The α,α' Annelation of Cyclic Ketones. Synthesis and Conformational Properties of Bicyclo[3.3.1]nonanone Derivatives

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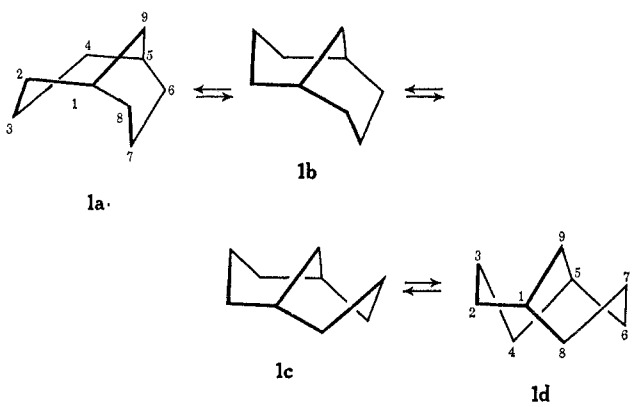
Reaction of enamines of 4-substituted cyclohexanones with methyl α-(bromomethyl)acrylate or dimethyl γ-bromomesaconate affords substituted bicyclo[3.3.1]nonan-9-ones with stereochemical properties useful for conformational studies. Dimethyl 7-*t*-butylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (**10**), dimethyl 7,7-dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (**9**), compounds unsubstituted in the 7 position, and their derivatives have been synthesized and studied. Boat–chair and diboat conformations are required by the configurations prepared.

The potential conformational mobility of the bicyclo[3.3.1]nonane ring makes it an interesting system for study.[1] The serious 3,7 hydrogen transannular interaction of the idealized dichair form (**1a**) results in a distortion of the system which reduces the energy difference between it and the boat–chair conformation. In any structure having a boat–chair conformation (**1b**), the boat portion cannot assume the lower energy twist modification because of the fused and rigid chair half of structure. It is only in the diboat conformer (**1c**) that



1a **1b** **1c** **1d**

both rings can develop the twist modification (**1d**) and relieve the torsional and flagpole interactions of the pure boat which exist in the boat–chair form.[1a] Although the transannular 2,6 (or 4,8) hydrogen interaction would decrease the equilibrium population of **1d**, this conformation should have a favorable entropy of mixing term relative to the other isomers because of two enantiomeric forms. Only conformation **1d** is flexible. Though bicyclononanes have been shown to be essentially dichair,[1c,d] certain 9-keto derivatives might be expected to have a considerable equilibrium distribution toward the boat–chair and ditwist–boat conformers because of the removal of flagpole hydrogen and some torsional interactions.[2] In addition, because of the above arguments, there is a question as to relative conformational populations of boat–chair and ditwist–boat forms when the configuration of a substituent requires that one ring be held in a boat.[3]

The development of the α,α'-annelation procedure has afforded a convenient path to compounds which may be studied to answer the above questions.[4] Thus, annelation of pyrrolidinenamine of cyclohexanone (**2**) with methyl α-(bromomethyl)acrylate derived *in situ* from methyl β,β'-dibromoisobutyrate (**3**) provided the keto ester **7** in good yield (Scheme I). The reaction, which proceeds *via* a C-alkylation–proton transfer–Michael condensations path (**2** → **4** → **6**) with kinetic or concerted protonation of the Michael product[4] affords the 3-*endo* ester **7a** as the sole product (**2** → **7**). This configuration was substantiated by isomerization of **7** to *exo* ester **8**. To account for the observed stereochemistry, it must be assumed that ring A (original enamine) of the intermediate involving protonation from the least hindered side (**5**) is in a boatlike conformation while ring B is chairlike. This eliminates development of the severe 3-carbomethoxy–7-hydrogen interaction in the protonation transition state leading to the product. Only after protonation can both rings undergo conformational change to provide the more stable boat–chair conformer (**6b**) of this *endo* configuration. Conformations corresponding to **7c** and **7d** are unlikely because of severe carbomethoxy–methylene interactions. The chair conformation of ring A of **7** and **8** (**7a** and **8a** *vs.* **7b** and **8b**) was suggested from arguments extrapolated from the 7-*t*-butyl-substituted compounds (see below), although a small equilibrium population of ring A boat forms might be present.

In a similar condensation of dimethyl γ-bromomesaconate (**9**) with cyclohexanone enamine (**2**), there was produced a 76% yield of bicyclononanone diester **10** (Scheme II). Treatment with sodium methoxide–methanol afforded the isomeric ester assigned configuration **11** and assumed to have the depicted conformation. Sodium borohydride reduction of **10** yielded a hydroxy diester **12**, which did not undergo complete γ-lactone formation until heated to 170° for 2 hr. The γ-lactone **13** was converted into an epimeric γ-lactone ester **14** by *t*-butoxide–*t*-butyl alcohol treatment. Further, sodium methoxide–methanol converted the γ-lactone into a 4:1 mixture of δ-lactone esters **15** and **16**.

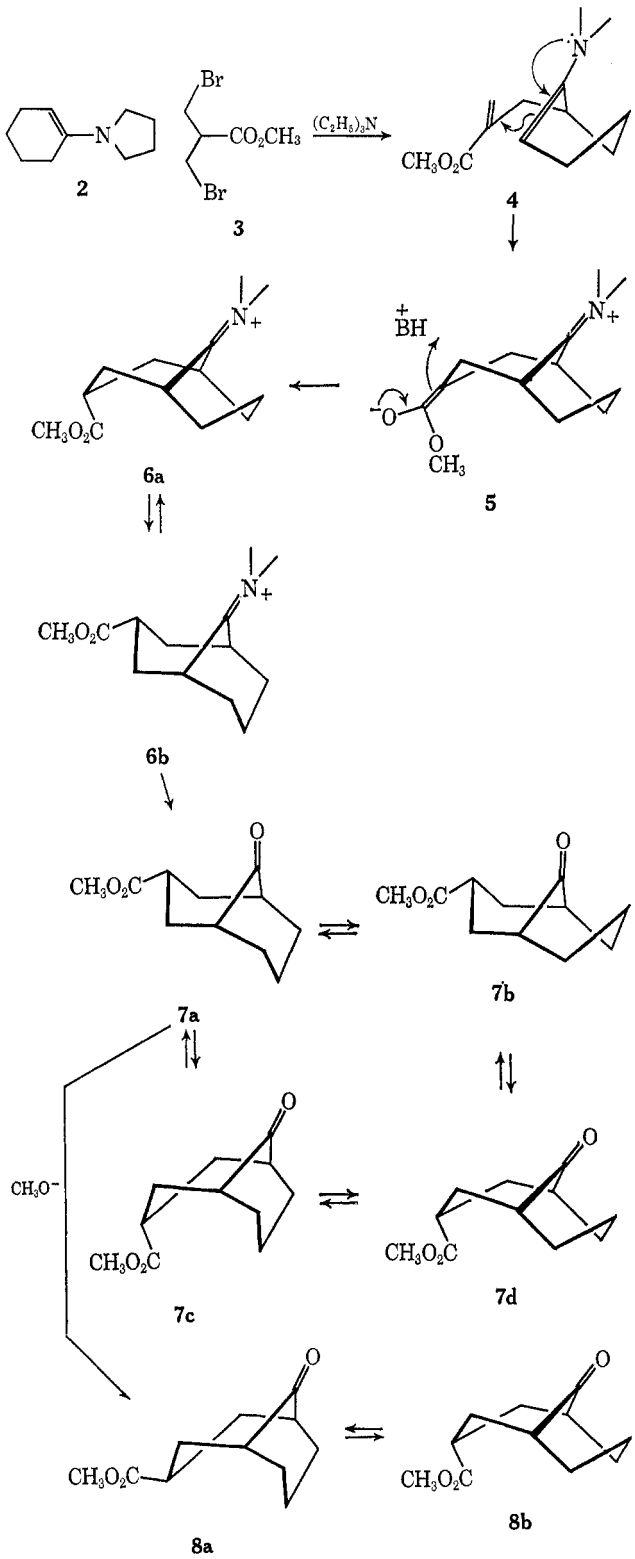
(1) (a) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); (b) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); (c) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965); (d) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); (e) R. A. Appleton, C. Egan, J. M. Evans, S. H. Brahone, and J. R. Dixon, *J. Chem. Soc.*, 1110 (1968); (f) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967); (g) W. D. K. MacRosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965); (h) L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966); (i) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Hong, *J. Org. Chem.*, **32**, 1372 (1967); (j) E. N. Marvel, G. J. Gleicher, D. Sturmer, and K. Salisbury, *ibid.*, **33**, 3393 (1968).

(2) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, in "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., pp 115–471. See, however, N. C. Webb and M. R. Becker, *J. Chem. Soc., B*, 1317 (1967).

(3) The conformations depicted are, of course, idealized representations of the actual conformations.

(4) (a) R. P. Nelson and R. G. Lawton, *J. Amer. Chem. Soc.*, **88**, 3884 (1966); (b) R. P. Nelson, J. M. McEuen, and R. G. Lawton, *J. Org. Chem.*, **34**, 1225 (1969).

SCHEME I



Mechanistic consideration of the formation of **10** and the above chemistry indicate the *trans* configuration of the diester functions (2-*exo*,3-*endo*). The resistance of **12** to γ-lactone formation compared with the bicyclooctan-8-one diester[4] appeared to be a consequence of the necessary conformational inversion of ring A from chair to boat to avoid a 3-carbomethoxy-7-methylene interaction in the γ-lactone having ring A chair. δ-Lactone formation occurs by C-3 ester epimerization, opening of the γ-lactone, conformational inversion to a boat form, and condensation to δ-lactone **15**, which is then epimerized at the C-2 ester to an equilibrium mixture of **15** and **16**.

δ-Lactone **16** was also produced by heating the mixture of alcohols derived from sodium borohydride reduction of 2-*endo*,3-*exo* diester **11**. This interrelation established the configuration of **16** as well as **15**.

The most stable conformation of the 2-*exo*,3-*endo* diester should be **10** (ring A chair, B boat), since the alternative conformation (ring A boat, B chair) would have serious 6,8-methylene-3-carbomethoxy axial interactions in addition to an axial 2-carbomethoxyl group. This analysis compares favorably with that for the monoester **7**. Again, the presence of some equilibrium population of diboat conformation corresponding to **7b** cannot be excluded for **10**, but this must be small on the basis of evidence from the 7-*t*-butyl-substituted case (see below).[5]

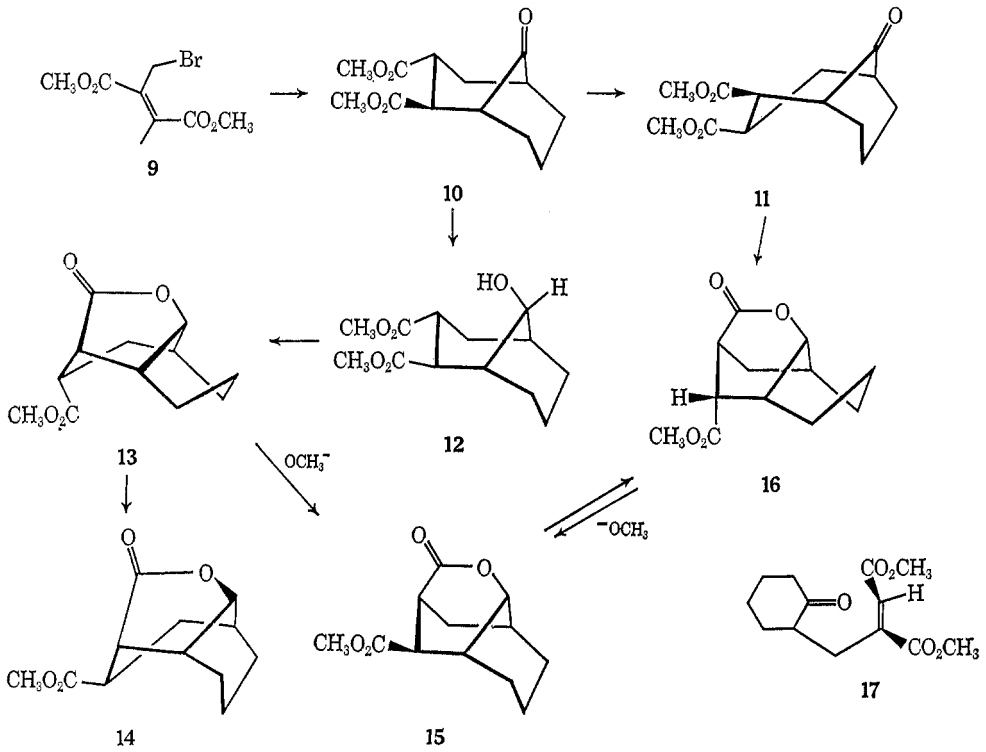
When the annelation (**9** + **2**) was carried out in ether solvent, an intermediate iminium salt precipitated. Upon hydrolysis, this salt afforded the C-alkylated product (**17**) which had not undergone the Michael reaction. The structure of **17** supported the C-alkylation–Michael reaction pathway over the previously questioned N-alkylation–Claisen rearrangement or SN2′–Michael reaction routes.[4]

A system which clarified certain conformational ambiguities of the previous structures was provided by the reaction of bromo diester **9** with the pyrrolidinenamine of 4-*t*-butylcyclohexanone. The reaction produced a major isomer **18** and a minor isomer **19** in a 9:1 ratio (Scheme III). Each of these compounds was completely isomerized by sodium methoxide–methanol to a new isomer, **20** and **21**, respectively, indicating that the original ketones differed in configuration at the *t*-butyl center. The major isomer **18** was reduced with borohydride to a mixture of alcohols **22**, which upon heating afforded γ-lactone **23** and the C_9 epimeric alcohol (Scheme IV). Epimerization of γ-lactone **23** with *t*-butoxide–*t*-butanol afforded a new γ-lactone, **24**. Treatment of the alcohol mixture with sodium methoxide–methanol provided δ-lactone **25**. The combined evidence indicates the *trans*-2-*exo*,3-*endo* configuration of the ester functions and supports the hypothesis of a parallel mechanistic pathway for the formation of the major isomer of the 7-*t*-butyl (**18**) and the unsubstituted compound (**10**).

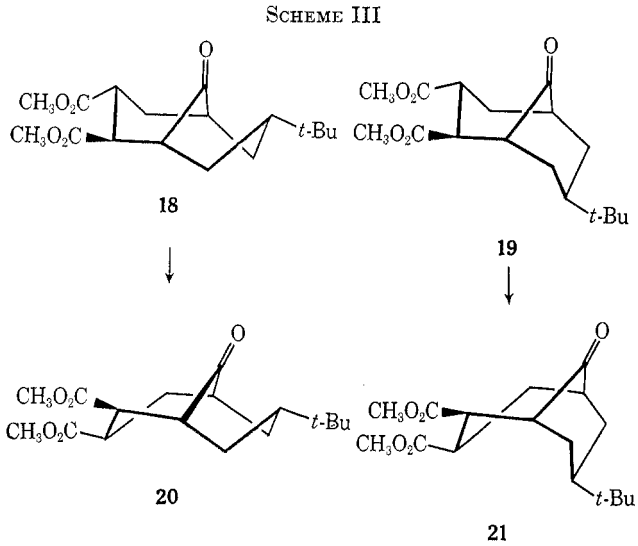
At the alkylation stage of the α,α′-annelation reaction, both *cis* and *trans* configurations of the *t*-butyl moiety are possible relative to the mesaconate side chain (represented conformationally in **26a** and **27**, Scheme V). For the Michael reaction to take place, it is obviously necessary that the mesaconate side chain reside axially. In the *trans* intermediate **27** this conformation is easily obtained, but for the *cis* intermediate **26** the conformational change is unlikely if a chairlike cyclohexanone enamine is maintained. However, as indicated previously with **7** and **10**, conformational principles suggest that the intramolecular Michael reac-

(5) The X-ray analysis of cyclooctane-1,2-dicarboxylic acid (*cis* and *trans*) provides a good model for this system. Both isomers have a boat–chair conformation. See J. D. Dunitz and A. Nugnoli, *Chem. Commun.*, 166 (1966).

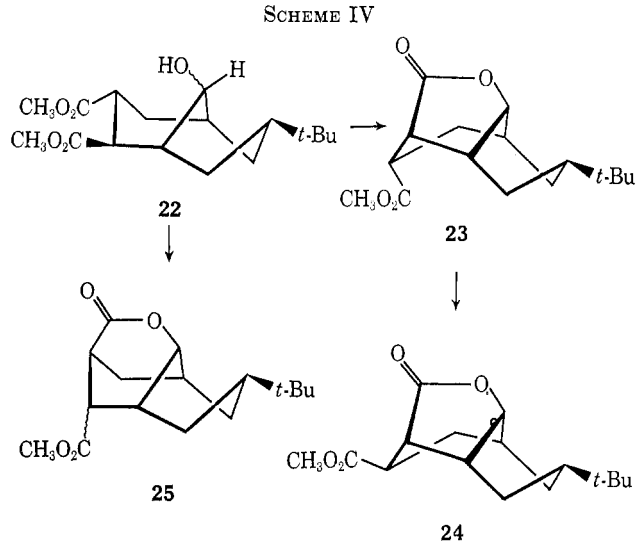
Scheme II



Scheme III



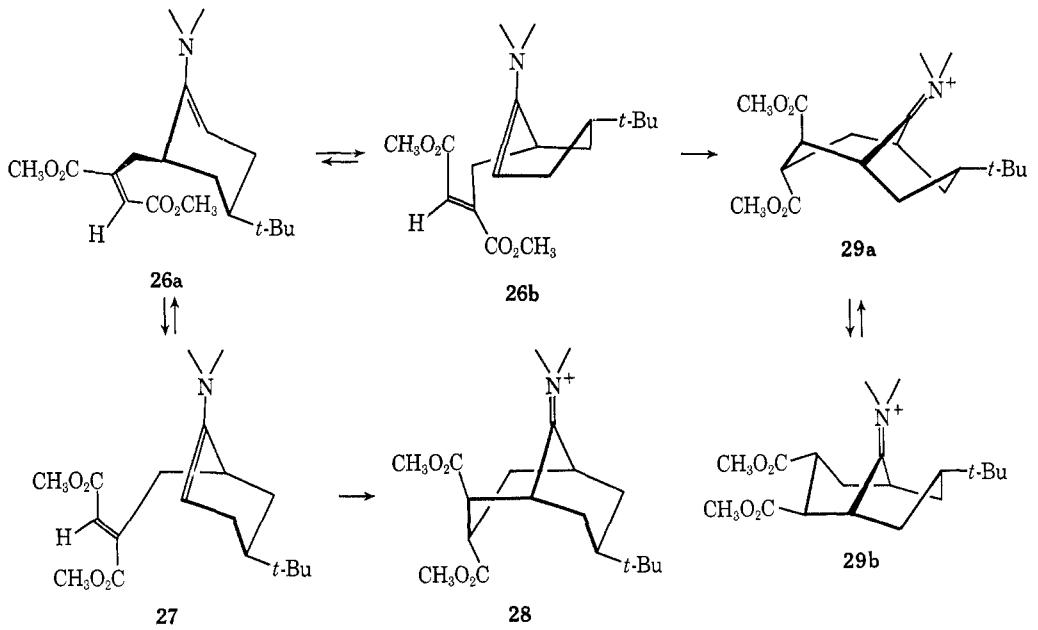
Scheme IV



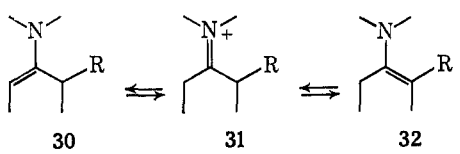
tion takes place with ring A in a boatlike form. This implies that the *trans* configuration **27** should undergo the final Michael closure with difficulty because of the development of the 3-carbomethoxy-7-hydrogen interaction in the intermediate leading to **28**. With this configuration, ring A cannot attain the boatlike conformation which maintains the axial side chain because the *t*-butyl group has frozen ring A in the chair conformation. However, the *cis* intermediate **26a** should undergo the intramolecular Michael reaction with facility, since with ring A in a boatlike form **27b** possesses a *bowsprit t*-butyl function and the 3-carbomethoxy–7-position interaction is avoided (**29**). Since the *cis* and *trans* intermediates **26** and **27** may be equilibrated under the reaction conditions by means of a proton addition and abstraction (**30** → **32** → **30**, Scheme VI), the above analysis suggested a 2-*exo*,3-*endo* diester 7-*endo*-*t*-butyl configuration for the major isomer. The interesting feature of this stereochemistry is that, in contrast to **7** and **10**, ring A of **18** cannot undergo conformational inversion (which would give an axial *t*-butyl), and therefore a diboat- or- ditwist–boatlike conformation is required. Ring B is expected to be boatlike because of the two axial carbomethoxy groups and the 3-carbomethoxy–6,8-methylene interactions in the chair form.

A comparison of the rate of γ-lactone formation in alcohols **12** and **22** further clarified the stereochemistry and conformation of these systems. The rate of γ-lactone formation in the major *t*-butyl isomer **22** was more than ten times faster than that of the unsubstituted compound **12** (pmr, appearance of lactone H). If the major isomer had an *exo*-7-*t*-butyl configuration, γ-lactone formation would be very slow in comparison with **12**, as the 3-carbomethoxy–7-hydrogen interaction

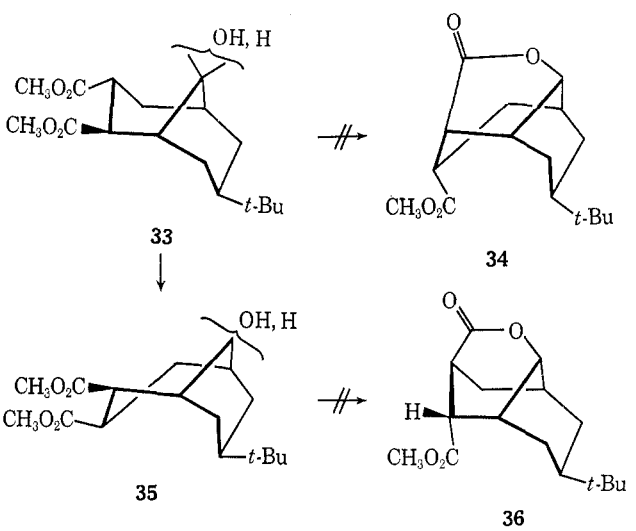
SCHEME V



SCHEME VI



SCHEME VII



would have to be accommodated (ring A could not move to a boat). The *endo*-7-*t*-butyl configuration **22** with ring B held in the boat conformation allows more rapid γ-lactone formation because of its higher ground-state energy. For **22**, the required conformational change of ring A in γ-lactone formation has already occurred. Also, since γ-lactone formation in **22** is still slow relative to that for the corresponding bicyclo[3.2.1]octanone diester alcohol,[4b] we assume that in the alcohol, and therefore also in the ketone, the ester functions, although 2-*exo*,3-*endo*, are not positioned in an *axial* manner (ketone corresponding to **29a**) but are *gunnel* and *bowsprit* (**18**).[6]

The stereochemistry of the ester functions of the minor isomer **19** has not been established with certainty. However, as would be expected, the mixture of alcohols **33** derived from **19** forms neither γ-lactone **34** upon long heating at 200° nor δ-lactone **36** after methoxide isomerization of the ester functions (Scheme VII). The unalterable chair conformation of ring A (equatorial *t*-butyl group) will not allow γ-lactone formation with the resultant 7-hydrogen–3-carbomethoxy interactions (**34**) or δ-lactone formation after ester isomerization because of development of the 2-carbomethoxy–7-methylene interactions (**36**).

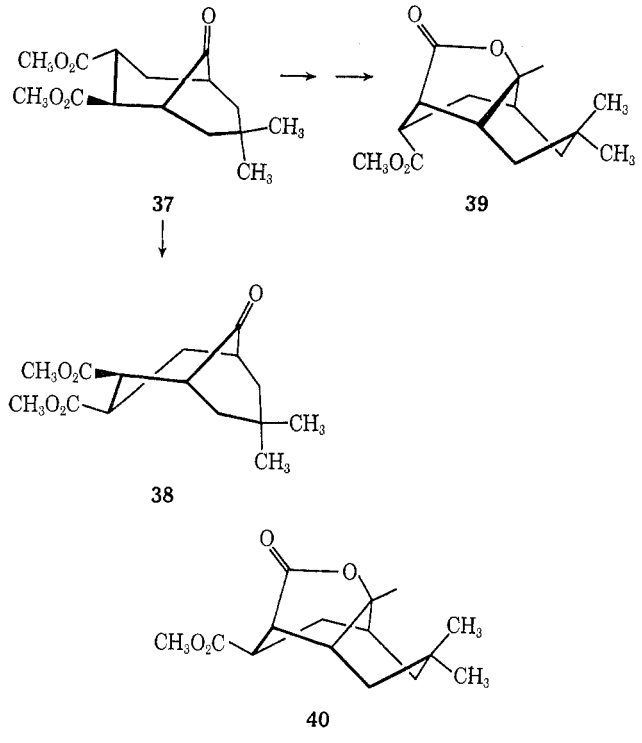
The complete isomerization of **18** and **19** to **20** and **21**, respectively, suggests a qualitative lower limit to the relative energy differences between these structures. Ignoring the differing substitution on rings A and B and assuming that the conformations are controlled by the ring system, when the diboatlike conformation **18** with ring A fixed in a boat was isomerized, the equilibrium lay totally toward the boat (A ring)–chair (B ring) conformation (**20**) as determined by the configurational change. Similarly, in **19**, where ring A is fixed in a chair and ring B is in a boatlike conformation, isomerization is complete, giving the dichair conformation **21**. Therefore, the conformations differ in energy in the order diboat > boat–chair > dichair for bicyclononanones.[7]

The same arguments were applied to annelations involving dimethyl bromomesaconate (**9**) in the preparation of ketone **37** (Scheme VIII). Chemical and spectral evidence similar to that presented for the previous systems was used to demonstrate that the ester functions were *trans* (2-*exo*,3-*endo*) and that ring B existed in the boatlike conformation. However, the conformation of ring A of the 7,7-dimethyl compound **37** remains a question. Inspection of models suggests a boat A ring which is distinctly flattened. In the γ-lactone **39**, where ring A is fixed in a boat to relieve the 3-*endo*-carbomethoxy–7-*endo*-methyl interaction, steric compres-

(6) In discussing the four distinct positions on the fixed boatlike cyclohexane moiety of structures such as **10**, a nautical nomenclature has been retained. Structure **10** would possess a *gunnel* 2-carbomethoxy function and a *keel* 2 hydrogen as well as a *bowsprit* 3-carbomethoxy and a *flagpole* 3 hydrogen.

(7) Calculations[1j] for the system using the Wiberg approach tend to support these conformations.

Scheme VIII



sion deshielding by the *exo* flagpole methyl on the lactone hydrogen was observed in the nmr. This is only slightly shifted upon isomerization of **39** to **40**, suggesting that ring A remains boatlike. This is consistent with the previous analysis. In the protonation transition state leading to **37**, the A ring must again lie boatlike and this moiety has both flagpole and bowsprit methyls. In this intermediate and in **37** there are no serious interactions because ring A is boatlike and C-9 is sp^2. However, in **39** and **40** some angle distortion must occur to accommodate the flagpole methyl and hydrogen.

Studies of the exact differences in energy and conformation of these structures are continuing, as are further investigations of changes due to alternate patterns of substitution and functionality. Other evidence in support of these hypotheses, including X-ray analysis of the intermediates, is also under study.

Experimental Section

Infrared spectra were taken using a Perkin-Elmer Model 237 spectrophotometer and were determined as thin films or in chloroform solution. Proton magnetic resonance spectra were determined in deuteriochloroform solution with a Varian A-60 instrument using tetramethylsilane as an internal reference. Chemical shifts are reported using the τ scale. Melting points were determined in open-capillary tubes using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalysis was performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectral analysis was performed by the Morgan Schaeffer Corp., Montreal, Canada.

Methyl β,β'-Dibromoisobutyrate (3).—To a solution of 60 g (0.25 mol) of β,β'-dibromoisobutyric acid[4] in 75 ml of 1,2-dichlorethane was added 30 ml (0.75 mol) of methanol and 1.2 ml of 98% sulfuric acid. The mixture was stirred and held at reflux for 19 hr, and cooled. The organic solution was washed several times with water, saturated sodium bicarbonate, and saturated sodium chloride, and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under vacuum provided 56 g of oil which was then distilled to yield 46 g (71%) of the ester: bp 60–62° (0.4 mm); ir ($CHCl_3$) 1740, 1440, 1427, 1337, and 1025 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (s, 3 H), 6.34 (d, 4 H), and 6.82 (quintuplet, 1 H).

Anal. Calcd for $C_5H_8O_2Br_2$: C, 23.10; H, 3.10; Br, 61.49. Found: C, 23.29; H, 3.09; Br, 61.35.

Methyl Bicyclo[3.3.1]nonan-9-one-3-*endo*-carboxylate (7).—To a solution of 7.55 g (0.05 mol) of the pyrrolidineamine of cyclohexanone (**2**) and 5.10 g (0.05 mol) of triethylamine in 60 ml of dry acetonitrile was added dropwise with stirring 13.0 g (0.05 mol) of methyl β,β'-dibromoisobutyrate dissolved in 40 ml of acetonitrile. The reaction mixture was maintained at reflux for 13 hr. Hydrolysis of the iminium salt was accomplished by addition of 5 ml of 5% aqueous acetic acid followed by a 1-hr reflux period. The mixture was cooled and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with 5% aqueous hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was evaporated under vacuum to provide 8.65 g (87%) of the desired nonanone. The product consisted of a single isomer as determined by pmr analysis: ir ($CHCl_3$) 1737, 1720, 1478, 1125, and 1080 cm^{-1}; pmr (C_6H_6) τ 6.67 (s, 3 H) and 7.40–9.20 (broad, overlapping multiplets).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.31.

Methyl Bicyclo[3.3.1]nonan-9-one-3-*exo*-carboxylate (8).—This compound was prepared by epimerization of the corresponding *endo* compound. To a solution of 0.0068 g (0.0003 g-atom) of sodium in 10 ml of dry methanol was added 0.10 g (0.53 mol) of the *endo* isomer **7**. The mixture was maintained at reflux under nitrogen for 1 hr, cooled, and neutralized with 5% aqueous acetic acid, and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with saturated sodium bicarbonate and saturated sodium chloride. Drying over anhydrous magnesium sulfate followed by filtration and evaporation of the solvent yielded 0.035 g (35%) of oil which was shown by glpc analysis (5-ft, 20% Carbowax 20M) to be essentially a single isomer. Small amounts of **7** and a third compound were present: ir ($CHCl_3$) 1737, 1720, 1450, and 1177 cm^{-1}; pmr (C_6H_6) τ 6.70 (s, 3 H) and 7.50–9.40 (broad, overlapping multiplets).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.16.

Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10).—To a solution of 29.5 g (0.195 mol) of the pyrrolidinenamine of cyclohexanone in 200 ml of acetonitrile was added dropwise 47.0 g (0.193 mol) of dimethyl γ-bromomesaconate. Throughout the mesaconate addition and during the subsequent 5-hr reflux period the reaction was maintained in a nitrogen atmosphere. The reaction was processed in the manner of bicyclononanone (**7**). Removal of solvent yielded 46.8 g of orange oil whose fractionation gave 37.8 g (76.3%) of dimethyl bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylates, bp 175–179° (2.25–2.50 mm). The product appeared to consist of a major isomer contaminated by *ca.* 15% of a second isomer, as determined by glpc analysis over a 6-ft, 6% LAC-728 (adipate ester) column held at 250°. When the product was allowed to stand, the oil crystallized, giving a white solid. Recrystallization from ether yielded purified material (**10**): mp 60–61° (after drying under vacuum over concentrated sulfuric acid); ir ($CHCl_3$) 1735, 1175, and 1040 cm^{-1}; pmr ($CDCl_3$) τ 6.29 (s, 3 H), 6.30 (s, 3 H), 7.40 (m, 5 H), and 8.08 (m, 7 H).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.31; H, 7.21.

The 2,4-dinitrophenylhydrazone derivative had a melting point of 201.5–202.5°.

Anal. Calcd for $C_{19}H_{22}N_4O_8$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.43; H, 5.17; N, 12.90.

Attempted Preparation of Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10) Using Ether As the Reaction Solvent.—To a solution under nitrogen of 4.65 g (0.0308 mol) of the pyrrolidinenamine of cyclohexanone in 95 ml of ether was added 7.30 g (0.0308 mol) of bromo ester **9**. Upon addition of the bromo ester a white precipitate formed. The reaction was stirred at room temperature for 4 hr, 3.05 g (0.0302 mol) of triethylamine was added, and the mixture was stirred for another 12 hr. Processing as in the preparation of nonanone **7** gave 5.91 g of yellow oil. Fractionation of the crude oil yielded 3.96 g (50.6%)

of yellow oil, bp 134–140° (0.5–0.7 mm). The infrared spectrum of the oil indicated that it possessed considerable unsaturated material, as evidenced by the absorption at 1640 cm^{-1}. When the oil was allowed to stand, a white solid separated. The solid was recrystallized from ether to give purified material, mp 74.5–76°, which proved to be the open-chain compound **17** resulting from C alkylation: ir $\nu_{max}^{CHCl_3}$ 1725, 1640, 1275, 1240, and 1120 cm^{-1}; pmr ($CDCl_3$) τ 3.25 (s, 1 H), 6.18 (s, 3 H), 6.24 (s, 3 H), 7.00 (m), 7.29 (m), 7.66 (m), and 8.15 (m).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14. Found: C, 61.46; H, 7.02.

Epimerization of Dimethyl Bicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (10) with Sodium Methoxide.—A solution of 5.01 g (0.0197 mol) of dimethyl[3.3.1]nonan-9-one and 0.500 g (0.00925 mol) of sodium methoxide in 40 ml of methanol was heated at reflux (oil bath) for 4 hr. Processing was the same as that used in the epimerization of nonanone **7**. Evaporation of solvent gave a brown oil which yielded 1.87 g (37.4%) of white, crystalline material on treatment with ether. The residual brown oil contained a considerable quantity of desired product (**11**) as evidenced by infrared analysis. A purified sample, mp 96–97.5°, was obtained by recrystallization from ether: ir ($CHCl_3$) 1735, 1280, and 1173 cm^{-1}; pmr ($CDCl_3$) τ 6.27 (s, 3 H), 6.31 (s, 3 H), 6.62 (m), 7.22 (m), 7.50 (m), and 7.96 (m).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.50; H, 7.16. Found: C, 61.41; H, 7.14.

Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13).—To a cooled solution of 5.01 g (0.0198 mol) of dimethyl bicyclo[3.3.1]nonan-9-one-2,3 dicarboxylate (**10**) in 35 ml of methanol was added slowly 0.643 g (0.0164 mol, 0.0656 equiv) of sodium borohydride. The mixture was allowed to stand at room temperature for 1 hr. Addition of an equal volume of water was followed by several extractions with ether. The combined extracts were dried over anhydrous magnesium sulfate and the ether was evaporated to yield 4.67 g of oil. Infrared analysis of the oil indicated that only a small amount of γ-lactone had formed, as evidenced by the relatively weak γ-lactone carbonyl absorption at 1770 cm^{-1}. Heating of the oil in an oil bath at 170° for 4 hr gave 4.37 g of brown oil whose infrared showed a considerable increase in the γ-lactone carbonyl absorption. Treatment of the oil with ether yielded 1.65 g (37.3%) of methyl bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-lactone (**13**), mp 107–108°. The residual oil contained a considerable quantity of γ-lactone which failed to crystallize: ir ($CHCl_3$) 1770, 1725, 1160, and 995 cm^{-1}; pmr ($CDCl_3$) τ 5.55 (t, 1 H), 6.20 (s, 3 H), 6.85 (m), 7.27 (m), 7.45 (m), 7.75 (m), and 8.05–8.60 (m).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.46; H, 7.27.

Attempted Epimerization of Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13) with Sodium Methoxide. Trial A.—A solution of 0.502 g (0.00224 mol) of γ-lactone **13** and 0.260 g (0.00481 mol) of sodium methoxide in 15 ml of methanol was heated at reflux (oil bath) for 11.25 hr. Cooling of the reaction mixture followed by processing, as in the epimerization of ketone **10**, yielded 0.188 g of yellow oil. The infrared spectrum showed the presence of δ-lactone ester, having carbonyl absorptions at 1755 cm^{-1} and 1735 cm^{-1}, respectively.

Trial B.—In a similar experiment a solution of 0.100 g (0.448 mmol) of γ-lactone **13** and 0.05 g (0.93 mmol) of sodium methoxide in 5 ml of methanol was stirred at room temperature for 12 hr. Work-up as in the above experiment yielded a yellow oil having an infrared spectrum identical with the oil obtained in trial A.

Column chromatography of 0.197 g of combined oils from trials A and B over 9 g of silicic acid adsorbant using 5% ether–benzene eluent gave 0.0251 g of δ-lactone **15** and 0.0884 g of δ-lactone **16**, bp 185° (0.5 mm) (Kugelrohr). The δ-lactone **16**, present as the minor component, was the initial isomer to come off the column: ir ($CHCl_3$) 750, 1725, and 1265 cm^{-1}; pmr ($CDCl_3$) 5.6 (t, 1 H), 6.22 (s, 3 H), 7.06 (m), 7.40 (m), 7.88 (m), and 8.51 (m).

The δ-lactone **15** was the major component: ir ($CHCl_3$) 1755, 1735, 1265, 1135, and 1050 cm^{-1}; pmr ($CDCl_3$) τ 5.75 (t, 1 H), 6.27 (s, 3 H), 7.10 (m, 1 H), 7.33 (m, 2 H), 7.69 (m, 1 H), and 8.45 (m, 8 H).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.27.

Methyl Bicyclo[3.3.1]nonan-9-ol-3-carboxy-2-*endo*-carboxylate δ-Lactone (16).—To a solution of 0.261 g (0.001 mol) of keto diester **11** in 5 ml of methanol was added slowly with stirring 0.038 g (0.001 mol) of sodium borohydride and the solution was allowed to stir for 0.5 hr. Processing as in the reduction of ketone **10** provided 0.287 g of crude oil. This oil was then heated in an oil bath under a nitrogen atmosphere for 2.5 hr to yield 0.251 g of an oil–solid mixture. Column chromatography of this mixture over 10 g of silicic acid adsorbant using 3% ether–benzene eluent gave 0.073 g of δ-lactone **16** contaminated with a small amount of unreduced ketone. The lactone was then further purified by glpc on a 5-ft, 10% SE-30 (silicone) column to give a pure solid, mp 79–81°. Spectral properties were identical with those found for the minor isomer derived from isomerization of γ-lactone **13**.

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.21.

Epimerization of Methyl Bicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (13) with Potassium *t*-Butoxide.—A solution of 0.0931 g (0.416 mmol) of γ-lactone **13** and 0.0140 g (0.125 mmol) of potassium *t*-butoxide in 3 ml of *t*-butyl alcohol was stirred at room temperature for $2^1/_3$ hr. After the reaction was processed *via* the method used in the epimerization of ketone **10**, 0.0848 g (90%) of yellow oil was obtained. A purified sample was prepared by column chromatography of the oil over 5 g of silicic acid adsorbent using 2% ether–benzene eluent. *Ca.* 5 mg of epimerized γ-lactone **14** was obtained: ir ($CHCl_3$) 1775, 1730, 1155, and 1005 cm^{-1}; pmr ($CDCl_3$) τ 5.60 (t, 1 H), 6.28 (s, 3 H), 7.10 (m), 7.20 (m), and 8.43 (m).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.13.

Dimethyl 7-*t*-Butylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylates.—To a solution of 6.15 g (0.03 mol) of the pyrrolidenenamine of 4-*t*-butylcyclohexanone in 50 ml of dry acetonitrile was added dropwise with stirring 7.10 g (0.03 mol) of dimethyl γ-bromomesaconate (**9**) dissolved in 25 ml of acetonitrile. The mixture was maintained at reflux for 20 hr under a nitrogen atmosphere. Hydrolysis of the iminium salt was accomplished by the addition of 15 ml of 5% acetic acid followed by a reflux period of 1 hr. The reaction mixture was processed in the manner of ketone **7** and the solvent was removed to yield 6.05 g (65%) of yellow oil, which partially solidified. Trituration of the oil–solid mixture with ether yielded 2.40 g of solid major isomer **18**, mp 127–128.5°. The residue was shown by pmr analysis to contain the minor isomer and about 10% of the major isomer. The major isomer was **18**: ir ($CHCl_3$) 1737 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (s, 3 H), 6.33 (s, 3 H) and 9.08 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.76; H, 8.38.

The minor isomer was **19**: ir ($CHCl_3$) 1737 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.23 (s, 3 H), 6.29 (s, 3 H), and 9.15 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.79; H, 8.42.

Epimerization of Dimethyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-one-2-*exo*-3-*endo*-dicarboxylate (18). Major Isomer.—To a solution of 0.65 g (0.0021 mol) of the major isomer **18** in 5 ml of dry methanol was added 0.11 g (0.002 mol) of sodium methoxide dissolved in 5 ml of dry methanol. The mixture was maintained at reflux under nitrogen for 4 hr and then processed as in the epimerization of ketone **10**. Removal of solvent yielded 0.3 g (60%) of oil which was purified by Kugelrohr distillation: bp 140–145° (bath) (0.1 mm); ir ($CHCl_3$) 1735 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 3 H), 6.37 (s, 3 H), and 9.15 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.38. Found: C, 65.76; H, 8.41.

Methyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (23).—To a solution of 0.62 g (0.002 mol) of major isomer **18** in 10 ml of dry methanol was added 0.46 g (0.012 mol) of sodium borohydride. The mixture was allowed to stand at 25° with stirring for 0.5 hr. Processing as in the case of lactone **13** provided 0.53 g (86%) of a product which consisted of the desired alcohol contaminated with the C_9-epimeric alcohol. Treatment of 0.42 g (0.0014 mol) of the alcohol at 200° for 2 hr under nitrogen provided 0.35 g (92%) of the oil–solid mixture, which upon sublimation gave 0.13 g of pure γ-lactone **23**: mp 115–116°; ir ($CHCl_3$) 1774 and 1727 cm^{-1}; pmr ($CDCl_3$) τ 5.67 (t, 1 H), 6.30 (s, 3 H), and 9.20 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.55; H, 8.64.

Epimerization of Dimethyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (23).—To a solution of 0.09 g (0.32 mmol) of γ-lactone 23 in 10 ml of dry *t*-butyl alcohol was added 0.041 g (0.18 mmol) of potassium *t*-butoxide. The reaction mixture was held at reflux for 3 hr and processed as

in the case of the isomerization of ester **15**. Removal of solvent yielded 0.41 g (45%) of the epimerized lactone **24**, which was recrystallized from ether–chloroform: mp 98–101°; ir ($CHCl_3$) 1775 and 1728 cm^{-1}; pmr ($CDCl_3$) τ 5.74 (t, 1 H), 6.35 (s, 3 H), and 9.20 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.60; H, 8.66.

Methyl 7-*endo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-3-carboxy-2-*endo*-carboxylate δ-Lactone (25).—To a solution of 0.37 g (0.0012 mol) of unisomerized alcohol from major isomer **22** in 15 ml of dry methanol was added 0.089 g (0.0016 mol) of sodium methoxide. The reaction mixture was maintained at reflux under nitrogen for 5 hr and processed in the manner of lactone **15**. Removal of solvent yielded 0.23 g (69%) of oil, which was purified by glpc on a 5-ft, 20% SE-30 (silicone) column to yield the γ-lactone **25**: mp 98–101°; ir ($CHCl_3$) 1753 and 1729 cm^{-1}; pmr ($CDCl_3$) τ 5.85 (t, 1 H), 6.34 (s, 3 H), and 9.12 (s, 9 H).

Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.64. Found: C, 68.59; H, 8.74.

Epimerization of Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-one-2-*exo*,3-*endo*-dicarboxylate (19). Minor Isomer.—To a solution of 0.29 g (0.93 mmol) of crude minor isomer in 10 ml of dry methanol was added 0.062 g (0.0012 mol) of sodium methoxide. The reaction mixture was held at reflux under nitrogen for 2 hr and processed as in the epimerization of ketone **10**. Removal of solvent and Kugelrohr distillation yielded 0.21 g (69%) of epimerized compound: ir ($CHCl_3$) 1735 and 1725 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 6 H) and 9.13 (s, 9 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.38. Found: C, 65.89; H, 8.45.

Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-*exo*,3-*endo*-dicarboxylate (33).—To a solution of 0.36 g (0.0012 mol) of unisomerized minor isomer **19** in 5 ml of dry methanol was added 0.076 g (0.0019 mol) of sodium borohydride. The mixture was stirred at 25° for 0.5 hr and processed as in the reduction of ketone **10** to yield 0.32 g (89%) of alcohol. The alcohol was heated at 190° for 2 hr but no evidence of γ-lactone formation was seen in the ir spectrum of alcohols **33**: ir ($CHCl_3$) 3610, 3450, 1735, and 1430 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (s, 6 H), and 9.21 (s, 9 H).

Dimethyl 7-*exo*-*t*-Butylbicyclo[3.3.1]nonan-9-ol-2-*endo*,3-*endo*-dicarboxylate.—To a solution of 0.23 g (0.72 mmol) of minor isomer alcohol **33** in 10 ml of dry methanol was added 0.044 g (0.80 mmol) of sodium methoxide. The reaction mixture was held at reflux under nitrogen for 2 hr and processed as in the isomerization of ketone **10** to provide 0.15 g (65%) of isomerized alcohol **35**. Again, heating of the alcohol at 180° for several hours produced no lactone from alcohols **35**: ir ($CHCl_3$) 3605, 3425, 1727, 1435, and 1360 cm^{-1}; pmr ($CDCl_3$) τ 6.40 (s, 6 H) and 9.17 (s, 9 H).

Dimethyl 7-7-Dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (37).—To a solution of 2.39 g (0.0134 mol) of the pyrrolidinenamine of 4,4-dimethylcyclohexanone in 15 ml of acetonitrile was added dropwise 3.18 g (0.0134 mol) of dimethyl γ-bromosaconate (**9**). Throughout the mesaconate addition and during the subsequent $10^1/_3$-hr reflux period the reaction was maintained in a nitrogen atmosphere. The imine salt was hydrolyzed by adding 1 ml of 5% aqueous acetic acid followed by an additional 30-min reflux period. The reaction was processed as in the preparation of ketone **7**. Evaporation of solvent yielded an orange oil whose fractionation gave 1.09 g (28.7%) of yellow oil, bp 142–144° (0.25 mm). The product appeared to consist of a single isomer, as indicated by pmr spectral data: ir ($CHCl_3$) 1735, 1435, 1275, and 1160 cm^{-1}; pmr ($CDCl_3$) τ 6.26 (s, 3 H), 6.30 (s, 3 H), 7.00 (m), 8.93 (s, 3 H), and 9.08 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.87; H, 7.98.

Epimerization of Dimethyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-one-2,3-dicarboxylate (37) with Sodium Methoxide.—To a solution of 0.148 g (0.533 mmol) of dimethyl 7,7-dimethylbicyclo-[3.3.1]nonan-9-one-2,3-dicarboxylate (**37**) in 5 ml of methanol was added 0.05 g (0.93 mmol) of sodium methoxide. The solution was maintained at reflux with an oil bath for 1 hr. The reaction mixture was treated according to the procedure used in the epimerization of ketone **7**. Evaporation of solvent gave 0.143 g (96.6%) of yellow oil which yielded 0.0815 g (57.0%) of white crystals, mp 102.5–103.5°, on treatment with ether. The residual oil, however, still contained considerable product. The product was characterized as epimerized keto diester **38** from its pmr spectrum: ir ($CHCl_3$) 1735, 1460, 1435, 1215, and 1170 cm^{-1}; pmr ($CDCl_3$) 6.30 (s, 6 H), 6.69 (m), 8.06 (m), 8.99 (s, 3 H), and 9.08 (s, 3 H).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.89; H, 7.81.

Methyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-ol-2-endo-carboxy-3-carboxylate γ-Lactone (39).—A solution of 0.202 g (0.701 mmol) of ketone **37** was dissolved in 1.5 ml of methanol. After the solution was cooled (15°), 0.0293 g (0.774 mmol) of sodium borohydride was added slowly with shaking. When the solution ceased bubbling, the reaction mixture was allowed to stand at room temperature for 20 min. Processing of the mixture as in the reduction of ketone **7**, followed by drying over anhydrous magnesium sulfate and evaporation of solvent, yielded 0.201 g (100%) of clear oil. The product was alcohol rather than γ-lactone, as evidenced by the infrared absorptions at 3600 (sharp) and 3500 cm^{-1} (broad). However, heating of the product at 200° for 2 hr in an oil bath gave 0.165 g (93.4%) of an orange oil which was the desired γ-lactone **39**. A sample was collected on glpc from a 5 ft × 0.5 in. 10% SE-30 on Gas-Chrom Q column for analysis.

The spectral properties of the alcohol follow: ir ($CHCl_3$) 3660, 3500, 1730, 1175, 1060, and 1020 cm^{-1}; pmr ($CDCl_3$) 6.32 (s, 6 H), 6.66 (m), 7.41 (s), 7.75 (m), 8.37 (m), 8.80 (s, 3 H), and 9.11 (s, 3 H).

The spectral properties of the γ-lactone **39** follow: ir ($CHCl_3$) 1775, 1730, 1450, 1430, 1170, and 1000 cm^{-1}; pmr ($CDCl_3$) 6.24 (s, 3 H), 6.87 (m), 7.23 (m), 7.79 (m), 8.16 (m), 8.96 (s, 3 H), 9.11 (s, 3 H) and 4.99 (t, 1 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.52; H, 8.02.

Epimerization of Methyl 7,7-Dimethylbicyclo[3.3.1]nonan-9-ol-2-carboxy-3-carboxylate γ-Lactone (39) with Potassium *t*-Butoxide.—A 0.149-g portion of crude γ-lactone **39** was purified *via* Kugelrohr distillation to give 0.1120 g (0.476 mmol) of yellow oil, bp 125° (0.05 mm). The distilled γ-lactone (0.120 g, 0.476 mmol) was dissolved in 3 ml of *t*-butyl alcohol (dried with calcium hydride) and treated with 0.015 g (0.13 mmol) of potassium *t*-butoxide. Stirring of the reaction mixture for 1 hr at room temperature followed by processing as in the epimerization of γ-lactone **14** yielded 0.0963 g (80.1%) of yellow oil. Column chromatography of the above oil over 5.00 g of silicic acid using 1% ether in benzene and 2% ether in benzene as eluents gave 0.0366 g (38.0%) of starting material and 0.0304 g (31.6%) of epimerized γ-lactone **40**: ir ($CHCl_3$) 1775, 1730, 1470, 1435, 1165, and 1000 cm^{-1}; pmr ($CDCl_3$) 5.09 (t, 1 H), 6.26 (s, 3 H), 6.88, 7.15, 7.81, 8.05, 8.28, 8.52 (multiplets), 8.97 (s, 3 H), and 8.93 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.58; H, 8.07.

Registry No.—**3**, 22262-60-8; **7**, 22262-61-9; **8**, 22262-62-0; **10**, 22262-63-1; 2,4-dinitrophenylhydrazone of **10**, 22262-64-2; **11**, 13015-13-9; **13**, 13015-26-4; **14**, 10555-68-7; **15**, 22262-68-6; **16**, 22262-69-7; **17**, 22262-70-0; **18**, 22262-71-1; **19**, 22262-72-2; **20**, 22262-73-3; **21**, 22262-74-4; **23**, 22262-75-5; **25**, 22287-48-5; **37**, 22262-76-6; **38**, 22319-55-7; **39**, 22262-77-7; **40**, 22262-78-8.