), 3.64 (m, 1 H), 4.05 (m, 1 H), 7.00 (br s, 2 H); IR 3600–2920, 1720 cm^{-1}; MS, *m/e* (relative intensity) 166 (85.4), 148 (34.1), 121 (65.9), 81 (100.0); exact mass calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1033.

7-*exo*-Carboxybicyclo[3.3.1]nonan-3-one (4a). A solution of 225 mg (1.24 mmol) of **17** in 20 mL of acetone was titrated with Jones reagent at room temperature until the orange color of the reagent persisted in the reaction mixture. After stirring for 30 min, 1 mL of isopropyl alcohol was added. The solution was diluted with 50 mL of methylene chloride and washed with three 10-mL portions of water and dried. Removal of solvent gave 170 mg (75%) of **4a** as a crystalline solid: mp 174.0–175.5 °C; ^{1}H NMR δ 1.7–2.0 (m, 6 H), 2.2–2.6 (m, 7 H), 8.30 (br s, 1 H); IR 3500–2940, 1720 cm^{-1}; MS, *m/e* (relative intensity) 182 (M$^+$, 34.6), 164 (2.7), 136 (22.1), 108 (100.0), 95 (13.6); exact mass calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0968.

7-*exo*-Carbomethoxybicyclo[3.3.1]nonan-3-one (4b). In a manner similar to the esterification of **3a** to **3b**, treatment of 170 mg (0.93 mmol) of **4a** with diazomethane gave 182 mg (100%) of **4b** as a crystalline solid: mp 84.5–85.5 °C after sublimation; the ^{1}H NMR spectrum is given in Table I and the ^{13}C NMR spectrum in Table II; IR 2940, 1730, 1710 cm^{-1}; MS, *m/e* (relative intensity) 196 (M$^+$, 37.2), 165 (16.8), 164 (14.7), 136 (53.9), 108 (100.0); exact mass calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1094.

7-*exo*-(Hydroxymethyl)bicyclo[3.3.1]nonen-3-*endo*-ol (18). A solution of 150 mg (0.82 mmol) of **17** and 62 mg (1.63 mmol) of lithium aluminum hydride in 5 mL of THF was heated at reflux for 12 h under nitrogen. Upon cooling and quenching with 0.06 mL of water, 0.06 mL of 15% aqueous sodium hydroxide, and 0.18 mL of water, the mixture was filtered through a sintered glass funnel and the alumina salts washed with 20 mL of hot THF. Drying and removal of solvent gave 134 mg (97%) **18** as a crystalline solid after recrystallization from acetone: mp 101.0–102.0 °C; ^{1}H NMR (acetone-d_6) δ 1.7–2.6 (m, 12 H), 3.25 (s, 2 H), 3.50 (m, 4 H); MS, *m/e* (relative intensity) 134 (23.1), 121 (39.0), 93 (100.0); exact mass calcd for $C_{10}H_{18}O_2$, 170.1307, found 170.1326.

7-*exo*-Formylbicyclo[3.3.1]nonan-3-one (19). A solution of 67 mg (0.39 mmol) of **18** and 1.5 g (3.9 mmol) of pyridinium dichromate in 10 mL of methylene chloride was stirred overnight under nitrogen at room temperature. The solution was diluted with 20 mL of diethyl ether and filtered through a short Florosil column. Removal of solvent gave 45 mg (70%) of **19** as a crystalline solid: mp 89.0–90.5 °C; ^{1}H NMR (benzene-d_6) δ 1.09 (d of t, 1 H, *J* = 13.9 and 2.6 Hz), 1.13 (t of d, 2 H, *J* = 13.1 and 3.1 Hz), 1.24 (d, 1 H, *J* = 13.9 Hz), 1.47 (d, 2 H, *J* = 13.1 Hz), 1.81 (br s, 2 H), 1.98 (d of d, 2 H, *J* = 16.2 and 6.2 Hz), 2.15 (t of t, 1 H, *J* = 13.1 and 4.6 Hz), 2.20, (d, 2 H, *J* = 16.2 Hz), 9.06 (s, 1 H); IR 2950, 1740, 1710 cm^{-1}; MS, *m/e* (relative intensity) 166 (M$^+$, 100.0), 151 (22.2), 137 (29.3), 108 (66.3), 95 (92.2), 84 (68.1), 67 (91.9); exact mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0983.

7-Carbomethoxytricyclo[3.3.1.0^{3,7}]nonan-3-ol (5b). To a solution of 10 mL of 0.044 M sodium methoxide in methanol under nitrogen at room temperature was added 370 mg (1.89 mmol) of **3b** in 5 mL of methanol. After stirring at room temperature for 30 min, a solution of saturated aqueous ammonium chloride was added. Extraction with three 20-mL portions of diethyl ether followed by drying and removal of solvent gave 360 mg (97%) of an oil consisting of **3b** (30%) and **5b** (70%), as determined by analytical GLC. Hydroxy ester **5b** was isolated as a clear, colorless oil by preparative gas chromatography using a 20 ft × $^3/_8$ in. 10% SE-30 on Chromabsorb W column; ^{1}H NMR δ 1.50 (d of t, 1 H, *J* = 13.0 and 2.2 Hz), 1.57 (d, 1 H, *J* = 13.0 Hz), 1.70 (d, 2 H, *J* = 10.0 Hz), 1.92 (s, 4 H), 2.2–2.6 (m, 4 H), 2.85 (s, 1 H, exchangeable with D_2O), 3.72 (s, 3 H); ^{13}C NMR δ 176.13, 86.25, 54.70, 51.84, 50.37, 46.36, 35.48, 33.42; IR 3600, 2970, 1730 cm^{-1}; MS, *m/e* (relative intensity) 196 (M$^+$, 5.1), 164 (100.0), 136 (76.3), 95 (19.5); exact mass calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1053.

Base Treatment of 5b. A sample of **5b** was submitted to sodium methoxide in methanol, as described above for **3b**. It gave a mixture of **3b** (30%) and **5b** (70%), the equilibrium mixture, in essentially quantitative yield.

Base Treatment of 4b. A sample of **4b** was submitted to sodium methoxide in methanol as described above for **3b**. Starting **4b** was recovered quantitatively. Under no conditions, including reaction times up to 96 h and temperatures up to that of refluxing methanol, did **4b** produce either **3b** or **5b**. Prolonged reaction times and or elevated temperatures did, however, result in eventual decomposition of starting material.

Base Treatment of 3b in Methanol at Reflux. A sample of **3b** was submitted to sodium methoxide in methanol as described above and heated at reflux for 2 h. Analysis of the reaction mixture by GLC showed **4b** to be the only one of the three esters present.

Incorporation of Deuterium into 3b. A sample of **3b** was submitted to 0.010 M sodium methoxide-d_3 in methanol-d_4 as described above and stirred at room temperature under nitrogen for 30 min. Aliquots were taken, quenched with saturated ammonium chloride, immediately extracted with ether, and analyzed by capillary gas chromatography, GLC–MS, and 500-MHz ^{1}H NMR spectroscopy. An aliquot taken after 5 min showed complete exchange of the exo protons at C-2 and C-4 in the 70% of **3b** that remained unreacted and in the 30% of the **5b** formed after this period, but neither mass spectroscopy nor ^{1}H NMR showed any incorporation of deuterium at C-7 in **3b**. However, a sample taken at 30 min, well after equilibrium between **3b** and **5b** had been attained, did show incorporation of roughly 0.5 D at C-7 in **3b**. After an hour, both **3b** and **5b** showed incorporation of an additional three deuterium at the methoxyl group via transesterification. The endo protons at C-2 and C-4 remained unexchanged, even after 24 h under these conditions.

Incorporation of Deuterium into 4b. Exposure of a sample of **4b** to 0.044 M sodium methoxide in methanol-d_4 at room temperature resulted in the incorporation of seven deuteriums after 30 min. Analysis by 500-MHz ^{1}H NMR revealed that all four protons at C-2 and C-4 had exchanged and that transesterification had occurred. However, even after 24 h, deuterium incorporation at C-7 was only 40% complete.

7-Carboxytricyclo[3.3.1.0^{3,7}]nonan-3-ol (5a). A solution of 370 mg (1.89 mmol) of **5b** in 10 mL of methanol and 5 mL of 5% aqueous sodium hydroxide was stirred at room temperature for 12 h. To the reaction mixture was added 25 mL of saturated aqueous ammonium chloride, followed by acidification with the dropwise addition of concentrated hydrochloric acid. The acidified solution was saturated with sodium chloride and extracted with three 20-mL portions of methylene chloride and dried. Removal of solvent gave a crystalline solid, which consisted of two com-

ponents by TLC on silica gel (hexane/ethyl acetate, 1:1): **5a** (R_f 0.15) and **3a** (R_f 0.26). The two were separated by flash column chromatography on silica gel (10 g of Merck silica gel 60, 230–400 mesh), with hexane/ethyl acetate (1:1) as eluent, to give 74 mg (20%) of **3a** and 210 mg (61%) of **5a** as a crystalline solid: mp 165.0–166.0 °C ^{1}H NMR δ 1.68 (d, 1 H, J = 13.0 Hz), 1.74 (d, 1 H, J = 13.0 Hz), 1.90 (d, 2 H, J = 12.0 Hz), 2.0–2.2 (m, 4 H), 2.4–2.6 (m, 4 H), 7.0 (br s, 2 H, exchangeable with D_2O); ^{13}C NMR δ 180.51, 86.83, 54.70, 50.26, 46.14, 35.48, 33.34; IR 3600–3000, 1720 cm^{-1}; MS, m/e (relative intensity) 182 (M^+, 1.9), 164 (63.4), 136 (72.6), 95 (100.0); exact mass calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0975.

Direct Preparation of 5a from 3b. In order to check that both methods for preparing **5a** gave the same ratio of **5a** to **3a**, a solution of 13 mg (0.066 mmol) of **3b** in 1 mL of methanol and 0.5 mL of 5% aqueous sodium hydroxide was stirred at room temperature for 1.5 h. Following the workup described above, 11 mg (92%) of a mixture of **5a** and **3a** was isolated. The acids were dissolved in 5 mL of diethyl ether and converted to their corresponding methyl esters by treatment with diazomethane to give **5b** (75%) and **3b** (25%) by gas chromatographic analysis. Hydrolysis of **5b** to **5a** and **3a** followed by esterification to **5b** and **3b** as described above gave the identical 3:1 (**5b**:**3b**) ratio.

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Registry No. **3a**, 87801-59-0; **3b**, 87801-60-3; **3b**-d_2, 87801-61-4; **3b**-d_3, 87801-62-5; **3b**-d_6, 87801-63-6; **4a**, 87801-64-7; **4b**, 87801-65-8; **5a**, 87801-66-9; **5b**, 87801-67-0; **6**, 21933-00-6; **7**, 87801-68-1; **11**, 770-15-0; **16**, 21898-84-0; **17**, 87860-03-5; **18**, 87860-04-6; **19**, 87801-69-2.

Supplementary Material Available: Coordinates for the MM2-optimized chair–chair and chair–boat conformations of **3b** and chair–chair conformation of **4b** and the vicinal coupling constants computed at these geometries (4 pages). Ordering information is given on any current masthead page.

Site of Gas-Phase Cation Attachment. Protonation, Methylation, and Ethylation of Aniline, Phenol, and Thiophenol

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Attachment of gaseous cations (H^+, CH_3^+, and $C_2H_5^+$) to aniline, phenol, and thiophenol can be effected by using chemical ionization and the products characterized by mass spectrometry/mass spectrometry (MS/MS). Data taken at both low and high collision energies give consistent results, although individual MS/MS spectra show the expected strong dependence upon collision energy. The site of reaction is inferred from characteristic fragmentations of the mass-selected adduct ions. In the case of alkylation, direct comparison is made of the MS/MS spectra of the ion/molecule reaction products and spectra of model compounds representative of the isomeric structures under consideration. In the case of protonation, deuterium-labeling data were obtained. The results for alkylation show competitive ring and substituent reaction, with phenol reacting largely on the ring in contradistinction with the behavior of aniline and thiophenol. Protonation of phenol appears to occur exclusively on the ring, and this is also the favored site for aniline, although some N-protonation is evident from the spectra. The difference between aniline and phenol, and that between alkylation and protonation, is consistent with expected trends in thermodynamic stability.

Introduction

The combination of mass spectrometry/mass spectrometry (MS/MS)[1] with chemical ionization[2] provides a proven capability for ion characterization, in conjunction with a means of carrying out ion/molecule reactions. This combination early[3] yielded surprising information on competitive protonation of substituents in disubstituted aromatic compounds, with nitro and cyano groups being much more readily protonated than a methoxyl substituent. Thermodynamic data[4] from ion cyclotron resonance spectroscopy confirms that the order of product ion stabilities matches the observed order of reactivity.

The present enquiry into the site of alkylation and protonation is prompted, first, by an interest in intrinsic molecular properties such as proton affinity.[5] Second, there is interest in the effect of site of protonation on characteristic ionic fragmentations.[6] Third, it is important to be able to characterize chemical-ionization behavior under kinetic control and to distinguish it from that which occurs under thermodynamic control. In addition to equilibrium data from high-pressure mass spectrometry,[7] ion cyclotron resonance spectroscopy,[8] and the flowing

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