(50% yield) as a colorless oil: $[\alpha]^{26}_D$ -94.5° (c 0.308, EtOH); IR (neat film) 3400, 1025 cm^{-1}.

Methanesulfonate of (-)-24. To a chilled solution of (-)-**24** (100 mg, 0.595 mmol), $[\alpha]_D$ -94.5°, in dry pyridine (3 mL) was added methanesulfonyl chloride (205 mg, 1.78 mmol). The mixture was stirred for 3 h with ice cooling, allowed to stand overnight at room temperature, poured into ice-water, and extracted with $CHCl_3$. The extract was washed with 5% HCl, aqueous $NaHCO_3$ solution, and water and dried ($MgSO_4$). Removal of the solvent gave 130 mg of (-)-**25** (67% yield): mp 132-134 °C; $[\alpha]^{26}_D$ -35.7° (c 0.291, $CHCl_3$); IR (KBr) 1340, 1320, 1165, 930 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_6S_2$: C, 44.44; H, 6.22. Found: C, 44.25; H, 6.30.

(-)-3,6-Dimethyltricyclo[4.2.0.0^{3,8}]octane (26). To a suspension of (-)-**25** (120 mg, 0.370 mmol), $[\alpha]_D$ -35.7°, in dry ether (20 mL) was added $LiAlH_4$ (160 mg, 4.20 mmol) and then the mixture was refluxed for 20 h. Saturated aqueous NH_4Cl solution was added, the deposited inorganic solid was filtered, and the filtrate was dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity II) and fractions eluted with pentane afforded a colorless oil, which was distilled to furnish 23 mg of (-)-**26** (46% yield): bp 75-80 °C (air bath temperature) (30 mm); $[\alpha]^{26}_D$ -85.0° (c 0.178, EtOH); IR (neat film) 2940, 2870, 1450 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.88; H, 11.70.

(+)-Dimethyl *twist*-Brendane-3,6-dicarboxylate (33). Esterification of (+)-**13** (70 mg, 0.333 mmol), $[\alpha]_D$ +135° (c 0.610, MeOH) (optical purity 80%), with ethereal CH_2N_2 gave a solid product which was sublimed to furnish 56 mg of (+)-**33** (71% yield): mp 62-63 °C (sealed tube); $[\alpha]^{23}_D$ +113° (c 0.252, MeOH); IR (KBr) 1720, 1290, 1272, 1253, 1098 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.82; H, 7.63.

(+)-3,6-Bis(hydroxymethyl)-*twist*-brendane (34). Reduction of (+)-**33** (420 mg, 2.00 mmol), $[\alpha]_D$ +135°, with $LiAlH_4$ (114 mg, 3.00 mmol) was carried out as described for the preparation of (-)-**24**. Routine workup gave 330 mg of (+)-**34** (90% yield) as a white solid: mp 116-118 °C; $[\alpha]^{25}_D$ +134° (c 0.453, EtOH); IR (KBr) 3300, 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.21; H, 9.97.

(+)-3,6-Dimethyl-*twist*-brendane (36). A pyridine solution of (+)-**34** (453 mg, 2.39 mmol), $[\alpha]_D$ +134°, was treated with methanesulfonyl chloride (890 mg, 7.74 mmol) by the same manner described for the preparation of (-)-**25**, and 590 mg of (+)-**35** (73% yield) was obtained as a solid: $[\alpha]^{22}_D$ +60.3° (c 0.300, $CHCl_3$); IR (KBr) 1345, 1170, 945 cm^{-1}.

To a suspension of $LiAlH_4$ (715 mg, 18.8 mmol) in dry ether (80 mL) was added the dimesylate **35** (560 mg, 1.66 mmol), and the mixture was refluxed for 24 h. After workup as described for (-)-**26**, the crude product was chromatographed on neutral alumina (Woelm, activity III) and fractions eluted with pentane gave a colorless oil, which was distilled to furnish 70 mg of (+)-**36** (28% yield): bp 70-73 °C (air bath temperature) (20 mm); $[\alpha]^{25}_D$ +135° (c 0.241, EtOH); IR (neat film) 2940, 2870, 1450, 1375, 1335 cm^{-1}; ^1H NMR (CCl_4) δ 0.7-0.9 (m, 2 H), 0.95 (s, 6 H), 1.1-1.6 (m, 8 H), 1.7-1.9 (m, 2 H).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.79; H, 12.04.

Registry No. (-)-**10**, 73986-08-0; (+)-**11**, 63903-40-2; (-)-**12**, 73986-09-1; (+)-**13**, 63902-02-3; **14**, 74034-31-4; **15**, 74007-19-5; **16**, 73986-10-4; **17**, 63833-61-4; (±)-**18**, 73986-11-5; (-)-**18**, 74034-32-5; (+)-**18**, 74034-33-6; (-)-**20**, 73986-12-6; **21**, 49700-60-9; (-)-**22**, 74034-34-7; (-)-**24**, 73986-13-7; (-)-**25**, 73986-14-8; (-)-**26**, 73986-15-9; (-)-**27**, 73986-16-0; (-)-**28**, 73986-17-1; (+)-**31**, 63902-06-7; (+)-**33**, 73986-18-2; (+)-**34**, 73986-19-3; (+)-**35**, 73986-20-6; (+)-**36**, 73986-21-7.

Stereochemistry of Alkylation of Carboxylic Acid Salt and Ester α Anions Derived from Cyclic Systems

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A stereochemical study of the alkylation of α-lithiated carboxylate salts and esters has been performed. The α anions derived from the bicyclic acids *exo*-**1**, *endo*-**1**, and **7** (R = H) and the esters **4** and **7** (R = CH_3) yield predominantly exo alkylation. As an example, the α anion derived from ester **7** (R = CH_3) on treatment with CH_3I yields *exo*-**8** (R = R′ = CH_3) and *endo*-**9** (R = R′ = CH_3) in a 97:3 ratio, a highly stereoselective reaction. Addition of TMEDA to the reactions involving the α anions derived from *exo*- or *endo*-**1** did not change the stereochemical alkylation results. The α anions derived from the substituted cyclohexanecarboxylic acids **10**, **13**, **16**, **19**, or **22** (where R = H in each case) on methylation yield more axial methylation (axial/equatorial ratios of 0.4-2.7) than the α anions derived from the methyl esters corresponding to these acids. The α anions from the esters yield predominantly equatorial methylated products (e/a ratios varying from 4 to 9). The reasons for the different stereochemical results are discussed.

Many alkylations and other synthetic applications of α-metalated carboxylate salts[2] and esters[3] have appeared in recent literature. However, no studies of any depth have been reported which deal with the factors which might control the stereochemistry of alkylation of these reactive species.

Several reports dealing with the stereoselective methylations of ester enolates formed by Li/NH_3 reduction of substituted α,β-unsaturated esters have appeared.[4] High stereoselectivity was found in the Li/NH_3 reductive methylation of α anions of carboxylic acid salts in model studies of systems directed toward a synthesis of the gibberellins.[5] The Li/NH_3 reductive alkylations of 4-*tert*-

(1) Fellow of the Humphrey Chemical Co., North Haven, CT.

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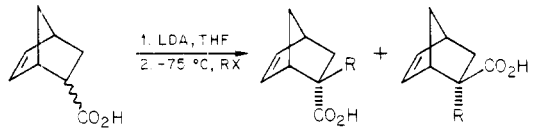
Table I. Alkylations of the Type 1 → 2 + 3



1 2 3

RX[a]	ratio (2:3)[b]	% unalkylated[c] 1 in crude rxn mixture
CH_3I[d]	66:34	<1 (endo)
CH_3I[e]	66:34	<1 (endo)
CH_3I[f]	66:34	traces
$(CH_3)_2SO_4$[f]	73:27	traces
CH_3CH_2I[f]	68:32	5 (exo), 4 (endo)
$CH_3(CH_2)_2I$[f]	82:12	5 (exo), 5 (endo)
$CH_3(CH_2)_3Br$[f]	88:12	4 (exo), 5 (endo)
$(CH_3)_2CHCH_2Br$[f]	81:19	34 (exo), 44 (endo)
$CH_2=CHCH_2Br$[f]	82:18	2 (exo), 6 (endo)
$(CH_3)_2CHI$[f]	72:28	16 (exo), 15 (endo)

[a] All alkylations were performed at −75 °C. The overall recovery of crude acids exceeded 85% in all cases. Reaction times: entries 1-4, 1 h; entries 5 and 8-10, 5 h; entries 6 and 7, 8 h. [b] Alkylated product ratio. Ratios were determined by GLC of the methyl esters prepared by treatment of the crude reaction product with CH_2N_2. The *exo*-2/*endo*-3 ratios for the methylated products could also be determined by proton NMR analysis of the crude acids (CH_3 absorptions)[11] and agreed favorably with the GLC data obtained for the methyl esters. The stereochemical assignments of the other unsaturated entries in Table I were determined by analogy to the methylated compounds,[12] in that the endo-alkylated methyl esters in each case were assumed to have a shorter retention time on a DEGS column. [c] Determined by GLC as in *b*. [d] From pure *endo*-1. [e] From pure *exo*-1. [f] From a mixture of *endo*-1 (88%) and *exo*-1 (12%).

butylbenzoic acid have been studied, and the cis/trans product ratio varied markedly with the alkylating agent.[6]

Attempted methylations of the α anion from 3,3-dimethylnorbornane-2-carboxylate were unsuccessful while the α anion from methyl 3,3-dimethylnorbornane-2-carboxylate gave a poor yield of exo-methylated product.[7] The methylation of a bicyclic ester α anion was unsuccessful[8] while attempted methylation of another bicyclic ester α anion led to a 2% product yield.[9] Stereoselective alkylations of α anions derived from lactones have been successfully accomplished in several cases.[10]

It was our intention to carry out a study aimed at determining the alkylation stereochemistry of enolate anions of several cyclic carboxylic acids and esters. The effects of altering the reaction parameters such as solvent, size and nature of the alkylating agent, choice of the countercation, reaction temperature, and potential intra- or intermolecular chelation effects were examined.

Results

Our initial alkylations were directed at the bicyclo[2.2.1]heptene skeleton, a system of rigid geometry. Pure *exo*- or *endo*-2-carboxybicyclo[2.2.1]hept-5-ene (*exo*-1 or *endo*-1) was treated with LDA in THF to produce the α anion, and then methyl iodide was added at −75 °C. The methylated products, *exo*-**2** (R = CH_3) and *endo*-**3** (R = CH_3), were formed in ca. a 2:1 ratio, respectively. This same product ratio was also obtained if a mixture of *exo*-1 and *endo*-1 (12:88 ratio) was used as the starting acid. The results of these and other alkylations (at −75 °C) are summarized in Table I.

Table II. Effect of TMEDA on the Alkylations[a] of 1

RX[b]	additive	ratio (2:3)[c]
CH_3I	none	66:34
CH_3I	TMEDA	66:34
CH_3CH_2I	none	68:32
CH_3CH_2I	TMEDA	69:31
$CH_2=CHCH_2Br$	none	82:18
$CH_2=CHCH_2Br$	TMEDA	80:20

[a] All alkylations were performed at −75 °C. In all cases, greater than 85% of the crude product was recovered. [b] Entry 1, from pure *endo*-1. All others from 12% *exo*-1/88% *endo*-1. [c] Alkylated product ratio.

Table III. Temperature Comparisons for Alkylations of 1

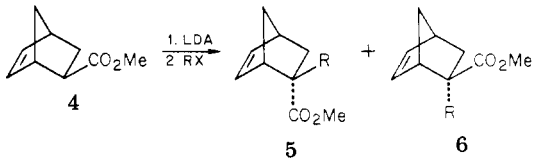
RX[a]	ratio (2:3)[g]	T, °C	t_{rxn}, h
$CH_3CH_2CH_2I$	82:18	−75	8
$CH_3CH_2CH_2I$	82:18	*f*	6
$CH_3CH_2CH_2I$	82:18	50[c]	6
$CH_3(CH_2)_2CH_2Br$	88:12	−75	8
$CH_3(CH_2)_2CH_2Br$	87:13	*f*	5
$CH_3(CH_2)_2CH_2Br$	84:16	50[c]	5
$CH_3(CH_2)_3CH_2Br$	84:16	50[c]	5
$CH_3(CH_2)_4CH_2Br$	87:13	50[c]	5
$(CH_3)_2CHCH_2Br$	81:19	−75	5
$(CH_3)_2CHCH_2Br$	82:18	*f*	20
$(CH_3)_2CHCH_2Br$	80:20	50[d]	6
$(CH_3)_2CHI$	72:28	−75	5
$(CH_3)_2CHI$	72:28	*f*	20
$(CH_3)_2CHI$	74:26	50[e]	6
$CH_3CHBrCH_2CH_3$[b]		50	6

[a] In all cases greater than 85% product recovery. Done by method A (no TMEDA). [b] An 86% yield of starting acid was recovered. [c] About 2% starting acid was recovered which was about 50% exo and 50% endo. [d] 3% *endo*-1 and 6% *exo*-1 were also present. [e] 6% *endo*-1 and 12% *exo*-1 were also present. [f] Room temperature. [g] Alkylated product ratio.

The addition of tetramethylethylenediamine (TMEDA) to the reaction mixture was investigated to determine if the alkylation product ratio would be altered. The role of the TMEDA would be to break up any possible α-anion molecular aggregates. As can be seen from the data presented in Table II, the exo/endo ratio of alkylated products was virtually unaffected.[2e]

The yields of alkylated products could be improved if the alkylations were performed at 50 °C. This perhaps indicates that the competitive E2 process is suppressed at the higher temperature, although the exo/endo alkylated product ratio is unaffected (Table III).

We next turned our attention to the enolate derived from *exo*-2-(carbomethoxy)bicyclo[2.2.1]hept-5-ene (**4**).



4 5 6

Treatment of 4 with LDA/THF at −75 °C leads to the enolate which on treatment with methyl iodide yields the methylated products *exo*-**5** (R = CH_3) and *endo*-**6** (R =

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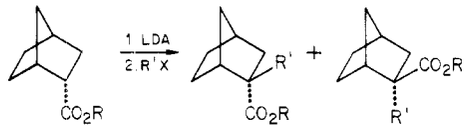
Table IV. Alkylations[a] of the Type 7 → 8 + 9



7 8 9

R	R'X	ratio (8:9)[b]
H	MeI	74:26
H	$(CH_3)_2SO_4$	78:22
H	EtI	85:15
Me	MeI	97:3

[a] All alkylations were performed at −75 °C. Product recovery >90%. [b] Alkylated product ratio.

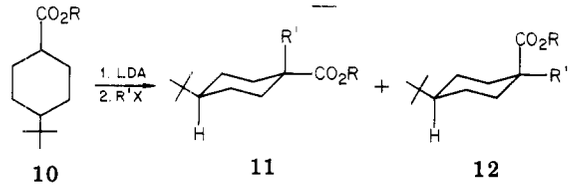
CH_3) in a 94:6, ratio, respectively. Alkylation of the ester enolate of **4** with *n*-butyl bromide at −75 °C leads to an *exo*-**5** (R = $CH_3(CH_2)_3$)/*endo*-**6** (R = $CH_3(CH_2)_3$) ratio of 87:13.

Exo methylation is more stereoselective in the ester α anion in comparison with the α anion derived from the acid. On the other hand, the butylation stereochemistry is nearly the same. In a previously reported study of a substituted ester related to **4**, oxygenation of the enolate led to an exo/endo product ratio of ca. 2:1.[13]

Alkylations of the α anion from *endo*-2-carboxybicyclo[2.2.1]heptane (**7**) gave somewhat greater exo alkylation than the corresponding unsaturated analogue **1**. These alkylation results are summarized in Table IV. Methylation of the corresponding methyl ester (**7**, R = CH_3) α anion leads to an **8** (R = CH_3, R′ = CH_3)/**9** (R = CH_3, R′ = CH_3) ratio of 97:3.

It is of interest to note that on GLC analysis (DEGS column) the saturated ester *exo*-**8** isomers elute more rapidly than the *endo*-**9** isomers in contrast to the unsaturated ester isomers for which *endo*-**3** has a shorter retention time than *exo*-**2**. This was substantiated by catalytic hydrogenation of methylated mixtures of **2** and **3** to yield **8** and **9** and by a study of retention times.

We next investigated the 4-*tert*-butylcyclohexanecarboxylic acid and ester systems. Reaction of **10** (R = H, a 36:64 mixture of cis/trans isomer) with 2 equiv of LDA followed by treatment of the α anion with methyl iodide at −75 °C (or at 50 °C) led to a 59:41 mixture of axial (**11**; R = H, R′ = CH_3) vs. equatorial (**12**; R = H, R′ = CH_3) methylated products in an overall 90% yield.



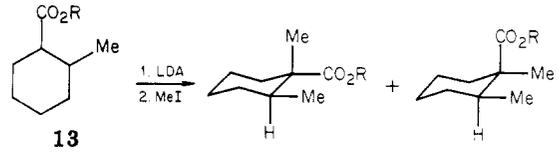
10 11 12

On the other hand, alkylation of the α anion derived from ester **10** (R = CH_3, a 50:50 cis/trans mixture) with methyl iodide at −75 °C led to an 84:16 mixture of equatorial (**12**; R = R′ = CH_3) vs. axial (**11**; R = R′ = CH_3) products in a 94% yield. Alkylation in a similar fashion with *n*-butyl bromide led to an 87:13 mixture of equatorial (**12**; R′ = *n*-butyl, R = CH_3) vs. axial (**11**; R′ = *n*-butyl, R = CH_3) products in a 93% yield.

The epimeric methylated carboxylic acid products **11** and **12** could be identified and separated by utilizing their different esterification rates toward BF_3 in methanol. The assignment of structures was confirmed by a comparison of the physical properties of the isolated acids with previously reported data.[14] These pure acids were converted into the methyl esters and used for retention time product analysis of the alkylation mixtures.

In several instances it has been shown that altering the alkali metal countercation results in changes in the stereochemical outcome of enolate alkylations.[15,16] We thus endeavored to determine such an effect on the 4-*tert*-butylcyclohexanecarboxylic acid and ester systems. Treatment of *cis*-4-*tert*-butylcyclohexanecarboxylic acid (**10**, R = H) with excess sodium naphthalenide followed by addition of methyl iodide improved the stereoselectivity of the methylation, the ratio of axial to equatorial attack going from 59:41 with lithium as counteranion to 83:17. Yields of C-alkylated products were poor (20%), however, and various attempts at improving the yields were unsuccessful. In order to show that this dramatic effect was not a result of the nature of the base, we used lithium naphthalenide to generate the α anion, and this gave the same results as those that were obtained with LDA. Use of potassium naphthalenide gave only traces of alkylated product acids. Presumably, the dianion is formed as a minor component of an equilibrium mixture, since treatment of pure *cis*-4-*tert*-butylcyclohexanecarboxylic acid with excess potassium naphthalenide followed by attempted methylation yielded mainly *trans*-4-*tert*-butylcyclohexanoic acid and only traces of alkylated products. This explanation could also be applied to the poor yields obtained with sodium naphthalenide. Treatment of methyl 4-*tert*-butylcyclohexanecarboxylate with either NaH or KH followed by addition of CH_3I led only to the isolation of unchanged starting material.

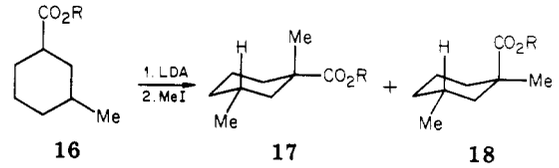
Dilithium 2-methylcyclohexanecarboxylate [generated from **13** (R = H) via LDA in THF] on methylation with methyl iodide gave a 30:70 product ratio of **14** (R = H) to **15** (R = H), favoring the *trans*-dimethyl adduct whether



13 14 15

the methylation was performed at −75 °C or at room temperature. The methyl ester enolate from **13** (R = CH_3) gave a 20:80 product ratio (methylation with methyl iodide) of **14** (R = CH_3) to **15** (R = CH_3) at −75 °C and a 75:25 ratio at 25 °C.

The 3-methylcyclohexanecarboxylic acid (**16**, R = H) and ester (**16**, R = CH_3) enolates were studied. The reaction of dilithium 3-methylcyclohexanecarboxylate with methyl iodide at −75 °C and at room temperature gave respective ratios of **17** (R = H) to **18** (R = H) of 48:52 and



16 17 18

45:55, favoring the *cis*-dimethyl adduct **18** (R = H). The α-lithio methyl ester enolate gave significantly greater stereoselectivity. Methylation at −75 °C and at room temperature gave, respectively, ratios of 10:90 and 24:76, favoring, as above, the *cis*-dimethyl adduct **18** (R = CH_3).

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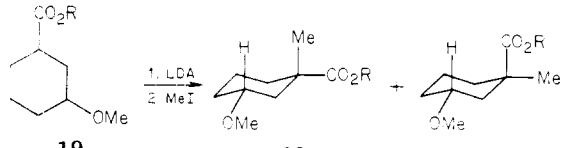
Methylation of the enolate anion (−75 °C) derived from the corresponding ethyl ester (**16**, R = CH_2CH_3) gave an identical result.

Many reports have appeared in the literature concerning the ability of a heteroatom (i.e., oxygen[17] or nitrogen[18]) to chelate either inter- or intramolecularly with the metal countercation of a carbanionic species. This heteroatom chelation effect has been shown to be an influential factor in governing regiochemically,[19] stereochemically,[20] or asymmetrically[21] selective (or specific) synthetic transformations. We were also interested in investigating the stereochemistry of alkylation of enolate anions of carboxylic acid salts and esters containing a heteroatom. As our model systems, we chose the 3- and 4-methoxycyclohexanecarboxylic acids and the corresponding methyl esters.

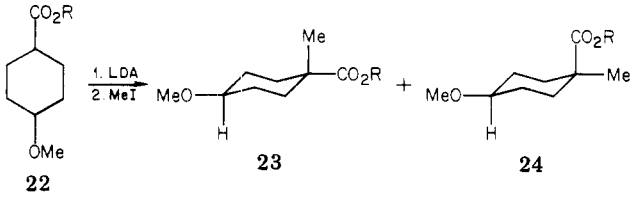
Treatment of 3-methoxycyclohexanecarboxylic acid **19** (R = H) with 2 equiv of LDA in THF followed by methylation with methyl iodide at −75 °C yielded the methylated products. It was determined that the axial methylated epimer **20** (R = H) was the major product of the



19 **20** **21**

reaction by a ratio of 73:27 over the equatorially alkylated adduct **21** (R = H). Conversely, the corresponding 3-methoxy methyl ester enolate prepared from **19** (R = CH_3) afforded a product mixture favoring the equatorially methylated epimer **21** (R = CH_3) in a ratio of 78:22.

Treatment of 4-methoxycyclohexanecarboxylic acid **22** (R = H) with 2 equiv of LDA in THF followed by methylation with methyl iodide and gas chromatographic analysis of the corresponding methyl esters of the crude isolated product acid showed two components. No ap-



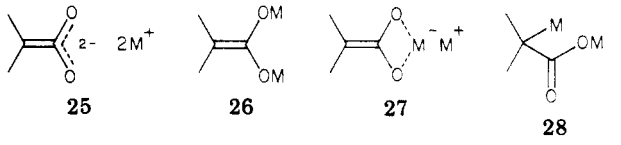
22 **23** **24**

preciable difference in reactivity was observed between the two epimers of the product mixture toward BF_3 in methanol. Identification of the products was ultimately accomplished via fractional crystallization of one of the components. Gas chromatographic analysis of the corresponding methyl ester showed it to be one pure isomer (the epimer of longer retention time). Treatment of the methoxy acid with trimethylsilyl iodide by the method of Jung and Lyster[22] followed by successful lactonization of the resulting hydroxy acid thus confirmed the structure of the crystallized epimer as **24** (R = H).

The α anion from acid **22** (R = H) on methylation with methyl iodide led to a **23** (R = H) to **24** (R = H) ratio of 46:54 at −75 °C and to a similar ratio at 25 °C. Methylation of the α anion derived from the ester **22** (R = Me) led to a **23** (R = CH_3) to **24** (R = CH_3) ratio of 16:84 (−75 °C).

Discussion

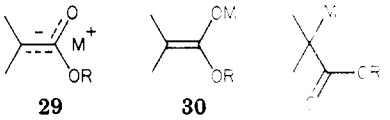
While the gross structure of the α anions derived from carboxylate salts can be described as structure **25**, the



25 **26** **27** **28**

natures of the solvent and the cation determine the true structure of the anion in solution (e.g., tight ion pair). These bidentate anions could exist in several cationotropic forms which might be in equilibrium[23] such as **26**,[24] **27**,[25] and **28**.[2e]

Similarly, the α anions derived from esters can be described as **29**, but again, the forms **30** and **31** may be in



29 **30** **31**

equilibrium, and aggregations could exist. In fact, the infrared spectra of several α-lithioisobutyrates indicate a keto structure such as **31**,[26] which is also supported by theoretical analysis.[27] Indeed, these esters of α-lithio acids form aggregates in solution and are readily soluble in THF,[29] which complicates the structural picture. It is to be noted that electrophiles such as $(CH_3)_3SiCl$ effect both C- and O-silylation while alkyl halides effect C-alkylations.[29]

Let us first turn our attention to the α anions derived from the bicyclic systems studied here. It might be noted that the sulfenylation of the α anion derived from **1** has been reported to lead predominantly to exo product.[29b] Exomethylation of the α anion derived from 2-cyanobicyclo[2.2.1]hept-5-ene has also been found.[29c] Since *exo*- or *endo*-**1** yields the same stereochemical result on methylation, the same intermediate must be involved. The observation that TMEDA does not change the stereoselectivity of alkylation suggests that higher aggregates are not present in the THF solutions. The main features that can be gleaned from the data of Tables I–III (for **1**) are the facts (1) that C-alkylation dominates in all cases, (2) that the alkylation stereochemistry is not a function of the temperature, and (3) that higher alkylation yields can be achieved at 50 °C. The size of the alkyl group of the alkylating agent has a modest effect of the enhancement

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Table V. Stereochemical Results from Substituted Cyclohexanes

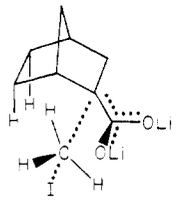
groups on cyclohexane	e/a ratio[a]	
	ester α anion	acid α anion
2-CH_3	80:20	70:30
3-CH_3	90:10[b]	52:48
3-OCH_3	78:22	27:73
4-*t*-Bu	85:15	41:59
4-OCH_3	84:16	54:46

[a] Ratio of the direction of attack (equatorial/axial) of CH_3I. All Comparisons are made at −75 °C. [b] Note here that at room temperature the ratio is 74:26.

of the exo/endo ratio. Secondary alkyl halides such as isopropyl iodide can be used as alkylating agents while *sec*-butyl bromide cannot be used.

The unalkylated recovered acid, in general, consisted of approximately equal amounts of *exo*-1 and *endo*-1, with *exo*-1 predominating in some runs performed at 50 °C. The exact significance of this recovery data is clouded by the facts that equilibration could occur on formation of the α-metalated species (diisopropylamine is present in the reaction medium), and quenching of the unalkylated α-metalated species with water could lead to C- or O-protonation (followed by tautomerization).[29d]

In the comparison of the stereochemical data for the α anions derived from unsaturated 1 and saturated 7 (R = H), the somewhat greater exo methylation in the latter case can most likely be attributed to the increased steric interaction of the electrophile approaching the endo face of the saturated acid α anion derived from 7 (R = H) as shown in **32**. In all the α anions derived from the carboxylate salts, the transition states would be expected to be reactant-like (very reactive α anions). On the other hand, the enolates derived from the esters would be less reactive and have reactant-like transition states with slightly greater C–C bond formation of the approaching electrophile in comparison to the dianions.



32

On this basis, the α anion derived from the unsaturated acid **1** compared with the α anion derived from the unsaturated ester **4** might be expected to lead to less exo product on methylation. The transition state in the latter would be more sterically demanding and would energetically favor exo approach of the methyl iodide. This trend would also follow in the α anion from **7** (R = H) compared to the α anion from ester **7** (R = CH_3).

In the cases of the substituted cyclohexanes, it might be useful to summarize the stereochemical results in the form presented in Table V.

In previous studies, it has been shown that the α anions from 1-acetyl-,[30] 1-cyano-,[30,31] and 1-benzothiazole-substituted[32] 4-*tert*-butylcyclohexanes lead predominantly to equatorially alkylated products.

In all cases of the ester α anions derived from the substituted cyclohexanes, equatorial incorporation of the methyl group predominates. The $-\Delta G°$ values for the CO_2CH_3 and CH_3 groups are 1.3 and 1.7 kcal/mol, respectively.[33] If, at the transition state, a slight distortion of the planar π enolate occurs, the methylation would favor the introduction of the CH_3 group into the equatorial position (some steric control of a transition state which has some developing tetrahedral character).

On the other hand, let us contrast the data for alkylations of the α anions derived from the acid salts and the ester α anions. In all cases, the amount of axial methylation increases and, indeed, in two cases is the predominant route. The $-\Delta G°$ for CO_2^- is 1.9,[33] and arguments based on product-like transition states (which we feel is unlikely) would favor axial introduction of the methyl group. The "ate" complexes of the α anions from the acid salts are probably more reactive than the enolate α anions derived from the esters, and less selectivity would also be expected as the equatorial and axial steric approaches are not drastically different.

The higher axial methylation which is found with Na^+ as the cation in the methylation of the 4-*tert*-butyl system might reflect a more ionic transition state in (higher carbon charge density in the axial position) comparison with Li^+.

Conclusions

From a synthetic standpoint, it is clear that α anions derived from esters are more stereoselective in alkylations, and in all the cyclic systems studied the exo or equatorial incorporation of the alkyl group predominates. In the cyclohexane systems studied here, the use of the α anion derived from the acid salt in comparison with the ester α anion leads to more axial alkylation. One has some control over the stereoselectivity of alkylation by the choice of either the α anion derived from the ester or the acid salt.

Experimental Section

Materials. Tetrahydrofuran was obtained dry and oxygen free by distillation from a solution of ketyl (benzophenone and sodium). Diisopropylamine was dried by being refluxed over calcium hydride and was freshly distilled prior to use. Tetramethylethylenediamine (TMEDA) was purified by sequential distillation from calcium hydride and α-naphthyl isocyanate and stored over 4A molecular sieves prior to use. All other solvents were distilled before use. *n*-Butyllithium (2.0–2.5 M in hexane) was purchased from Ventron Corp. and titrated prior to use. Product carboxylic acids were converted to the corresponding methyl esters for GLC analysis via diazomethane generated from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) and 5 M NaOH.

Equipment. Analyses by GLC were conducted on a F&M Model 700 gas chromatograph equipped with a flame-ionization detector and the following columns: column A, 8 ft × $^1/_4$ in., 10% DEGS on Chromosorb P; column B, 10 ft × $^1/_4$ in., 5% TRIS on Chromosorb G. All percentages are raw data from peak-heights vs. half-widths and are accurate to ±3%. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The proton NMR spectra were obtained by using a JEOL MH-100 or a JEOL C-60HL spectrophotometer using $CDCl_3$ as solvent with 1% Me_4Si as internal standard unless otherwise indicated. The infrared spectra were obtained by using a Perkin-Elmer 267 or 237B grating infrared spectrophotometer. Low-pressure catalytic hydrogenations (0–50 psi) were conducted in a Series 3910 Parr shaker-type hydrogenation apparatus.

***exo*- and *endo*-2-Carboxybicyclo[2.2.1]hept-5-enes (*exo*-1 and *endo*-1).** A variation of the procedure of Alder and coworkers[34] was utilized. The product was crystallized to afford

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the epimeric acids as a white solid, mp 37–41 °C. GLC analysis of the corresponding methyl esters (via diazomethane) at 120 °C (column A) showed two peaks in order of increasing retention time: exo (12%) and endo (88%).[12]

***endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (*endo*-1).** The procedure of Van Tamelen and Shamma[36] and Berson and Ben-Efraim[37] was used.

***exo*-2-Carboxybicyclo[2.2.1]hept-5-ene (*exo*-1).** A variation of the procedure of Roberts et al.[38] was utilized. Recrystallization from pentane afforded 4.85 g of pure *exo*-2-carboxybicyclo-[2.2.1]hept-5-ene (*exo*-1): mp 43–44 °C (lit.[37] mp 44–45 °C); IR (KBr) 2300–3500, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.24–1.72 (m, 3 H), 1.84–2.52 (m, 2 H), 2.88–3.22 (m, 2 H), 6.24 (s, 2 H), 12.38 (s, 1 H); GLC analysis of the corresponding methyl ester (via diazomethane) at 120 °C (column A) showed one peak.

General Preparation of the Dianions. Method A. *n*-BuLi (4.55 mL, 10 mmol, 2.2 M in hexane) was added to a solution of diisopropylamine (1.4 mL, 10 mmol) in 50 mL of anhydrous THF at −75 °C under a N_2 atmosphere, and the mixture was stirred for 0.5 h. A 5-mmol sample of the appropriate acid dissolved in 8 mL of anhydrous THF was then added via syringe. After the initial exothermic reaction had subsided, the reaction mixture was warmed to room temperature and then heated at 50 °C for 2 h.

Method B. TMEDA (1.5 mL, 10 mmol) was added to the THF and diisopropylamine prior to the *n*-butylithium addition.

Methylation of the Dianion Derived from *endo*- or *exo*-2-Carboxybicyclo[2.2.1]hept-5-ene (1). The resulting white suspension of the α anion was cooled to −75 °C, and methyl iodide (0.34 mL, 5.5 mmol) was added. Stirring at −75 °C was continued for 1 h, and then the mixture was warmed to room temperature and quenched with ice/H_2O containing 40 mL of pentane. The layers were separated, and the organic phase was washed 1 time with 20 mL of cold H_2O. The combined aqueous fractions were then washed three times with 30-mL portions of ether, acidified (2 N HCl), and extracted four times with 30-mL portions of pentane. The pentane extracts were washed one time with 30 mL of cold H_2O, one time with 30 mL of 10% $Na_2S_2O_3$ solution, and one time with 30 mL of saturated NaCl solution. The pentane extracts were then dried (Na_2SO_4), and the solvent was evaporated to leave 0.67 g (88%) of a 2:1 mixture of *exo*-2-methyl-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene and *endo*-2-methyl-*exo*-2-carboxybicyclo[2.2.1]hept-5-ene as evidenced by comparison with previously reported ^1H NMR[11] data and their relative GLC retention times:[12] NMR ($CDCl_3$) δ 1.15 (s, 3 H, *exo*-methyl), 1.47 (s, 3 H, *endo*-methyl); GLC analysis of the corresponding methyl esters (via diazomethane) at 120 °C (column A) showed two peaks [retention times: *exo*-methyl, 19.0 min (66.0%); *endo*-methyl, 17.2 min (34.0%)].

Alkylations of Lithium 2-Lithiobicyclo[2.2.1]hept-5-ene-2-carboxylate. The resulting white suspension of the dianion of 2-carboxybicyclo[2.2.1]hept-5-ene in THF as prepared by either methods A or B was adjusted to the desired temperature, and the alkylating agent (5.5 mmol) was added. The reaction temperature was maintained with stirring for 1–20 h. The reaction was worked up as in the methylation experiment. The GLC analytical data for the methyl esters obtained by treatment of the crude acids with CH_2N_2 were previously tabulated in Tables I, II, and III of the text.

***exo*-2-(Carbomethoxy)bicyclo[2.2.1]hept-5-ene (4).** *exo*-2-Carboxybicyclo[2.2.1]hept-5-ene (8.63 g, 63 mmol) was taken up in 60 mL of methanol, *p*-toluenesulfonic acid (0.2 g) was added as catalyst, and the mixture was refluxed for 23 h. The reaction mixture was then cooled to room temperature and poured into 150 mL of cold H_2O and extracted three times with 40-mL portions of hexane. The combined hexane extracts were then in turn washed two times with 40-mL portions of cold H_2O, one time with 40 mL of saturated $NaHCO_3$ solution, and one time with 40 mL of saturated NaCl solution. The hexane extracts were then dried (Na_2SO_4), and the solvent was evaporated. The residue was distilled to afford pure *exo*-2-(carbomethoxy)bicyclo[2.2.1]-hept-5-ene: bp 93–94 °C (22 mm) [lit.[39] bp 86.5 °C (17 mm)]; NMR ($CDCl_3$) δ 1.26–1.68 (br m, 3 H), 1.88–2.42 (m, 2 H), 2.94–3.22 (br d, 2 H), 3.81 (s, 3 H), 6.34 (s, 2 H); GLC analysis at 145 °C (column A) showed one peak.

Methylation of the Enolate Anion of 2-(Carbomethoxy)-bicyclo[2.2.1]hept-5-ene (4). *n*-Butyllithium (2.2 mL, 5 mmol, 2.3 M in hexane) was added to a solution of diisopropylamine (0.7 mL, 5 mmol) in 40 mL of anhydrous THF at −75 °C under a N_2 atmosphere, and the mixture was stirred for 20 min. *exo*-2-(Carbomethoxy)bicyclo[2.2.1]hept-5-ene (0.76 g, 5 mmol) dissolved in 8 mL of anhydrous THF was added at such a rate so as to keep the reaction temperature below −65 °C. The resultant clear, almost colorless solution was stirred at dry ice temperature for 1 h, and methyl iodide (3.1 mL, 5 mmol) was added. Stirring at −75 °C was continued for an additional 2 h, whereupon the reaction was warmed to room temperature and then poured into ice/water containing 30 mL of pentane. The layers were separated, and the aqueous portion was extracted three times more with 25-mL portions of pentane. The extracts were then washed two times with 30 mL of cold H_2O, one time with 30 mL of 10% $Na_2S_2O_3$ solution, and one time with 30 mL of saturated NaCl solution. The extracts were then dried (Na_2SO_4), and the solvent was evaporated to leave 0.75 g (90.3%) of an epimeric mixture of *endo*- and *exo*-2-methyl-2-(carbomethoxy)bicyclo[2.2.1]hept-5-enes as pale yellow oil: NMR ($CDCl_3$) δ 1.36–1.80 (m, 6 H), 2.01 (m, 1 H), 2.80–3.02 (br s, 2 H), 3.71, 3.80 (s, 3 H), 6.26 (m, 2 H); GLC analysis at 145 °C (column A) showed two product peaks [*endo*-methyl (**6**, R = CH_3; 6.5%) and *exo*-methyl (**5**, R = CH_3; 93.5%) in order of increasing retention time].

***endo*-2-Carboxybicyclo[2.2.1]heptane (7, R = H).** *endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (*endo*-1; 13.0 g, 94 mmol) was dissolved in 200 mL of ethyl acetate, and 10% palladium on powdered charcoal (Matheson, 0.5 g) was added as a catalyst. The H_2 pressure was maintained at 30 psi until the theoretical amount of hydrogen had been taken up. The reaction mixture was then filtered through Celite and the solvent evaporated. The resultant semisolid material was taken up in 60 mL of pentane and recrystallized to afford 11.2 g (84%) of *endo*-2-carboxybicyclo-[2.2.1]heptane: mp 63–66 °C (lit.[37] mp 64–66 °C); NMR ($CDCl_3$) δ 1.23–1.88 (m, 8 H), 2.23–2.48 (m, 1 H), 2.53–3.12 (m, 2 H); GLC analysis of the corresponding methyl ester (via diazomethane) at 116 °C (column A) showed one peak.

Alkylations of the Dianion of 2-Carboxybicyclo[2.2.1]-heptane. The cloudy suspension of the dianion of 2-carboxybicyclo[2.2.1]heptane (prepared via the general preparation described above) was cooled to −75 °C, and the alkylating agent, CH_3I, $(CH_3)_2SO_4$, or CH_3CH_2I (5.5 mmol), was added. Stirring at ambient temperature was continued overnight. Workup as previously described for the dianions for 1 afforded an epimeric mixture of *endo*- and *exo*-2-alkyl-2-carboxybicyclo[2.2.1]heptanes.

***endo*-2-(Carbomethoxy)bicyclo[2.2.1]heptane (7, R = CH_3).** *endo*-2-Carboxybicyclo[2.2.1]heptane (1.89 g, 13.5 mmol) was taken up in 100 mL of methanol. *p*-Toluenesulfonic acid (0.1 g) was added as catalyst and the mixture refluxed overnight. The reaction mixture was cooled to room temperature, poured into 500 mL of cold H_2O, and extracted five times with 50-mL portions pentane. The pentane extracts were then washed two times with 50-mL portions of cold H_2O, one time with 50 mL of saturated $NaHCO_3$ solution, and one time with 50 mL of saturated NaCl solution. The pentane extracts were then dried (Na_2SO_4), and the solvent was evaporated to leave a pale yellow oil. Distillation afforded 1.77 g (85.2%) of pure *endo*-2-(carbomethoxy)bicyclo-[2.2.1]heptane as a colorless oil: bp 75 °C (oil bath temperature 18 mm) [lit.[40] bp 90 °C (21 mm)]; NMR ($CDCl_3$) δ 1.06–1.84 (br m, 8 H), 2.17–2.97 (br m, 3 H), 3.68 (s, 3 H); GLC analysis, 118 °C, one peak.

Methylation of the Enolate Anion of 2-(Carbomethoxy)-bicyclo[2.2.1]heptane. The α anion was prepared as in the case of **4**. Stirring at dry ice temperature was continued for 1 h, whereupon methyl iodide (0.13 mL, 2 mmol) was added and the

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stirring continued at −75 °C for an additional hour. The reaction mixture was then warmed to room temperature. Workup by the procedure described for the unsaturated ester afforded 0.31 g (91.7%) of an epimeric mixture of *endo*- and *exo*-2-methyl-2-(carbomethoxy)bicyclo[2.2.1]heptanes as a pale yellow oil: NMR ($CDCl_3$) δ 1.11–1.80 (br m, 7 H), 1.28 (s, 3 H), 2.08–2.46 (m, 3 H), 3.80 (s, 3 H); GLC analysis, 117 °C, two peaks [retention times: *exo*-methyl, 8.1 min (96.8%); *endo*-methyl, 9.0 min (3.2%)].

Preparation of an Epimeric Mixture of 2-Methyl-2-carboxybicyclo[2.2.1]heptanes. An epimeric mixture (2:1) of *exo*-2-methyl-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene and *endo*-2-methyl-*exo*-2-carboxybicyclo[2.2.1]hept-5-ene (0.63 g, 4 mmol) was taken up in 50 mL of ethanol, and 10% palladium on powdered charcoal (0.5 g) was added. The hydrogen pressure was maintained at 40 psi until the uptake ceased. The reaction mixture was then filtered through Celite and the solvent evaporated. GLC analysis of the corresponding methyl esters (via diazomethane) at 117 °C (column A) showed two peaks [retention times: *exo*-methyl, 8.15 min (66%); *endo*-methyl, 9.0 (34%)].

Preparation of an Epimeric Mixture of 2-Ethyl-2-carboxybicyclo[2.2.1]heptanes. An epimeric mixture (2:1) of *exo*-2-ethyl-2-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene and *endo*-2-ethyl-*exo*-2-carboxybicyclo[2.2.1]hept-5-ene (0.78 g, 4.7 mmol) was hydrogenated as in the methyl case above. GLC analyses of the corresponding methyl esters (via CH_2N_2) at 113 °C (column A) showed two peaks of retention times 25.3 (*exo*-ethyl, 68%) and 27.1 min (*endo*-ethyl, 32%).

Preparation of an Epimeric Mixture of *cis*- and *trans*-4-*tert*-Butylcyclohexanecarboxylic Acids. 4-*tert*-Butylbenzoic acid (21 g) was taken up in 100 mL of glacial acetic acid, and platinum oxide (0.5 g) was added as a catalyst. The hydrogen pressure was maintained at 50 psi until the uptake ceased. The reaction mixture was filtered through Celite and the filtrate diluted with 700 mL of H_2O. The precipitated product was taken up in 150 mL of ether and washed three times with 50-mL portions of cold H_2O and two times with 50-mL portions of saturated NaCl solution. The ether portion was then dried ($MgSO_4$) and filtered. The ether solution was diluted with 100 mL of hexane and the volume reduced to 75 mL. Crystallization afforded the *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids (20.2 g) as an epimeric mixture: NMR ($CDCl_3$) δ 0.85, 0.87 (s, 9 H), 0.95–2.87 (m, 10 H), 12.13 (br s, 1 H); GLC of corresponding methyl esters (via diazomethane) at 163 °C showed two peaks [retention times: cis, 7.6 min (36%); trans, 9.8 min (64%)].

Separation of *cis*- and *trans*-4-*tert*-Butylcyclohexanecarboxylic Acids. The procedure of Van Bekkum et al.[41] was used. Recrystallization from acetone/water afforded pure *trans*-4-*tert*-butylcyclohexanecarboxylic acid: mp 173.5–175 °C (lit.[41] mp 175–176 °C); GLC of the corresponding methyl ester (via diazomethane) at 163 °C (column A) showed only one peak (retention time 9.8 min). Crystallization afforded 1.41 g of pure *cis*-4-*tert*-butylcyclohexanecarboxylic acid: mp 117–118 °C (lit.[41] mp 116–118 °C); GLC one peak (retention time 7.6 min).

Methylation of Dilithium 4-*tert*-Butylcyclohexanecarboxylate at −75 °C. The α anion was prepared by the general procedure. The suspension was cooled at −75 °C, and methyl iodide (0.50 mL, 8 mmol) was added. Stirring at dry ice temperature was continued for 2 h, and then the mixture was warmed to room temperature. Workup by the general procedure afforded 0.89 g of an epimeric mixture (41:59) of the *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanecarboxylic acids: NMR ($CDCl_3$) δ 0.86, 0.89 (s, 9 H), 1.23, 1.26 (s, 3 H), 0.9–2.26 (m, 9 H), 11.53 (br s, 1 H); GLC analysis of the corresponding methyl esters (via diazomethane) at 159 °C (column B) showed two peaks [retention times: *cis*-carboxy, 4.6 min (41%); *trans*-carboxy, 7.4 min (59%)].

Preparation and Methylation of Dilithium 4-*tert*-Butylcyclohexanecarboxylate via Lithium Naphthalenide. Lithium metal (ribbon; 17.5 mg, 2.5 mmol) was added to a solution of naphthalene (160 mg, 1.25 mmol) in 40 mL of anhydrous THF at room temperature under a N_2 atmosphere. Stirring at room temperature was continued until all the lithium had been consumed (3 h). To the resultant dark green solution was added *trans*-4-*tert*-butylcyclohexanecarboxylic acid (92 mg, 0.5 mmol) dissolved in 8 mL of anhydrous THF, and then the mixture was heated at 50 °C for 2.5 h. The resultant yellow/red solution was cooled to −75 °C, and methyl iodide (0.31 mL, 5.0 mmol) was added. Stirring at dry ice temperature was continued for 45 min. The mixture was then warmed to room temperature and stirred for an additional 45 min. Workup afforded 86 mg (86.9%) of an epimeric mixture of *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanecarboxylic acids: NMR ($CDCl_3$) δ 0.86, 0.89 (s, 9 H), 1.23, 1.26 (s, 3 H), 0.9–2.46 (m, 9 H), 11.45 (br s, 1 H); GLC analysis of the corresponding methyl esters (diazomethane) at 159 °C (column B) showed two peaks (retention times: *cis*-carbomethoxy, 4.6 min (42%); *trans*-carbomethoxy, 7.4 min (58%).

1-Methyl-*trans*-4-*tert*-butylcyclohexanecarboxylic Acid. An epimeric mixture of *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanecarboxylic acids (0.2 g, 1 mmol) was added to 10 mL of 10% BF_3 in methanol, and the mixture was heated on a steam bath for 5 min. The reaction mixture was then poured into 30 mL of 5% NaOH solution and extracted three times with 20-mL portions of pentane. The pentane extracts were then dried (Na_2SO_4), and the solvent was evaporated. The residue was then taken up in 50 mL of 95% ethanol and KOH (5.6 g, 100 mmol). The reaction mixture was then heated at reflux overnight, cooled to room temperature, and poured into 150 mL of cold H_2O. The aqueous fraction was then washed three times with 30-mL portions of ether, acidified (2 N HCl), and extracted three times with 30-mL portions of hexane. The hexane extracts were then back-washed three times with 30-mL portions of cold H_2O and 1 time with 30 mL of saturated NaCl solution. The hexane extracts were then dried (Na_2CO_4), and the solvent was evaporated. Recrystallization of the resultant crude white solid from pentane afforded pure 1-methyl-*trans*-4-*tert*-butylcyclohexanecarboxylic acid: mp 141.5–142 °C (lit.[14] mp 143–144 °C); GLC analysis of the corresponding methyl ester (diazomethane) at 159 °C (column B) showed one peak (retention time 7.4 min) and that at 170 °C (column B) showed one peak (retention time 4.2 min).

1-Methyl-*cis*-4-*tert*-butylcyclohexanecarboxylic Acid. An epimeric mixture of *cis*- and *trans*-1-methyl-4-*tert*-butylcyclohexanecarboxylic acids (0.2 g, 1 mmol) was added to 10 mL of 10% BF_3 in methanol, and the mixture was refluxed for 1.5 h. The reaction mixture was cooled, poured into 30 mL of cold 5% NaOH solution, and extracted three times with 30-mL portions of pentane. The aqueous fraction was then acidified (2 N HCl), and the product that precipitated was collected by filtration and air-dried. Recrystallization from pentane afforded pure 1-methyl-*cis*-4-*tert*-butylcyclohexanecarboxylic acid: mp 130–130.5 °C (lit.[42] mp 132–133 °C); GLC analysis of the corresponding methyl ester (diazomethane) at 159 °C (column B) showed one peak (retention time 4.6 min) and that at 170 °C (column B) showed one peak (retention time 2.7 min).

Methylation of Disodium 4-*tert*-Butylcyclohexanecarboxylate. Sodium metal (10 mg, 4.2 mmol) was added to a solution of naphthalene (0.64 g, 5 mmol) and TMEDA (0.8 mL, 5 mmol) in 40 mL of anhydrous THF at room temperature under a N_2 atmosphere, and the mixture was stirred for 25 h. *cis*-4-*tert*-Butylcyclohexanecarboxylic acid (0.37 g, 2 mmol) dissolved in 8 mL of anhydrous THF was then added. The reaction mixture was then heated at 50 °C for 21 h. The reaction mixture was then cooled to −75 °C and methyl iodide (0.51 mL, 2.4 mmol) was added. Stirring at dry ice temperature was continued for 2 h, and then the reaction mixture was warmed to room temperature and stirred for an additional 3 h. Workup by the general procedure afforded 0.36 g of a white solid. GLC analysis of the corresponding methyl esters (via diazomethane) at 170 °C (column B) showed four peaks [retention times: methyl 1-methyl-*cis*-4-*tert*-butylcyclohexanecarboxylate, 2.7 min (4.91%); methyl *cis*-4-*tert*-butylcyclohexanecarboxylate, 3.6 min (2.59%); methyl 1-methyl-*trans*-4-*tert*-butylcyclohexanecarboxylate, 4.2 min (22.9%); methyl *trans*-4-*tert*-butylcyclohexanecarboxylate, 4.8 min (69.5%)].

Attempted Preparation and Methylation of Dipotassium 4-*tert*-Butylcyclohexanecarboxylate. Potassium metal (0.16

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(42) Yoshimura, M.; Nojima, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2164.

g, 4.2 mmol) was added to a solution of naphthalene (0.64 g, 5 mmol) and TMEDA (0.8 mL, 5 mmol) in 40 mL of anhydrous THF at room temperature under a N_2 atmosphere, and the mixture was stirred for 25 h. *cis*-4-*tert*-Butylcyclohexanecarboxylic acid (0.37 g, 2 mmol) dissolved in 8 mL of anhydrous THF was added. The reaction mixture was then heated at 50 °C for 21 h and cooled to −75 °C, and methyl iodide (0.15 mL, 2.4 mmol) added. Stirring at dry ice temperature was continued for 2 h, whereupon the reaction mixture was warmed to room temperature and stirred for an additional 2 h. Workup by the general procedure afforded 0.35 g (95%) of pure *trans*-4-*tert*-butylcyclohexanecarboxylic acid: mp 173.5–175 °C (lit.[41] mp 175–176 °C); GLC analysis of the corresponding methyl ester (via diazomethane) at 170 °C (column B) showed one peak (retention time 4.8 min).

Methyl 4-*tert*-Butylcyclohexanecarboxylate. An epimeric mixture (36:64) of *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylic acids (7.35 g, 40 mmol) was taken up in 50 mL of methanol, *p*-toluenesulfonic acid (0.5 g) was added as catalyst, and the mixture was heated at reflux for 15 h. The reaction mixture was then cooled to room temperature, poured into 250 mL of ice/H_2O, and extracted five times with 30-mL portions of hexane. The hexane extracts were then washed two times with 30-mL portions of cold H_2O, two times with 40-mL portions dilute $NaHCO_3$ solution, and one time with 40 mL of saturated NaCl solution. The hexane extracts were then dried, and the solvent was evaporated. Distillation of the residue afforded 7.35 g (86%) of an epimeric mixture (50:50) of methyl *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylates: bp 66–67.5 °C (0.8 mm); NMR ($CDCl_3$) δ 0.82, 0.85 (s, 9 H), 3.68, 3.70 (s, 3 H), 0.9–2.73 (br m, 10 H); GLC analysis at 155 °C (column A) showed two peaks [retention times: cis, 6.8 min (49.2%); trans, 9.1 min (50.8%)].

Reaction of Methyl α-Lithio-4-*tert*-Butylcyclohexanecarboxylate with Methyl Iodide. The anion was prepared as in the case of 4, and to the pale yellow solution of methyl α-lithio-4-*tert*-butylcyclohexanecarboxylate at −75 °C in THF (5 mmol) was added methyl iodide (0.34 mL, 5.5 mmol). Stirring at dry ice temperature was continued for 1 h, and then the mixture was warmed to room temperature. Workup by the general procedure afforded 0.998 g (94.2%) of an epimeric mixture of methyl 1-methyl-*cis*-4-*tert*-butylcyclohexanecarboxylate and methyl 1-methyl-*trans*-4-*tert*-butylcyclohexanecarboxylate as a pale yellow oil: NMR ($CDCl_3$) δ 0.84, 0.88 (s, 9 H), 1.17, 1.22 (s, 3 H), 3.80 (s, 3 H), 0.94–2.52 (br m, 9 H); GLC analysis at 170 °C (column B) showed two peaks [retention times: methyl 1-methyl-*cis*-4-*tert*-butylcyclohexanecarboxylate, 2.7 min (84%); methyl 1-methyl-*trans*-4-*tert*-butylcyclohexanecarboxylate, 4.2 min (16%)].

***cis*- and *trans*-2-Methylcyclohexanecarboxylic Acids.** *o*-Toluic acid (13.9 g, 102 mmol) was taken up in 100 mL of absolute ethanol and 5% rhodium on alumina (1.0 g) added as catalyst. The hydrogen pressure was maintained at 50 psi until the theoretical amount of H_2 had been taken up. The reaction mixture was then filtered through Celite and the solvent evaporated. Distillation of the residue afforded 11.8 g (81.5%) of an epimeric mixture of *cis*- and *trans*-2-methylcyclohexanecarboxylic acids: bp 90–92 °C (1.5 mm) [lit.[43] bp 77–78 °C (0.25 mm)]; NMR ($CDCl_3$) δ 0.95 (d, 3 H), 1.14–1.94 (br, m, 8 H), 2.22 (m, 1 H), 12.01 (s, 1 H).

The α anion which was prepared according to the general procedure was cooled to −75 °C, and methyl iodide (0.22 mL, 3.8 mmol) was added. Stirring at room temperature was continued for 2.5 h. Workup by the general procedure afforded 0.52 g (94.3%) of an epimeric mixture of 1-methyl-*cis*-2-methylcyclohexanecarboxylic acid and 1-methyl-*trans*-2-methylcyclohexanecarboxylic acid: NMR ($CDCl_3$) δ 0.83, 1.05 (d, 3 H), 1.27 (s, 3 H), 0.89–2.22 (br m, 9 H), 11.73 (s, 1 H); GLC analysis[44] of the corresponding methyl esters (via diazomethane) at 125 °C (column A) showed two peaks [retention times: 1-methyl-*cis*-2-methylcyclohexanecarboxylic acid, 6.25 min (69.7%); 1-methyl-*trans*-2-methylcyclohexanecarboxylic acid, 7.75 min (30.3%)].

Methyl 2-Methylcyclohexanecarboxylate. The epimeric mixture of *cis*- and *trans*-2-methylcyclohexanecarboxylic acids (3.0 g, 21 mmol) was then taken up in 150 mL of methanol and *p*-toluenesulfonic acid (0.2 g) added as catalyst. The reaction mixture was then heated at reflux overnight. The reaction mixture was then cooled to room temperature, and the bulk of the methanol was evaporated. The residue was poured into 60 mL of dilute $NaHCO_3$ solution and extracted four times with 20-mL portions of pentane. The pentane extracts were then dried, and the solvent was evaporated. The residue was distilled to afford 2.86 g (87.3%) of an epimeric mixture of methyl *cis*- and *trans*-2-methylcyclohexanecarboxylates: bp 93–95 °C (oil bath temperature, 15 mm) [lit.[45] bp 88 °C (7 mm)]; NMR ($CDCl_3$) δ 0.90 (d, 3 H), 1.24–2.70 (br m, 10 H), 3.65 (s, H).

Methylation of Methyl α-Lithio-2-methylcyclohexanecarboxylate at Room Temperature. The α anion was prepared according to the procedure described for 4, and the solution of methyl α-lithio-2-methylcyclohexanecarboxylate (3.2 mmol) in 40 mL of anhydrous THF was warmed to 25 °C, and methyl iodide (0.22 mL, 3.5 mmol) was added. Stirring at room temperature was continued for 1 h. Workup by the general procedure afforded 0.514 g (94.5%) of a colorless oil: NMR ($CDCl_3$) δ 0.79, 1.09 (d, 3 H), 0.84–2.29 (br m, 9 H), 1.28 (s, 3 H), 3.79 (s, 3 H); GLC analysis[44] at 125 °C (column A) showed two peaks [retention times: methyl 1-methyl-*cis*-2-methylcyclohexanecarboxylate, 6.3 min (74.9%); methyl 1-methyl-*trans*-2-methylcyclohexanecarboxylate, 7.8 min (25.1%)].

***cis*- and *trans*-3-Methylcyclohexanecarboxylic Acid.** *m*-Toluic acid (21.1 g, 155 mmol) was taken up in 200 mL of absolute ethanol and 1.5 g of 5% rhodium on alumina added as catalyst. The hydrogen pressure was maintained at 50 psi until the theoretical amount of H_2 had been taken up. The reaction mixture was filtered through Celite and the ethanol evaporated. The residue was distilled to afford 19.7 g (89.1%) of an epimeric mixture of *cis*- and *trans*-3-methylcyclohexanecarboxylic acids: bp 89–92 °C (1.2 mm) [lit.[46] bp 136–137 °C (17 mm)]; NMR ($CDCl_3$) δ 0.93 (d, 3 H), 0.74–2.84 (br m, 10 H), 12.02 (s, 1 H).

Methyl *cis*- and *trans*-3-Methylcyclohexanecarboxylate. 3-Methylcyclohexanecarboxylic acid (3.0 g, 21 mmol) was taken up in 150 mL of methanol, and *p*-toluenesulfonic acid (0.2 g) was added as catalyst. The reaction mixture was then heated at reflux overnight. The reaction mixture was then cooled and the bulk of the methanol evaporated. The residue was poured into 70 mL of dilute $NaHCO_3$ solution and extracted four times with 20-mL portions of pentane. The combined pentane extracts were then washed one time with 20 mL of cold H_2O and one time with 20 mL of saturated NaCl solution. The pentane extracts were then dried (Na_2SO_4), and the solvent was evaporated. Distillation of the residue afforded 2.99 g (91.3%) of methyl 3-methylcyclohexanecarboxylate as a colorless oil: bp 80–82 °C (bath temperature, 20 mm) [lit.[47] bp 82.2–82.5 °C (20 mm)]; NMR ($CDCl_3$) δ 0.92 (d, 3 H), 0.73–2.79 (br m, 10 H), 3.69 (s, 3 H).

Reaction of Dilithium 3-Methylcyclohexanecarboxylate with Methyl Iodide at Room Temperature. The α anion was prepared via the general procedure, and the solution was warmed to 25 °C. Methyl iodide (0.23 mL, 3.8 mmol) was added. Stirring at room temperature was continued for 1 h. Workup by the general procedure afforded 0.54 g (97.5%) of an epimeric mixture of *cis*- and *trans*-1,3-dimethylcyclohexanecarboxylic acids: NMR ($CDCl_3$) δ 0.68–2.36 (br m, 9 H), 0.87 (br d, 3 H), 1.22, 1.26 (s, 3 H); GLC analysis of corresponding methyl esters (diazomethane) at 139 °C (column A) showed two peaks [retention times: methyl 1-methyl-*trans*-3-methylcyclohexanecarboxylate, 3.4 min (54.8%); methyl 1-methyl-*cis*-3-methylcyclohexanecarboxylate, 4.7 min (45.2%)].

Reaction of Methyl α-Lithio-3-methylcyclohexanecarboxylate with Methyl Iodide at Room Temperature. The solution of methyl α-lithio-3-methylcyclohexanecarboxylate as prepared via the procedure described for 4 was warmed to 25 °C, and methyl iodide (0.22 mL, 3.5 mmol) was added. Stirring at room temperature was continued for 1 h. Workup by the general procedure afforded 0.507 g (93.2%) of an epimeric mixture of methyl *cis*- and *trans*-1,3-dimethylcyclohexanecarboxylates as a

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colorless oil: NMR ($CDCl_3$) δ 0.54–2.42 (br m, 9 H), 0.92 (d, 3 H), 1.20, 1.27 (s, 3 H), 3.82 (s, 3 H); GLC analysis at 139 °C (column A) showed two peaks [retention times: methyl 1-methyl-*trans*-3-methylcyclohexanecarboxylate, 3.6 min (75.6%); methyl 1-methyl-*cis*-3-methylcyclohexanecarboxylate, 5.1 min (24.4%)].

Ethyl 3-Methylcyclohexanecarboxylate. To 130 mL of benzene were added 3-methylcyclohexanecarboxylic acid (14.24 g, 0.1 mmol), absolute ethanol (25 mL, 430 mmol), and H_2SO_4 (catalyst). The resultant mixture was then heated at reflux for 20 h with continuous removal of H_2O (Dean–Stark trap). The reaction mixture was then cooled, poured into a separatory funnel, and washed two times with 25-mL portions of saturated K_2CO_3 solution, two times with 25-mL portions of cold water, and two times with 25-mL portions of saturated NaCl solution. The organic fraction was then dried ($MgSO_4$), and the solvent was evaporated. The residue was distilled to afford 14.74 g (86.5%) ethyl 3-methyl-cyclohexanecarboxylate as a colorless oil: bp 44–47 °C (1.1 mm) (lit.[48] bp 208–210 °C); NMR ($CDCl_3$) δ 0.91 (d, 3 H), 1.25 (t, 3 H), 0.98–2.75 (br m, 10 H), 4.13 (q, 2 H).

Methylation of Ethyl α-Lithio-3-methylcyclohexanecarboxylate. To the resultant clear pale yellow solution of the α anion prepared via the procedure for **4** was added methyl iodide (0.2 mL, 3.3 mmol), and stirring at −75 °C was continued for 1 h. The reaction mixture was then warmed to room temperature. Workup by the general procedure afforded 0.51 g (92.4%) of an epimeric mixture of ethyl *cis*- and *trans*-1,3-dimethylcyclohexanecarboxylates as a colorless oil: NMR ($CDCl_3$) δ 0.88 (d, 3 H), 1.15 (s, 3 H), 1.27 (t, 3 H), 0.66–2.36 (br m, 9 H), 4.17 (q, 2 H); GLC analysis at 136 °C (column A) showed two peaks [retention times: ethyl 1-methyl-*trans*-3-methylcyclohexanecarboxylate, 4.3 min (90.0%); ethyl 1-methyl-*cis*-3-methylcyclohexanecarboxylate, 5.1 min (10.0%)].

3-Methoxycyclohexanecarboxylic Acid. Lithium metal (2.6 g, 375 mmol) was added to a solution of *m*-anisic acid (22.8 g, 150 mmol) in 1200 mL of liquid NH_3 at −75 °C. The reaction mixture was then warmed to reflux temperature and lithium metal added in small pieces until a blue color was maintained. After 20 min the reaction mixture was cooled again to −75 °C, and NH_4Cl (40.6 g, 760 mmol) was added to quench the reaction. The cooling bath and reflux condenser were removed, and the ammonia was evaporated overnight. The residue was taken up in 250 mL of H_2O, and this was evacuated briefly to remove residual NH_3. The aqueous solution was then acidified carefully at 0 °C (cold 2 N HCl) with repeated extraction with ether during the gradual acidification process. The ether extracts were then dried ($MgSO_4$), and the solvent was evaporated. Approximately half of the yellow oily residue was taken up in 150 mL of absolute ethanol and 10% palladium on carbon (0.5 g) added as catalyst. The hydrogen pressure was maintained at 40 psi until the uptake ceased. The reaction mixture was then filtered through Celite and the solvent evaporated. The residue was distilled to afford 8.04 g of an epimer mixture of *cis*- and *trans*-3-methoxycyclohexanecarboxylic acids: bp 105–113 °C (0.9 mm) [lit.[49] bp (trans isomer) 123–125 °C (2 mm)]; NMR ($CDCl_3$) δ 1.13–2.60 (br m, 9 H), 3.36, 3.40 (s, 3 H), 3.08–3.68 (br m, 1 H). The cis isomer could be fractionally crystallized from pentane: mp 44–51 °C (lit.[49] mp 51–52 °C); NMR ($CDCl_3$) δ 1.13–2.60 (br m, 9 H), 3.30 (m, 1 H), 3.40 (s, 3 H).

Methylation of Dilithium 3-Methoxycyclohexanecarboxylate. The α anion was prepared as described under the general procedure. The clear, pale yellow solution was cooled to −75 °C, and methyl iodide (0.34 mL, 5.5 mmol) was added. Stirring at −75 °C was continued for 2 h, and then the reaction mixture was warmed to room temperature. Workup by the general procedure afforded 0.815 g (94.8%) of an epimeric mixture of *cis*- and *trans*-1-methyl-3-methoxycyclohexanecarboxylic acids: NMR ($CDCl_3$) δ 0.88–2.36 (br, m, 9 H), 1.28, 1.32 (s, 3 H), 3.38–3.70 (m, 1 H), 3.45, 3.51 (s, 3 H); GLC analysis of the corresponding methyl esters (diazomethane) at 150 °C (column A) showed two peaks [retention times: methyl 1-methyl-*trans*-3-methoxycyclohexanecarboxylate, 5.85 min (26.6%); methyl 1-methyl-*cis*-3-methoxycyclohexanecarboxylate, 7.1 min (73.4%)]; mass spectrum calcd for $C_9H_{16}O_3$, *m/e* 172 (M^+).

Reaction of *cis*- and *trans*-1-Methyl-3-methoxycyclohexanecarboxylic Acids with Boron Trifloride in Methanol. An epimeric mixture (73:27) of *cis*- and *trans*-1-methyl-3-methoxycyclohexanecarboxylic acids (100 g, 0.6 mmol) was taken up in 10 mL of 10% BF_3 in methanol and the mixture refluxed on a steam bath for 5 min. The reaction mixture was then poured into 50 mL of 5% NaOH solution, and this mixture was extracted three times with 30-mL portions of pentane. The combined pentane extracts were then dried (Na_2SO_4) and concentrated to 5 mL. GLC analysis at 150 °C (column A) showed only one peak (retention time for methyl 1-methyl-*cis*-3-methoxycyclohexanecarboxylate 7.1 min).

Methyl *cis*- and *trans*-3-Methoxycyclohexanecarboxylates. Methyl *cis*- and *trans*-3-methoxycyclohexanecarboxylates were prepared by refluxing the acids overnight in methanol with *p*-toluenesulfonic acid (catalyst), followed by the normal workup procedure and distillation: bp 115–121 °C [lit.[50] bp 116–120 °C (26 mm)]; NMR ($CDCl_3$) δ 1.12–2.52 (br m, 9 H), 3.52 (m, 1 H), 3.32, 3.36 (s, 3 H), 3.64 (s, 3 H).

Methylation of Methyl α-Lithio-3-methoxycyclohexanecarboxylate. Methyl iodide (0.34 mL, 5.5 mmol) was added to the α anion prepared as previously described for **4**. Stirring at −75 °C was continued for an additional hour, whereupon the reaction mixture was warmed to room temperature. Workup by the general procedure afforded 0.86 g (92.5%) of an epimeric mixture of methyl *cis*- and *trans*-1-methyl-3-methoxycyclohexanecarboxylates: NMR ($CDCl_3$) δ 0.84–2.60 (br m, 9 H), 1.16, 1.18 (s, 3 H), 2.98–3.24 (m, 1 H), 3.24, 3.28 (s, 3 H), 3.80 (s, 3 H); GLC analysis at 149 °C (column A) showed two peaks (retention times: methyl 1-methyl-*trans*-3-methoxycyclohexanecarboxylate, 4.45 min (78.2%); methyl 1-methyl-*cis*-3-methoxyhexanecarboxylate, 5.48 min (21.8%); mass spectrum calcd for $C_{10}H_{18}O_3$, *m/e* 186 (M^+).

Methyl *cis*- and *trans*-4-Methoxycyclohexanecarboxylates. Methyl 4-methoxybenzoate (10.0 g, 60 mmol) was taken up in approximately 50 mL of acetic acid, and 5% rhodium on alumina (0.5 g) was added as a catalyst. The hydrogen pressure was maintained at 50 psi until the uptake ceased. The reaction mixture was then filtered through Celite and the bulk of the solvent evaporated. The residue was poured into 75 mL of H_2O and the product extracted three times with 30-mL portions of hexane. The hexane extracts were then washed two times with 20-mL portions of cold H_2O, and one time with 25 mL of saturated NaCl solution. The hexane fraction was dried (Na_2SO_4) and the solvent evaporated. The residue was distilled to afford 4.9 g (47.2%) of an epimeric mixture of methyl 4-methoxycyclohexanecarboxylates: bp 115 °C (oil bath temperature, 18 mm) [lit.[49] bp 122–124 °C (30 mm)]; NMR ($CDCl_3$) δ 1.12–2.54 (br m, 9 H), 3.10–3.44 (m, 1 H), 3.30, 3.34 (s, 3 H), 3.66 (s, 3 H).

4-Methoxycyclohexanecarboxylic Acid. Methyl 4-methoxycyclohexanecarboxylate (3.65 g, 21 mmol) was taken up in 45 mL of 95% ethanol, and KOH (5 g, 90 mmol) was added. The reaction mixture was then heated at reflux for 24 h. The reaction mixture was then cooled to room temperature and the bulk of the solvent evaporated. The residue was taken up in 75 mL of H_2O and washed two times with 20-mL portions of ether. The aqueous fraction was then acidified (2 N HCl) and extracted three times with 30-mL portions of pentane. The pentane extracts were then dried (Na_2SO_4), and the solvent was evaporated. The residue was distilled to afford 2.1 g (63.3%) of an epimeric mixture of *cis*- and *trans*-4-methoxycyclohexanecarboxylic acids: bp 170 °C (bath temperature, 18 mm) [lit.[51] bp 142 °C (6 mm)]; NMR ($CDCl_3$) δ 1.16–2.58 (br m, 9 H), 3.28–3.52 (m, 1 H), 3.32, 3.36 (s, 3 H).

Methylation of Methyl α-Lithio-4-methoxycyclohexanecarboxylate at −75 °C. The solution of methyl α-lithio-4-methoxycyclohexanecarboxylate in THF prepared as described in a previous example was cooled to −75 °C, and methyl iodide (0.17 mL, 2.6 mmol) was added. Stirring at room temperature was continued for 2 h. Workup by the general procedure afforded 0.43 g (97.9%) of an epimeric mixture of methyl *cis*- and

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trans-1-methyl-4-methoxycyclohexanecarboxylates as a pale yellow oil: NMR ($CDCl_3$) δ 0.82–2.38 (br m, 8 H), 1.17 (s, 3 H), 3.31 (s, 3 H), 2.92–3.31 (m, 1 H), 3.66 (s, 3 H); GLC analysis at 148 °C (column A) showed two peaks [retention times: methyl 1-methyl-*trans*-4-methoxycyclohexanecarboxylate, 6.9 min (15.9%); methyl 1-methyl-*cis*-4-methoxycyclohexanecarboxylate, 8.75 min (84.1%)]; mass spectrum calcd for $C_{10}H_{18}O_3$, *m/e* 186 (M^+).

Methylation of Dilithium 4-Methoxycyclohexanecarboxylate at Room Temperature. The solution of dilithium 4-methoxycyclohexanecarboxylate in THF as prepared by the general procedure was cooled to room temperature, and methyl iodide (0.44 mL, 6.9 mmol) was added. Stirring at room temperature was continued for 1.5 h. Workup by the general procedure afforded 1.015 g (94.0%) of an epimeric mixture of *cis*- and *trans*-1-methyl-4-methoxycyclohexanecarboxylic acids: NMR ($CDCl_3$) δ 0.96–2.40 (br m, 8 H), 1.21, 1.23 (s, 3 H), 3.16 (m, 1 H), 3.36 (s, 3 H), 11.24 (s, 1 H); GLC analysis of the corresponding methyl esters (diazomethane) at 148 °C (column A) showed two peaks [retention times: methyl 1-methyl-*trans*-4-methoxycyclohexanecarboxylate, 6.85 (47.8%); methyl 1-methyl-*cis*-4-methoxycyclohexanecarboxylate, 8.7 min (52.2%)]; mass spectrum calcd for $C_9H_{16}O_3$, *m/e* 172 (M^+).

Preparation of the Lactone of 1-Methyl-4-hydroxycyclohexanecarboxylic Acid. The mixture of *cis*- and *trans*-1-methyl-4-methoxycyclohexanecarboxylic acids was taken up in 15 mL of pentane. Fractional crystallization afforded 0.131 g of pure 1-methyl-*cis*-4-methoxycyclohexanecarboxylic acid: mp 116–117.5 °C; NMR ($CDCl_3$) δ 0.96–2.40 (br m, 8 H), 1.21 (s, 3 H), 3.14 (m, 1 H), 3.36 (s, 3 H), 11.24 (s, 1 H); GLC analysis of the corresponding methyl ester (diazomethane) at 148 °C (column A) showed one peak (retention time for methyl 1-methyl-*cis*-4-methoxycyclohexanecarboxylate 8.75 min); mass spectrum calcd for $C_9H_{16}O_3$, *m/e* 172 (M^+).

The following procedure is that of Jung et al.[22] To a solution of 1-methyl-*cis*-4-methoxycyclohexanecarboxylic acid (131 mg, 0.76 mmol) in 10 mL of CCl_4 under a N_2 atmosphere was added trimethylsilyl iodide (0.24 mL, 1.7 mmol), and the reaction mixture was stirred in the dark for 5 h. The reaction mixture was then poured into 40 mL of H_2O and heated briefly on a steam bath. The aqueous portion was then continuously extracted with ether. The extracts were then dried ($MgSO_4$), and the solvent was evaporated. The residue was taken up in 50 mL of benzene, *p*-toluenesulfonic acid was added as catalyst, and the reaction mixture was heated at reflux for 6 h. The reaction mixture was then cooled to room temperature and poured into 50 mL of 5% $NaHCO_3$ solution, and the layers were separated. The organic fraction was then washed one time with 35 mL of cold H_2O and one time with 35 mL of saturated NaCl solution. The organic fraction was then dried ($MgSO_4$) and the solvent evaporated. Attempted sublimation (85 °C at 18 mm) of the residue afforded the lactone of 1-methyl-*cis*-4-hydroxycyclohexanecarboxylic acid as a colorless oil: NMR ($CDCl_3$) δ 1.19 (s, 3 H), 1.56–2.09 (m, 8 H), 4.59 (m, 1 H); IR (neat) 1740 cm^{-1}; mass spectrum calcd for $C_{18}H_{12}O_2$, *m/e* 140 (M^+).

Registry No. *endo*-**1**, 1195-12-6; *endo*-**1** methyl ester, 2903-75-5; *exo*-**1**, 934-30-5; **2** (R = CH_3), 32190-81-1; **2** (R = CH_2CH_3), 73873-18-4; **2** (R = $(CH_2)_2CH_3$), 73873-19-5; **2** (R = $(CH_2)_3CH_3$), 73873-20-8; **2** (R = $CH_2CH(CH_3)_2$), 73873-21-9; **2** (R = $CH_2CH{=}CH_2$), 73873-22-0; **2** (R = $CH(CH_3)_2$), 73873-23-1; **2** (R = $(CH_2)_4CH_3$), 73873-24-2; **2** (R = $(CH_2)_5CH_3$), 73873-25-3; **3** (R = CH_3), 32190-82-2; **3** (R = CH_2CH_3), 73873-26-4; **3** (R = $(CH_2)_2CH_3$), 73873-27-5; **3** (R = $(CH_2)_3CH_3$), 73873-28-6; **3** (R = $CH_2CH(CH_3)_2$), 73873-29-7; **3** (R = $CH_2CH{=}CH_2$), 73873-30-0; **3** (R = $CH(CH_3)_2$), 73873-31-1; **3** (R = $(CH_2)_4CH_3$), 73873-32-2; **3** (R = $(CH_2)_5CH_3$), 73873-33-3; **4**, 769-85-7; **5** (R = CH_3), 7167-29-5; **5** (R = CH_2CH_3), 58864-17-8; **5** (R = $(CH_2)_2CH_3$), 73873-34-4; **5** (R = $(CH_2)_3CH_3$), 58864-19-0; **5** (R = $CH_2CH(CH_3)_2$), 73873-35-5; **5** (R = $CH_2CH{=}CH_2$), 73873-36-6; **5** (R = $CH(CH_3)_2$), 73873-37-7; **6** (R = CH_3), 7167-28-4; **6** (R = CH_2CH_3), 58864-18-9; **6** (R = $(CH_2)_2CH_3$), 73873-38-8; **6** (R = $(CH_2)_3CH_3$), 58864-20-3; **6** (R = $CH_2CH(CH_3)_2$), 73873-39-9; **6** (R = $CH_2CH{=}CH_2$), 73873-40-2; **6** (R = $CH(CH_3)_2$), 73873-41-3; **7** (R = H), 934-28-1; **7** (R = CH_3), 16646-41-6; **8** (R = H, R′ = CH_3), 16646-40-5; **8** (R = H, R′ = CH_2CH_3), 73873-42-4; **8** (R = R′ = CH_3), 28738-72-9; **8** (R = CH_3, R′ = CH_2CH_3), 73873-43-5; **9** (R = H, R′ = CH_3), 42856-29-1; **9** (R = H, R′ = CH_2CH_3), 73873-44-6; **9** (R = R′ = CH_3), 61109-88-4; **9** (R = CH_3, R′ = CH_2CH_3), 73873-45-7; *cis*-**10** (R = H), 943-28-2; *cis*-**10** (R = CH_3), 17177-76-3; *trans*-**10** (R = H), 943-29-3; *trans*-**10** (R = CH_3), 17177-75-2; **11** (R = H, R′ = CH_3), 27069-57-4; **11** (R = R′ = CH_3), 42829-54-9; **12** (R = H, R′ = CH_3), 31752-57-5; **12** (R = R′ = CH_3), 42829-53-8; *cis*-**13** (R = H), 7076-91-7; *cis*-**13** (R = CH_3), 7605-55-2; *trans*-**13** (R = H), 15177-62-5; *trans*-**13** (R = CH_3), 7605-54-1; **14** (R = H), 13277-92-4; **14** (R = CH_3), 73873-46-8; **15** (R = H), 61279-11-6; **15** (R = CH_3), 73873-47-9; **16** (R = CH_2CH_3), 7133-30-4; *cis*-**16** (R = H), 73873-48-0; *cis*-**16** (R = CH_3), 7605-52-9; *trans*-**16** (R = H), 73873-49-1; *trans*-**16** (R = CH_3), 7605-53-0; **17** (R = H), 38864-08-3; **17** (R = CH_3), 38864-09-4; **17** (R = CH_2CH_3), 73873-50-4; **18** (R = H), 38864-02-7; **18** (R = CH_3), 38864-04-9; **18** (R = CH_2CH_3), 73873-51-5; *cis*-**19** (R = H), 73873-52-6; *cis*-**19** (R = CH_3), 73873-53-7; *trans*-**19** (R = H), 73873-54-8; *trans*-**19** (R = CH_3), 73873-55-9; **20** (R = H), 73891-33-5; **20** (R = CH_3), 73873-56-0; **21** (R = H), 73873-57-1; **21** (R = CH_3), 73873-58-2; *cis*-**22** (R = H), 73873-59-3; *cis*-**22** (R = CH_3), 73873-60-6; *trans*-**22** (R = H), 73873-61-7; *trans*-**22** (R = CH_3), 73873-62-8; **23** (R = H), 73873-63-9; **23** (R = CH_3), 73873-64-0; **24** (R = H), 73873-65-1; **24** (R = CH_3), 73873-66-2; methyl iodide, 74-88-4; dimethyl sulfate, 77-78-1; ethyl iodide, 75-03-6; propyl iodide, 107-08-4; butyl bromide, 109-65-9; isobutyl bromide, 78-77-3; 2-bromo-1-propene, 557-93-7; isopropyl iodide, 75-30-9; 1-bromopentane, 110-53-2; 1-bromohexane, 111-25-1; diazomethane, 334-88-3; lithium 2-lithiobicyclo[2.2.1]hept-5-ene-2-carboxylate, 73873-67-3; 2-(carbomethoxy)-2-lithiobicyclo[2.2.1]hept-5-ene, 73873-68-4; lithium 2-lithiobicyclo[2.2.1]heptane-2-carboxylate, 73873-69-5; 2-(carbomethoxy)-2-lithiobicyclo[2.2.1]heptane, 73873-70-8; 4-*tert*-butylbenzoic acid, 98-73-7; dilithium 4-*tert*-butylcyclohexanecarboxylate, 73873-71-9; disodium 4-*tert*-butylcyclohexanecarboxylate, 73873-72-0; methyl α-lithio-4-*tert*-butylcyclohexanecarboxylate, 73873-73-1; *o*-toluic acid, 118-90-1; lithium α-lithio-2-methylcyclohexanecarboxylate, 73873-74-2; methyl α-lithio-2-methylcyclohexanecarboxylate, 73891-34-6; *m*-toluic acid, 99-04-7; dilithium 3-methylcyclohexanecarboxylate, 73873-75-3; methyl α-lithio-3-methylcyclohexanecarboxylate, 73873-76-4; ethyl α-lithio-3-methylcyclohexanecarboxylate, 73873-77-5; *m*-anisic acid, 586-38-9; dilithium 3-methoxycyclohexanecarboxylate, 73873-78-6; methyl α-lithio-3-methoxycyclohexanecarboxylate, 73873-79-7; methyl 4-methoxybenzoate, 121-98-2; methyl α-lithio-4-methoxycyclohexanecarboxylate, 73873-80-0; dilithium 4-methoxycyclohexanecarboxylate, 73873-81-1; 1-methyl-*cis*-4-hydroxycyclohexanecarboxylic acid lactone, 73873-82-2.