Stereochemistry of Decarbalkoxylation of Cyclic Geminal Diesters Effected by Water and Lithium Chloride in Me_2SO[1]

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Received January 11, 1980

The stereochemical consequences of the decarbalkoxylation of cyclic geminal diesters by $LiCl-H_2O-Me_2SO$ have been examined. The norbornene diester **13** and the norbornane diester **16** lead predominantly to the exo esters **14** and **17**, respectively. The 2-methylcyclohexane diester **22** leads to esters containing more cis (**23**) than trans (**24**) isomer. The diesters **19**, **25**, and **28** lead to nearly equal amounts of the cis and trans esters. In these latter cases, the enolates generated from the esters (via LDA) are protonated in a nonstereoselective fashion on quenching with water. This is suggestive of an enolate intermediate in the decarbalkoxylation reaction. The implications of these stereochemical results are discussed.

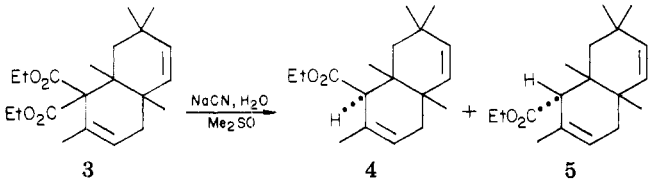
Over the past decade or so we have reported studies of the synthetic applications of the decarbalkoxylations of malonate esters **1** to esters **2** (and the related β-keto esters and α-cyano esters) using various salts in aqueous Me_2SO and other dipolar aprotic solvents.[2]

$$\underset{\mathbf{1}}{R^1R^2C(CO_2R^3)_2} \rightarrow \underset{\mathbf{2}}{R^1R^2CHCO_2R^3}$$

We now wish to report experiments on the stereochemistry of the decarbalkoxylation of some cyclic geminal diesters and their possible application to synthetic endeavors.

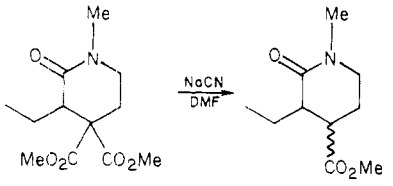
Although the decarbalkoxylations of geminal diesters and related systems have been known for a number of years and have been extensively used in synthetic organic chemistry, there are few reported examples where the stereochemistry of the resultant products has been examined.

van Tamelen[3] and co-workers report that the decarbethoxylation of **3** results in a ratio of 8:1 of **4** and **5**, respectively, in an overall 70% conversion.



3 **4** **5**

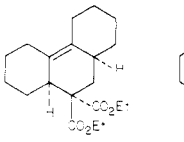
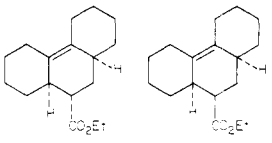
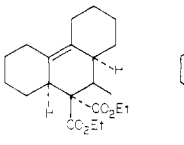
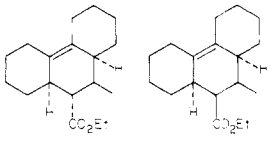
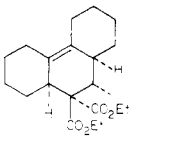
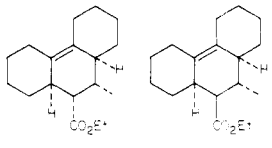
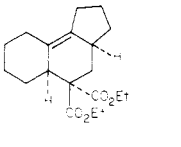
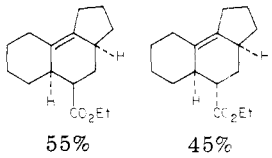
Dolby and Biere[4] report that the decarbomethoxylation of **6** leads to **7** as an undefined mixture of diastereomers in 70% yield.



6 **7**

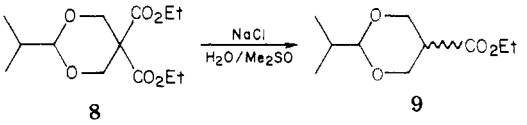
Christol and co-workers[5,6] report results obtained during their stereochemical studies of tricyclic systems (see Table I). It can be seen that in the [6·6·6] ring system some stereoselectivity is achieved but that little selectivity is apparent in the [6·6·5] ring system. They report for two of these diesters (Table I, entries 1 and 4) that the thermodynamic distribution of monoesters is identical with that found from decarbethoxylation of the corresponding diester.

Table I. Stereochemistry in Tricyclic Systems

reactant[a]	products and distribution	ref
	 80% 20%	5
	 98% 2%	5
	 70/30 (no definite stereochemical assignments)	5
	 55% 45%	6

[a] $NaCN/Me_2SO$.

It has been reported that the decarbethoxylation of 5,5-dicarbethoxy-2-isopropyl-1,3-dioxane (**8**) with NaCl/H_2O/Me_2SO upon reflux for 7 h gives the corresponding monoester (**9**) with a cis/trans ratio of 1:3.[7] It has also been demonstrated that the predominant stereochemistry of the system is initially cis. Under the reaction conditions,



8 **9**

(1) Presented in part at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 10–14, 1979; Abstract ORGN 75.

(2) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. Synthetic applications and mechanistic considerations are presented in this paper.

(3) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229.

(4) Dolby, L. J.; Biere, H. *J. Org. Chem.* **1970**, *35*, 3843.

(5) Christol, H.; Moers, D.; Pietrasanta, Y. *Bull. Soc. Chim. Fr.* **1970**, 4072.

(6) Christol, H.; Pietrasanta, F.; Pietrasanta, Y. *Bull. Soc. Chim. Fr.* **1972**, 566.

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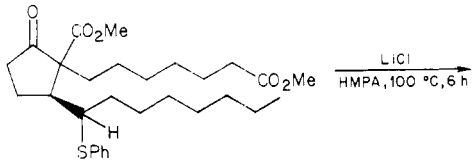
equilibration occurs to give the thermodynamically stable trans isomer.[8]

There are also examples of the decarbalkoxylations of β-keto esters studied during the synthesis of prostaglandins and related systems.[9] Kondo and co-workers, in their synthesis of 11-deoxy-PGE_1, report that the decarbomethoxylation of **10** gives **11** in 92% yield as one stereo-



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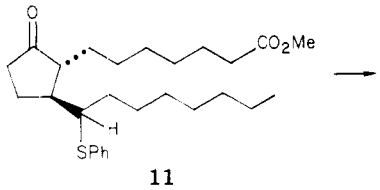

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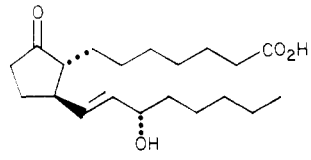


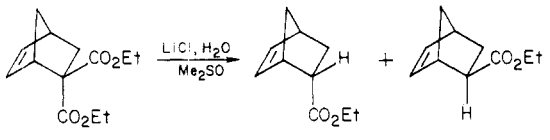
12

isomer (trans), which can be converted into product **12**.[10] It is not clear if the resultant stereochemistry is a result of decarbomethoxylation or equilibration, since 2,3-disubstituted cyclopentanone systems are known to equilibrate, favoring the trans isomer under basic conditions.[11]

Results and Discussion

It became of interest to undertake a systematic study of the stereochemical consequences of the decarbalkoxylation of some simple cyclic geminal diesters. The $LiCl/H_2O/Me_2SO$ system was chosen since it has previously been found to be quite effective[2] and circumvents the use of potentially hazardous cyanide.

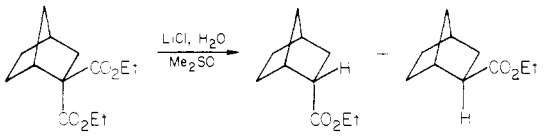
The first model compound examined was diethyl bicyclo[2.2.2]hept-5-ene-2,2-dicarboxylate (**13**), which was



13 **14** **15**

conveniently prepared from a Diels–Alder reaction of cyclopentadiene with diethyl methylenemalonate. Decarbethoxylation of **13** with the $LiCl/H_2O/Me_2SO$ system gave a product distribution of 80% endo ester **14** and 20% exo ester **15**. The overall yield was quite low, 22%, which is attributable to thermal decomposition of the norbornene system. Similar decomposition was found for the attempted decarboxylation of the corresponding diacid.[12]

Hydrogenation of **13** over Pd/C gave the analogous saturated system **16**. The decarbethoxylation of **16** gave an endo/exo (**17**/**18**) ratio of 69:31 in 63% yield. In both

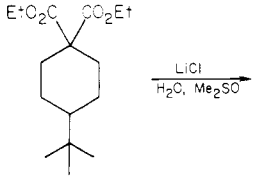


16 **17** **18**

cases there is selectivity, but the selectivity is not as great in the saturated case as in the unsaturated system. The thermodynamic equilibrium for the corresponding methyl ester has been reported to be 1.1, favoring the exo ester at 25 °C.[13] For the unsaturated analogue the value at 25 °C is 1.35[13] and at 100 °C[14] is 1.09.

Diethyl 4-*tert*-butyl-1,1-cyclohexanedicarboxylate (**19**) was synthesized in several steps from *p*-*tert*-butylbenzoic acid. Hydrogenation of *p*-*tert*-butylbenzoic acid over Pt gives 4-*tert*-butylcyclohexanecarboxylic acid which has predominantly cis stereochemistry. This acid was esterified by using ethanol/benzene with a catalytic amount of concentrated sulfuric acid. The diester was then prepared by reaction of the monoester with lithium diisopropylamide (LDA) in THF at −70 °C followed by addition of ethyl chloroformate.

Decarbethoxylation of **19** was found to give a 50:50 ratio of cis to trans monoesters **20** and **21**, respectively. Var-



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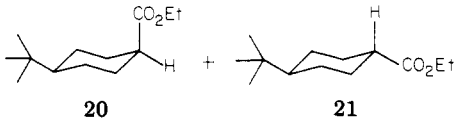


20 **21**

iation of the bath temperature in the range of 170–215 °C did not effect the product distribution. At higher temperature it was observed that decomposition of the solvent was less of a problem, possibly due to the shorter times necessary to effect reaction. A 68:32 mixture of cis/trans esters was subjected to the same reaction conditions, and this led to a 65% recovery of starting material after 3 h with no change in the mixture composition. Therefore, equilibration under the reaction conditions is not occurring. This compares with a 70.7 ± 0.5% cis product distribution resulting from thermal decarboxylation of the corresponding diacid in pyridine.[15] The thermodynamic product distribution of esters is 84.7 ± 0.6% trans for treatment of either pure **20** or **21** with sodium ethoxide in refluxing ethanol.[16] Fearing that there may be an effect of the cation used, we repeated the experiment using lithium ethoxide. The results are essentially identical, with an equilibrium concentration that was 82.1 ± 0.8% trans.

It became of interest to look at the result of protonation of the enolate formed at low temperature. To this end,

(8) Private communication from Dr. Harold D. Banks, University of Bridgeport, Bridgeport, CT. Banks has extensively studied the stereochemistry of this system and other related heterocyclic systems.

(9) (a) Torii, S.; Tanaka, H.; Mandai, T. *J. Org. Chem.* **1975**, *40*, 2221. (b) Scribner, R. M. *Tetrahedron Lett.* **1976**, 3853. McCurry, P. M., Jr.; Abe, K. *Ibid.* **1974**, 1387. (d) Trost, B. M.; Vladuchick, W. C. *J. Org. Chem.* **1979**, *44*, 148. (e) Greene, A.; Crabbe, P. *Tetrahedron Lett.* **1975**, 2215.

(10) Kondo, K.; Umemoto, T.; Takahatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977**, 113.

(11) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(12) Roberts, J. D.; Trumbull, E. R., Jr.; Bennett, W.; Armstrong, R. *J. Am. Chem. Soc.* **1950**, *72*, 3116.

(13) Davis, D. D.; Bigelow, W. B. *Tetrahedron Lett.* **1973**, 149.

(14) Ouellette, R. J.; Booth, G. E. *J. Org. Chem.* **1965**, *30*, 423.

(15) Banks, H. D.; Jacobs, W. *J. Org. Chem.* **1975**, *40*, 790.

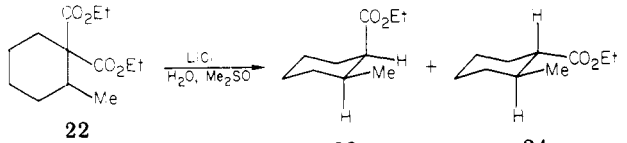
(16) Eliel, E. L.; Haubenstock, H.; Acharya, R. V. *J. Am. Chem. Soc.* **1961**, *83*, 2351.

ethyl *cis*-4-*tert*-butylcyclohexanecarboxylate (**20**) was treated with LDA at −75 °C and the reaction quenched with water. The resulting distribution was 50% cis, **20**, and 50% trans, **21**, identical with the distribution obtained upon decarbethoxylation of the diester.

The dimethyl ester was also examined due to the thought that the mechanistic pathway would be shifted toward a more predominant $B_{AL}2$-type cleavage.[2] The resulting distribution of products from decarbomethoxylation was identical with that for the diethyl ester.

Upon examination of the data thus far collected, it was decided to look at the placement of substituents on the cyclohexane ring. To this aim, the series of the three possible methyl-substituted malonates were prepared. These can be conveniently prepared by hydrogenation of the appropriately substituted toluic acid. It was found that the use of Rh/alumina catalyst in ethanol was effective for this conversion. Esterification of the monoacids followed by treatment with LDA and ethyl chloroformate gave the desired diethyl esters.

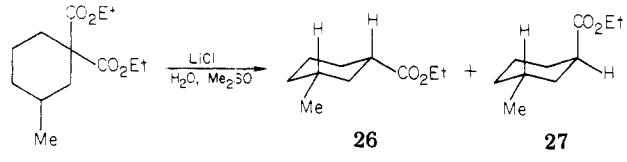
Diethyl 2-methyl-1,1-cyclohexanedicarboxylate (**22**) resulted in a product ratio of 60:40 cis to trans esters (**23** and **24**, respectively) upon decarbethoxylation in $LiCl/H_2O/Me_2SO$ in a 72% yield. Again, in this case, the enolate



22 23 24

was formed at low temperature and quenched with water. The resulting product distribution was 72% cis (**23**) and 28% trans (**24**). This is slightly more selective than the decarbethoxylation experiment; however, the selectivity is for the same product. The thermodynamic equilibrium using lithium ethoxide in refluxing ethanol was determined to be 76.4 ± 0.6% *trans*-**24** starting from *cis*-**23**.

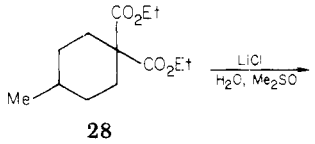
Movement of the methyl group by one carbon, diethyl 3-methyl-1,1-cyclohexanedicarboxylate (**25**), results in a product distribution that is 50% cis (**26**) and 50% trans (**27**) in an overall 79% yield. Quenching of the low-tem-



25 26 27

perature enolate of **26** with water gave a distribution that was 52% cis (**26**) and 48% trans (**27**), not very different from the result of decarbethoxylation of the diester. The thermodynamic equilibrium was found to be 83.0 ± 1.1% cis (**26**).

The 4-methyl isomer, diethyl 4-methyl-1,1-cyclohexanedicarboxylate (**28**), gave as expected a 50% cis (**29**) and 50% trans (**30**) product distribution in 76% yield upon



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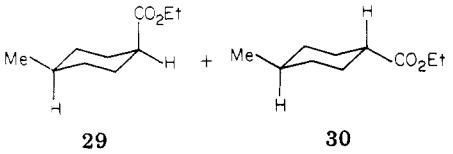
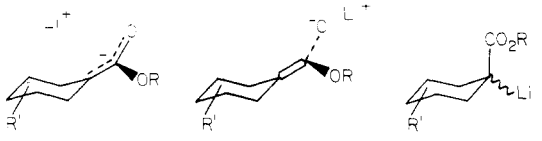


29 30

decarbethoxylation. The lithium enolate of **29** upon being quenched with water yields a mixture of 54% cis (**29**) and 46% trans (**30**) compounds. Again the distribution obtained was similar to the results of decarbethoxylation of the diester. The thermodynamic equilibrium constant for the corresponding methyl esters has been estimated by NMR to be 3.7, favoring the trans isomer ($NaOCH_3/CH_3OH$/HMPT).[13] It was found that with lithium ethoxide in ethanol the equilibrium favored the trans isomers by an amount (78.9 ± 0.1% trans, K = 3.7) which was essentially the same as the estimate for the methyl ester.

Since the results of the decarbalkoxylation experiments and the quenching of the low-temperature enolates are almost identical in all cases, it is reasonable to assume that the same intermediate is involved. The α anion of an ester can be depicted as the charge-delocalized species **31**;



31 32 33

however, the localized forms **32** and **33** may be in equilibrium, and aggregations could exist.[17] In addition, the natures of the solvent and the cation also dictate the true nature of the species in solution. Whatever the true nature of the intermediate, protonation may occur at one of two sites, either carbon or oxygen, with subsequent rearrangement.[18] Excluding the possibility of oxygen protonation, let us attempt to rationalize some of the stereochemical results presented here.

In the decarbethoxylations of the bicyclic systems **13** and **16**, the endo esters are the dominant products. Clearly this is not the result of thermodynamic control or equilibration during the reaction since the exo esters are the energetically favorable species. In these cases there is a stereoselectivity for kinetic protonation of the intermediate enolate ester from the least hindered exo direction.[19] An early reactant-like transition state is probably occurring during the protonation stage. This type of argument might also be used to rationalize the 60:40 cis/trans ester ratio found in the decarbethoxylation of diester **22** (approach of water from the less hindered equatorial direction).

In the cases of the diesters **19**, **25**, and **28** (where the substituents are quite distant from the reaction site), the products are again clearly not those based on thermodynamic considerations. In these cases it appears that the approach of the water molecule to the enolate can occur with equal facility (equal energy) from the axial or the equatorial direction, which leads to a nearly equal distribution of cis and trans esters.

It might also be noted that the ester enolate derived from the 4-*tert*-butyl- and 3-methylcyclohexane methyl esters (from LDA) shows a high selectivity for equatorial methylation with methyl iodide.[20] This is also true for the methylation of the enolate derived from methyl 4-*tert*-butylcyclohexyl ketone.[18a] This same enolate shows little selectivity upon quenching with aqueous acetic acid.

(17) (a) Lohman, L.; Lim, D. *J. Organomet. Chem.* **1973**, *50*, 9. (b) Kriz, J.; Schmidt, P. *Tetrahedron* **1972**, *28*, 1033. (c) Halaska, V.; Lochmann, L. *Collect. Czech. Chem. Commun.* **1973**, *38*, 1780. (d) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

(18) (a) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943. (b) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(19) Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091 and references therein cited.

(20) Dundulis, E. A., Ph.D. Thesis, University of Vermont, 1979; unpublished results.

The structural features of these enolates are such that the steric constraints at the transition state for alkylations are more demanding than those for the smaller electrophile water or hydronium ion.

The observation that 3 leads mainly to ester 4 is consistent with less steric hindrance to protonation of the intermediate enolate from the α direction. The results presented in Table I are a little more difficult to rationalize since entries 1 and 4 are indeed the products obtained on equilibration. In these cases it is possible that the least hindered approach of water (wet Me_2SO) is from the β direction if it is possible that equilibration occurred during the reaction (OH^- present in trace amounts in the NaCN).

Further studies of model systems, in which one face of the molecule is severely hindered, to test the steric hindrance factor will be performed.

Experimental Section

General Methods. NMR spectra were obtained with a JEOL JNM-MH-100 spectrophotometer using $CDCl_3$ as a solvent with 1% Me_4Si as an internal standard unless otherwise stated. IR spectra were recorded on a Perkin-Elmer Model 267 grating infrared spectrophotometer or a Beckman IR spectrophotometer. Liquid samples were recorded as thin films and solids as KBr pellets or in a solution of CCl_4 or $CHCl_3$. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. GC analyses were performed on an F&M Model 700 gas chromatograph equipped with a H_2 flame detector and using N_2 as the carrier gas. The columns used were as follows: column A, 8 ft × $^1/_4$ in., 10% DEGS on Chromosorb P; column B, 10 ft × $^1/_4$ in., 5% TRIS [1,2,3-tris(2-cyanoethoxy)propane] on Chromosorb G. Alternatively, a Gow-Mac 69-100 chromatograph equipped with a thermal conductivity detector was used with He as the carrier gas. This was equipped with a 4 ft × $^1/_4$ in., 20% DC-200 on Chromosorb column (column C).

Hydrogenations were performed with a Parr pressure reaction apparatus using an initial pressure of 50–55 psi of hydrogen. Solvents were removed in vacuo by using a Buchler flash evaporator. All reactions were magnetically stirred unless otherwise stated and run on the atmosphere protected by drying tubes containing anhydrous $CaSO_4$ (Drierite) unless otherwise stated.

Materials. Me_2SO (dimethyl sulfoxide) was kindly supplied by Crown Zellerbach or purchased from Fisher Scientific Co. (certified grade) or Mallinckrodt (AR grade). The Me_2SO was purified by distillation under reduced pressure from CaH_2 and stored over 4A molecular sieves in a septum-fitted flask under an N_2 atmosphere. Salts were used as received with the exception of preliminary drying in some cases. Ethanol for equilibrium studies was dried by distillation of absolute ethanol from Na onto molecular sieves and stored under an N_2 atmosphere in a septum-fitted flask. Tetrahydrofuran (THF) was obtained from Aldrich and purified after preliminary drying with KOH by double distillation from Na–benzophenone ketyl; the last distillation was just prior to use. *n*-Butyllithium was obtained from Alfa Ventron as a solution in hexane. Diisopropylamine was obtained from Aldrich and distilled from CaH_2 prior to use. Organic starting materials were obtained from Aldrich, Eastman Organics, Pfaltz and Bauer, or ICN Life Science Group (K&K) and were used as received except in the case of the substituted benzoic acids which were recrystallized from appropriate solvents.

Diethyl Bicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (13). Diester **13** was prepared from cyclopentadiene and diethyl methylenemalonate[21] according to a published procedure.[22] Distillation yielded **13**: 10.2460 g (80.9%); bp 85–89 °C (0.53 mm) [lit.[12] 109–111.5 °C (2 mm)]; NMR ($CDCl_3$) δ 1.26 (6 H, overlapping triplets), 1.63 (2 H, q), 2.1 (2 H, m), 2.96 (1 H, br s), 3.25 (1 H, br s), 4.24 (4 H, overlapping q), 6.04–6.76 (2 H, m).

Diethyl Bicyclo[2.2.1]heptane-2,2-dicarboxylate (16). Diester **13** (9.38 g, 0.039 mmol) was hydrogenated in 100 mL of ethyl acetate in the presence of 10% Pd/C. When the theoretical amount of hydrogen was consumed, the reaction was filtered through a Celite pad and the ethyl acetate removed in vacuo. The residue was distilled to yield **16**: 8.5896 g (90.9%); bp 90–92 °C (0.6 mm) [lit.[22] 124–125 °C (6 mm)]; NMR ($CDCl_3$) δ 2.02–2.16 (13 H, complex), 2.2–3.02 (3 H), 4.35 (4 H, complex); IR 2960, 2880, 1725, 1250, 1205, 1140 cm^{-1}.

Diethyl 4-*tert*-Butyl-1,1-cyclohexanedicarboxylate (19). *p*-*tert*-Butylbenzoic acid (5.0172 g, 0.028 mol) was dissolved in 100 mL of glacial acetic acid and 1.0 g of platinum oxide was added. The mixture was hydrogenated until the theoretical amount of hydrogen was used. The reaction mixture was filtered through a Celite pad which was washed well with acetic acid. The mixture was concentrated in vacuo and then poured into an equal volume of ice–water. The precipitate was filtered, washed with water, air-dried, and dried for 16 h at 4 mm to obtain 4.9376 g (95%) of 4-*tert*-butylcyclohexanecarboxylic acid as a white solid (mp 92–102 °C) as a mixture of stereoisomers (lit.[23] mp 118–118.5 °C, cis, 175–176 °C, trans): NMR ($CDCl_3$) δ 0.87 (9 H, s), 0.96–2.88 (10 H, m), 11.04 (1 H, br s). The crude acid thus obtained can be recrystallized from ether–hexane.

4-*tert*-Butylcyclohexanecarboxylic acid (7.0358 g, 0.038 mol) was combined in a flask with ethanol (7.0011 g, 0.15 mol), concentrated sulfuric acid (5 drops), and 50 mL of benzene. The flask was fitted with a Dean–Stark trap and heated to reflux overnight, azeotropically removing water. The reaction was cooled and transferred to a separatory funnel, and saturated K_2CO_3 solution was added until the aqueous phase tested basic. The layers were separated, and the aqueous phase was extracted three times with 25-mL portions of ether. The combined organic layers were extracted with 10 mL of water and 10 mL of saturated NaCl solution and dried over anhydrous $MgSO_4$. The organic layer was filtered and the solvent removed in vacuo. The residue was distilled to give 7.1886 g of ethyl 4-*tert*-butylcyclohexanecarboxylate (88.68%): bp 77–79 °C (1.2 mm) [lit.[24] bp 134–137 °C (28 mm), cis]; NMR ($CDCl_3$) δ 0.88 (9 H, 2 s overlapping), 0.98–2.82 (13 H, m), 4.32 (2 H, 2 q overlapping); IR 2960, 2880, 1735, 1200, 1150 cm^{-1}.

A flame-dried, three-necked flask fitted with an N_2 inlet, a septum, and a low-temperature thermometer was charged with ca. 125 mL of THF, and diisopropylamine (4.2 mL, 3.03 g, 0.03 mol) was added. The mixture was cooled to −70 °C. *n*-Butyllithium (13 mL, 2.3 M, 0.03 mol) was added via syringe and the mixture allowed to stir 30 min. Ethyl 4-*tert*-butylcyclohexanecarboxylate (6.3597 g, 0.03 mol) was added dissolved in 10 mL of THF in such a manner that the temperature never went above −60 °C. After 1 h ethyl chloroformate (2.9 mL, 3.29 g, 0.03 mol) was added dropwise and the reaction allowed to stir for 1.5 h. The mixture was then warmed to room temperature and transferred into a separatory funnel containing 100 mL of crushed ice and water plus 5 mL of concentrated HCl. Ether (25 mL) was added, and the layers were separated. The aqueous phase was extracted three times with 50-mL portions of ether. The combined organic layers were extracted with 10 mL of 10% HCl, 10 mL of H_2O, 10 mL of saturated K_2CO_3 solution, 10 mL of H_2O, and two portions of 10 mL of saturated NaCl solution. The organic layer was then dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was distilled to yield 7.5941 g (89%) of **19**: bp 115–118 °C (1.1 mm) [lit.[25] bp 132 °C (2.5 mm)]; NMR ($CDCl_3$) δ 0.88 (9 H, 2 s overlapping), 0.98–2.73 (16 H, m), 4.32 (4 H, quintet); IR 2960, 2880, 1740, 1250 cm^{-1}.

Dimethyl 4-*tert*-Butyl-1,1-cyclohexanedicarboxylate. Crude 4-*tert*-butylcyclohexanecarboxylic acid (20.0047 g, 0.11 mol) was combined with 100 mL of methanol and concentrated sulfuric acid (5 drops). The mixture was refluxed for 5 days. After cooling, the mixture was transferred to a separatory funnel containing 100 mL of ice–water and 20 mL of saturated K_2CO_3 solution. The basic aqueous solution was extracted five times with 50-mL portions of ether. The combined ether layers were washed with

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50 mL of water followed by 10 mL of saturated NaCl solution and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated in vacuo. The residue was distilled to yield 15.7986 g (73%) of methyl 4-*tert*-butylcyclohexanecarboxylate, bp 86–87 °C (1.0 mm) [lit. bp 54–56 °C (0.5 mm), cis,[26] 102–103 °C (9 mm), trans].[27]

The methyl 4-*tert*-butylcyclohexanecarboxylate (5.9402 g, 0.03 mol) thus prepared was converted into dimethyl 4-*tert*-butylcyclohexane-1,1-dicarboxylate by using the same procedure as that used for the diethyl ester with the exception of the use of methyl chloroformate (2.89 g, 2.37 mL, 0.03 mol) in place of ethyl chloroformate. Distillation yielded the dimethyl ester: 5.9343 g (77%); bp 105–108 °C (1.0 mm); NMR ($CDCl_3$) δ 0.84 (9 H, s), 0.96–2.6 (9 H, m), 3.69 (6 H, s); IR 2950, 2870, 1735, 1245 cm^{-1}.

Diethyl 2-Methylcyclohexane-1,1-dicarboxylate (22). *o*-Toluic acid (13.8966 g, 0.10 mol) was dissolved in 100 mL of ethanol, and 1.0 g of 5% Rh/alumina catalyst was added. The mixture was hydrogenated until the theoretical amount of hydrogen had been used. The reaction was then filtered through Celite and the ethanol removed in vacuo. The residue was dissolved in ether, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo. The residue was distilled to obtain 11.8239 g (81.5%) of 2-methylcyclohexanecarboxylic acid [bp 90–92 °C (1.5 mm)] as a mixture of stereoisomers [lit.[28] bp 77–78 °C (0.25 mm)]: NMR ($CDCl_3$) δ 0.96 (3 H, d), 1.14–2.7 (10 H, m), 11.74 (1 H, s); IR 3100, 2930, 2850, 2680, 1700, 1450, 1420, 1260, 940 cm^{-1}.

2-Methylcyclohexanecarboxylic acid (7.1299 g, 0.05 mol) was combined with ethanol (8.84 g, 11.2 mL, 0.19 mol), benzene (50 mL), and concentrated sulfuric acid (4 drops). The flask was fitted with a Dean–Stark apparatus and heated to reflux, azeotropically removing water for 17 h. Workup by the previously described procedure followed by distillation gave the ethyl 2-methylcyclohexanecarboxylate: 5.2178 g (61.2%); bp 126–128 °C (aspirator pressure) [lit.[29] bp 88–90 °C (20 mm), cis]; GC analysis shows the composition of the ester to be 3% trans (eluted first) and 97% cis; NMR ($CDCl_3$) δ 0.88 (3 H, d), 1.06–2.66 (13 H, q), 4.12 (4 H, q); IR 2920, 2850, 1735, 1175, 1045 cm^{-1}.

Tetrahydrofuran (125 mL) was added to a three-necked, 250-mL flask which had been flamed dry under an N_2 atmosphere and fitted with a septum and a low-temperature thermometer. Diisopropylamine (2.6 g, 3.6 mL, 0.025 mol) was added via syringe, the flask cooled to −70 °C, *n*-butyllithium (11 mL, 2.3 M, 0.025 mol) added, and the mixture stirred at −70 °C for 0.5 h. Ethyl 2-methylcyclohexanecarboxylate (4.2503 g, 0.025 mol) was added dissolved in 15 mL of THF such that the temperature never went above −60 °C. The solution was stirred 1 h at −70 °C, ethyl chloroformate (2.17 g, 2.4 mL, 0.025 mol) was added in a similar manner, and the mixture was stirred at −70 °C for 1.5 h. Workup as in a previous example followed by distillation yielded **22**: 5.0958 g (84.2%); bp 98–100 °C (1.9 mm) [lit.[29] bp 86–87 °C (0.25 mm)]; NMR ($CDCl_3$) δ 1.00 (3 H, d), 1.12–2.48 (16 H, m), 4.2 (4 H, q); IR 2930, 2880, 1730, 1240, 1135, 1030 cm^{-1}.

Diethyl 3-Methylcyclohexane-1,1-dicarboxylate (25). *m*-Toluic acid (21.1127 g, 0.16 mol) was dissolved in 200 mL of ethanol, and 1.51 g of 5% Rh/alumina catalyst was added. The mixture was hydrogenated until the theoretical amount of hydrogen had been consumed. The mixture was filtered through Celite and the ethanol removed in vacuo. The residue was dissolved in ether, extracted with 10 mL of water followed by 10 mL of saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was filtered and the ether removed in vacuo. The residue was distilled to yield 3-methylcyclohexanecarboxylic acid: 19.6552 g (89.1%); bp 89–92 °C (1.2 mm) [lit.[30] bp 136–138 °C (17 mm)]; NMR ($CDCl_3$) δ 0.92 (3 H, d), 1.04–2.8 (10 H, m), 12.0 (1 H, s); IR 3050, 2940, 2870, 2670, 1700, 945 cm^{-1}.

3-Methylcyclohexanecarboxylic acid (14.2350 g, 0.10 mol) was combined with ethanol (19.7 g, 25 mL, 0.43 mol), benzene (130 mL), and concentrated sulfuric acid (6 drops) in a flask fitted with a Dean–Stark apparatus. The mixture was heated to reflux, azeotropically removing water for 20 h. Workup as above followed by distillation yielded ethyl 3-methylcyclohexanecarboxylate: 14.7379 g (86.5%); bp 44–47 °C (1.1 mm) (lit.[31] bp 208–210 °C); NMR ($CDCl_3$) δ 0.92 (3 H, d), 1.06–2.8 (13 H, m), 4.15 (4 H, 2 overlapping q); IR 2920, 2850, 1725, 1175, 1030 cm^{-1}.

Tetrahydrofuran (125 mL) was added to a flamed dry, three-necked flask under a N_2 atmosphere which had been fitted with a low-temperature thermometer and a septum. Diisopropylamine (3.03 g, 4.2 mL, 0.03 mol) was added via syringe and the flask cooled to −70 °C in a dry ice–acetone bath. *n*-Butyllithium (13 mL, 2.3 M, 0.03 mol) was added by syringe and the mixture stirred at −70 °C for 1 h. Ethyl 3-methylcyclohexanecarboxylate (5.1030 g, 0.03 mol) was added dissolved in 20 mL of THF in such a manner that the temperature did not exceed −60 °C. After 1 h at −70 °C ethyl chloroformate (3.29 g, 2.9 mL, 0.03 mol) was added in a similar fashion. This was stirred at −70 °C for 1.5 h and worked up as in the previous cases. The residue was distilled to yield **25**: 6.3756 g (87.8%); bp 88–93 °C (1.05 mm) [lit.[29] bp 81–82 °C (0.2 mm)]; NMR ($CDCl_3$) δ 0.90 (3 H, d), 1.1–2.52 (15 H, m), 4.17 (4 H, quintet); IR 2940, 2860, 1725, 1245, 1135, 1030 cm^{-1}.

Diethyl 4-Methylcyclohexane-1,1-dicarboxylate (28). *p*-Toluic acid (24.6 g, 0.18 mol) was dissolved in 150 mL of ethanol and hydrogenated over 5% Rh/alumina catalyst until the theoretical amount of hydrogen had been used. The reaction was filtered through Celite and the solvent removed in vacuo. The residue was distilled to yield 4-methylcyclohexanecarboxylic acid: 22.03 g (85.5%); bp 147–148 °C (aspirator pressure) [lit.[32] bp 135 °C (20 mm)]; NMR ($CDCl_3$) δ 0.90 (3 H, d), 1.04–2.7 (10 H, m), 11.92 (1 H, s); IR 3040, 2920, 2860, 2640, 1700, 1240, 940 cm^{-1}.

4-Methylcyclohexanecarboxylic acid (14.2279 g, 0.10 mol) was combined with ethanol (19.7 g, 25 mL, 0.43 mol) and concentrated sulfuric acid (6 drops) in benzene (130 mL). The mixture was refluxed for 20 h, removing water azeotropically with a Dean–Stark apparatus. Workup as in the previous example followed by distillation yielded ethyl 4-methylcyclohexanecarboxylate: 14.9802 g (88%); bp 129–130 °C (aspirator pressure) [lit.[33] bp 64 °C (3 mm)]; NMR ($CDCl_3$) δ 0.90 (3 H, d), 1.04–2.6 (13 H, m), 4.18 (2 H, q); IR 2910, 2850, 1725, 1185, 1140, 1040 cm^{-1}.

Tetrahydrofuran (125 mL) was added to a flamed dry, N_2 atmosphere, three-necked flask fitted with a septum and a low-temperature thermometer. Diisopropylamine (3.03 g, 4.2 mL, 0.03 mol) was added via syringe, and the solution was cooled to −70 °C. *n*-Butyllithium (13 mL, 2.3 M, 0.03 mol) was added and the mixture stirred at −70 °C for 1 h. Ethyl 4-methylcyclohexanecarboxylate (5.1000 g, 0.03 mol) was added dissolved in 20 mL of THF such that the temperature never exceeded −60 °C, and the mixture was then stirred at −70 °C for 1 h. Ethyl chloroformate (3.29 g, 2.9 mL, 0.03 mol) was added in a similar manner and the mixture then stirred for 1.5 h at −70 °C. The reaction was worked up as before. The residue was distilled to yield 6.2123 g (86%) of diethyl 4-methyl-1,1-cyclohexanedicarboxylate (**28**): bp 88–89 °C (1.0 mm) [lit.[25] bp 120 °C (12 mm)]; NMR ($CDCl_3$) δ 0.89 (3 H, d), 1.04–2.52 (15 H, m), 4.21 (4 H, quintet); IR 2940, 2860, 1725, 1230, 1130, 1025 cm^{-1}.

Decarbalkoxylations of the Malonate Esters. Decarbethoxylation of Diethyl Bicyclo[2.2.1]hept-5-ene-2,2-dicarboxylate (13). Typical Procedures. Run 1. Diester **13** (0.7149 g, 3.003 mmol) was combined in a flask with lithium chloride (0.1282 g, 3.024 mmol) and water (0.0541 g, 3.01 mmol) in 10 mL of Me_2SO. The flask was heated in an oil bath at 193 °C for 1 h. The cooled solution was poured into 15 mL of crushed ice and water and this was saturated with NaCl and extracted three times with 2 mL of pentane. The combined organic layers were dried over anhydrous Na_2SO_4 and analyzed by GC (column A) which showed 79.9 ± 0.7% endo ester **14** (eluted second) and 20.1 ± 0.7% exo ester **15** (eluted first).

Run 2. Diester **13** (2.3880 g, 0.01 mol) was combined with lithium chloride (0.428 g, 0.010 mol) and water (0.1844 g, 0.010 mol) in 25 mL of Me_2SO in a two-necked flask fitted with an internal thermometer. The flask was insulated in a heating mantle

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and heated. The mixture was heated to 150 °C where CO_2 bubbles were evidenced and then to 168–179 °C for 3 h. The cooled mixture was poured into a separatory funnel with 50 mL of crushed ice and water then extracted three times with 10 mL of pentane. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to yield crude ethyl bicyclo[2.2.1]hept-5-ene-2-carboxylate: 0.3714 g (22%); NMR ($CDCl_3$) δ 1.18–3.44 (10 H, m), 4.3 (2 H, 2 overlapping quartets), 6.08–6.52 (2 H, m).

Decarbethoxylation of Diethyl Bicyclo[2.2.1]heptane-2,2-dicarboxylate (16). Diethyl bicyclo[2.2.1]heptane-2,2-dicarboxylate (3.6010 g, 0.015 mol) was combined with lithium chloride (0.6385 g, 0.015 mol) and water (0.2703 g, 0.015 mol) in 25 mL of Me_2SO. The reaction was heated via a heating mantle until an internal temperature of 185 °C was reached for 4 h. The mixture was worked up as in the typical procedure described above. Distillation yielded the ethyl bicyclo[2.2.1]heptanecarboxylates: 1.4996 g (63%); bp 47–48 °C (0.65 mm); GC analysis (column A) showed 69% endo ester (eluted first) **17** and 31% exo ester **18** (eluted second); NMR ($CDCl_3$) δ 1.14–1.0 (11 H, m), 2.24–2.44 (1 H, m), 2.46–2.94 (2 H, m), 4.07–4.44 (2 H, m); IR 2940, 2860, 1720, 1165, 1025 cm^{-1}.

Decarbethoxylation of Diethyl 4-*tert*-Butylcyclohexane-1,1-dicarboxylate (19). Run 1. Diester **19** (0.8624 g, 3.037 mmol), lithium chloride (0.1287 g, 3.609 mmol), and water (0.0547 g, 3.04 mmol) were combined in 10 mL of Me_2SO. The flask was immersed in an oil bath and the temperature maintained at 184–185 °C for 3.5 h. The mixture was worked up as above and was analyzed by GC (column A) to give ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate [**21**, 51 ± 1.4% (eluted first)] and ethyl *cis*-4-*tert*-butylcyclohexanecarboxylate (**20**, 49 ± 1.4%).

Run 2. Diester **19** (4.2663 g, 0.015 mol), lithium chloride (0.6394 g, 0.015 mol), and water (0.2738 g, 0.015 mol) were combined in a flask with 35 mL of Me_2SO. The flask was immersed in an oil bath and heated at 200 °C for 5 h. The residue was distilled in a micro distillation apparatus to yield a mixture of ethyl *cis*- and *trans*-4-*tert*-butylcyclohexanecarboxylates **20** and **21**: 2.1921 g (69%); bp (bath temperature) 77–87 °C (0.8 mm) [lit.[34] bp 102–103 °C (1 mm)]; NMR ($CDCl_3$) δ 0.82 (9 H, s), 0.9–2.7 (22 H, m), 4.12 (2 H, m).

A mixture of ethyl *cis*-4-*tert*-butylcyclohexanecarboxylate (**20**, 68%) and ethyl *trans*-4-*tert*-butylcyclohexanecarboxylate (**21**, 32%) (0.7760 g, 3.660 mmol) was combined with lithium chloride (0.1551 g, 3.659 mmol) and water (0.0659 g, 3.66 mmol) in 10 mL of Me_2SO. The flask was immersed in an oil bath and heated to 192 ± 2 °C for 3 h. The cooled reaction mixture was poured into 15 mL of ice–water and the mixture was saturated with NaCl and extracted three times with 2 mL of pentane. The combined organic layers were dried over anhydrous Na_2SO_4 and analyzed by GC (column A) to give a ratio of *cis*-**20** and *trans*-**21** unchanged from the starting composition. The mixture was filtered and the solvent removed in vacuo to recover the starting esters (0.5038 g, 65%).

Decarbomethoxylation of Dimethyl 4-*tert*-Butylcyclohexane-1,1-dicarboxylate. Dimethyl 4-*tert*-butylcyclohexane-1,1-dicarboxylate (0.7691 g, 3.004 mmol), lithium chloride (0.1277 g, 3.013 mmol), and water (0.0541 g, 3.01 mmol) were combined with 10 mL of Me_2SO. The flask was immersed in an oil bath and heated to 194 ± 2 °C for 4 h. The reaction mixture was worked up as usual, and the solution was analyzed by GC (column B) to give 48.6 ± 0.5% methyl *cis*-4-*tert*-butylcyclohexanecarboxylate (eluted first) and 51.4 ± 0.5% methyl *trans*-4-*tert*-butylcyclohexanecarboxylate (eluted second). The solution was concentrated to yield 0.3687 g (62%) of the crude mixture: NMR ($CDCl_3$) δ 0.86 (9 H, s), 0.96–2.64 (10 H, m), 3.68 (3 H, 2 s); IR 2960, 2880, 1740, 1200 cm^{-1}.

Decarbethoxylation of Diethyl 2-Methylcyclohexane-1,1-dicarboxylate (22). Diester **22** (3.6318 g, 0.015 mol) was combined with lithium chloride (0.6361 g, 0.015 mol) and water (0.2713 g, 0.015 mol) in 25 mL of Me_2SO. The reaction mixture was heated in an oil bath at 187 ± 3 °C for 4 h. The mixture was worked up as usual and analyzed by GC (column B) to give 40 ± 1% ethyl *trans*-2-methylcyclohexanecarboxylate (**24**, eluted first) and 60 ± 1% ethyl *cis*-2-methylcyclohexanecarboxylate (**23**, eluted second). The solvent was removed in vacuo and the residue distilled in a micro distillation apparatus to yield **23** and **24** (1.8362 g, 72%) at a bath temperature of 126–134 °C (aspirator pressure) [lit.[29] bp 90 °C (22 mm), trans, and 88–90 °C (20 mm), cis]: NMR ($CDCl_3$) δ 0.8–1.04 (3 H, m), 1.2–2.6 (13 H, m), 4.14 (2 H, q); IR 2925, 2850, 1730, 1175, 1030 cm^{-1}.

Decarbalkoxylation of Diethyl 3-Methylcyclohexane-1,1-dicarboxylate (25). Diester **25** (3.6360 g, 0.015 mol) was combined with lithium chloride (0.6367 g, 0.015 mol) and water (0.2839 g, 0.016 mol) in 25 mL of Me_2SO. The mixture was heated in an oil bath at 192 ± 4 °C for 5.5 h. The reaction mixture was worked up as usual, and the residue was distilled in a micro distillation apparatus to yield a mixture of **26** and **27** (2.0262 g, 79%) at a bath temperature of 130 °C (aspirator pressure) (lit.[31] bp 208–210 °C). The product was analyzed by GC (column A) to give ethyl *trans*-3-methylcyclohexanecarboxylate (**27**, 50%) and ethyl *cis*-3-methylcyclohexanecarboxylate (**26**, 50%): NMR ($CDCl_3$) δ 0.88 (2 H, d), 1.12–2.68 (13 H, m), 4.15 (2 H, 2 overlapping q); IR 2910, 2850, 1730, 1180, 1030 cm^{-1}.

Decarbalkoxylation of Diethyl 4-Methylcyclohexane-1,1-dicarboxylate (28). Diester **28** (3.6336 g, 0.015 mol) was combined with lithium chloride (0.6384 g, 0.015 mol) and water (0.2721 g, 0.015 mol) in 25 mL of Me_2SO. The mixture was heated in an oil bath at 196 ± 2 °C for 5.5 h. The mixture was worked up as usual and analyzed by GC (column A) to give 49.5 ± 0.5% ethyl *cis*-4-methylcyclohexanecarboxylate (**29**, eluted first) and 50.05 ± 0.5% ethyl *trans*-4-methylcyclohexanecarboxylate (**30**). The solvent was removed in vacuo and the residue distilled in a micro distillation apparatus to yield a mixture of **29** and **30** (1.9483 g, 76%) at a bath temperature of 115 °C (aspirator pressure) [lit.[33] bp 64 °C (3 mm)]: NMR ($CDCl_3$) δ 0.89 (2 H, d), 1.14–2.65 (13 H, m), 3.99–4.32 (2 H, m); IR 2915, 2860, 1725, 1180, 1040 cm^{-1}.

General Procedure for Treatment of Monoesters with LDA Followed by Quenching with Water. Tetrahydrofuran (50 mL) was added to a three-necked flask which had been flame dried under an N_2 atmosphere and was fitted with a low-temperature thermometer and a septum. Diisopropylamine (0.31 g, 0.45 mL, 3.2 mmol) was added via syringe and the solution cooled to −70 °C. *n*-Butyllithium (1.3 mL, 2.3 M, 3.0 mmol) was added and the mixture stirred at −78 °C for 0.5 h. The ester substrate (3.0 mmol) was added dissolved in 5 mL of THF such that the temperature never exceeded −70 °C. The resulting solution was stirred for 1 h at −78 °C. Water (0.1 mL, 5.6 mmol) was added, and the mixture was stirred for 1 h and then allowed to warm slowly to room temperature. The solution was poured into 15 mL of cold water containing 1 mL of concentrated hydrochloric acid, and the layers were separated. The aqueous phase was extracted two times with 20 mL of ether. The combined organic phases were extracted with sufficient saturated K_2CO_3 solution (until the aqueous phase was basic) and then with 10 mL of saturated NaCl solution and dried over anhydrous $MgSO_4$. The mixture was filtered, concentrated in vacuo, and analyzed by GC.

Ethyl 4-*tert*-butylcyclohexanecarboxylate (0.6350 g, 3.0 mmol) was used, giving a product distribution by GC (column A) of 50 ± 1% trans (**20**, eluted first) and 50 ± 1% cis (**21**).

Ethyl 2-methylcyclohexanecarboxylate (0.5120 g, 3.0 mmol) was used, giving a product distribution by GC (column B) of 28 ± 4% trans (**24**, eluted first) and 72 ± 4% cis (**23**).

Ethyl 3-methylcyclohexanecarboxylate (0.5104 g, 3.0 mmol) was used, giving a product distribution by GC (column A) of 47.7 ± 0.6% trans (**27**, eluted first) and 52.3 ± 0.6% cis (**26**).

Ethyl 4-methylcyclohexanecarboxylate (0.5110 g, 3.0 mmol) was used, giving a product distribution by GC (column A) of 53.3 ± 0.6% cis (**29**, eluted first) and 46.7 ± 0.6% trans (**30**).

Thermodynamic Equilibrations. General Procedure.[16] The ester was added to a solution of lithium in 40 mL of ethanol, and the solution was heated at reflux for 70 h. The mixture was added to 120 mL of cold water and extracted three times with 25 mL of ether. The combined organic layers were washed with 5 mL of water followed by 10 mL of saturated NaCl solution and dried over anhydrous $MgSO_4$. The solutions were filtered, concentrated in vacuo, and then analyzed by GC.

Ethyl 4-*tert*-butylcyclohexanecarboxylate (1.8832 g, 8.88 mmol) and lithium (0.0081 g, 1.2 mmol) were used. GC analysis (column

(34) Karger, B. L.; Stern, R. L.; Zannucci, J. F. *Anal. Chem.* **1968**, *40*, 727.

A) gave **21** (trans, 82.1 ± 0.8%) and **20** (cis, 17.9 ± 0.8%).

Ethyl 2-methylcyclohexanecarboxylate (1.4632 g, 8.61 mmol) and lithium (0.0078 g, 1.1 mmol) were used. GC analysis (column B) gave **24** (trans, 76.4 ± 0.6%) and **23** (cis, 23.6 ± 0.6%).

Ethyl 3-methylcyclohexanecarboxylate (1.7093 g, 10.1 mmol) and lithium (0.0090 g, 1.1 mmol) were used. GC analysis (column A) gave **26** (cis, 83.0 ± 1.1%) and **27** (trans, 17.0 ± 1.1%).

Ethyl 4-methylcyclohexanecarboxylate (1.7046 g, 10.03 mmol) and lithium (0.0087 g, 1.2 mmol) were used. GC analysis gave **30** (trans, 78.9 ± 0.1%) and **29** (cis, 21.1 ± 0.1%).

Registry No. 13, 65132-76-5; **14**, 51789-95-8; **15**, 51789-92-5; **16**, 30934-87-3; **17**, 61242-71-5; **18**, 4755-79-7; **19**, 53695-41-3; **20**, 7214-36-0; **21**, 7214-35-9; **22**, 5222-56-0; **23**, 25144-01-8; **24**, 10479-71-7; **25**, 25118-34-7; **26**, 74542-23-7; **27**, 74542-24-8; **28**, 53695-40-2; **29**, 25244-23-9; **30**, 41692-50-6; cyclopentadiene, 542-92-7; diethyl methylenemalonate, 3377-20-6; *p-tert*-butylbenzoic acid, 98-73-7; *cis*-4-*tert*-butylcyclohexanecarboxylic acid, 943-28-2; *trans*-4-*tert*-butylcyclohexanecarboxylic acid, 943-29-3; ethanol, 64-17-5; ethyl chloroformate, 541-41-3; methanol, 67-56-1; methyl *cis*-4-*tert*-butylcyclohexanecarboxylate, 17177-76-3; methyl *trans*-4-*tert*-butylcyclohexanecarboxylate, 17177-75-2; dimethyl 4-*tert*-butylcyclohexanedicarboxylate, 74542-25-9; methyl chloroformate, 79-22-1; *o*-toluic acid, 118-90-1; *cis*-2-methylcyclohexanecarboxylic acid, 7076-91-7; *trans*-2-methylcyclohexanecarboxylic acid, 15177-62-5; *m*-toluic acid, 99-04-7; *cis*-3-methylcyclohexanecarboxylic acid, 73873-48-0; *trans*-3-methylcyclohexanecarboxylic acid, 73873-49-1; *p*-toluic acid, 99-94-5; *cis*-4-methylcyclohexanecarboxylic acid, 934-67-8; *trans*-4-methylcyclohexanecarboxylic acid, 13064-83-0; lithium chloride, 7447-41-8; dimethyl sulfoxide, 67-68-5.

Enantiomerically Pure Lactones. 2.[1] Approaches to Cis or Trans Multicyclic Lactones

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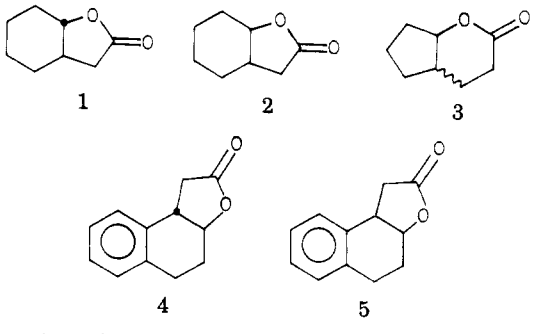
Received February 15, 1980

Enantiomerically pure bicyclic lactones **1–3** and tricyclic lactones **4** and **5** have been prepared by either of two procedures, each hinging upon the liquid chromatographic separation of rationally selected diastereomeric derivatives. After separation, the diastereomers are converted by a simple high-yield reaction sequence to the enantiomeric multiring lactones, none of which has been previously reported in optically active form. The relative strengths and weaknesses of each approach are discussed. Lactones **4** and **5** were α-methylated, these derivatives being suitable for the determination of enantiomeric purity and absolute configuration using the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

Multiringed lactones are widely dispersed throughout nature, literally hundreds of examples being known.[3] This ubiquity, coupled with frequent biological significance,[4] has caused a great deal of effort to be applied toward the synthesis of a host of multiringed lactones. Although most multiringed lactones occur naturally as a single enantiomer, it is interesting to note that most researchers in the field have been content to synthesize racemates. When optically active lactones have been prepared, it has usually been from a related available optically active natural product.

Our interest in developing chromatographic methods for the separation of optical isomers has led to straightforward preparation of a variety of optically active natural products, some of them being simple lactonic pheromones.[1] Accordingly, we sought to extend our basic approach to encompass lactones of greater structural complexity. We now describe two simple procedures for generation of chiral ring-fused lactone moieties of known absolute configuration and high enantiomeric purity. These procedures are illustrated by the synthesis of enantiomers of both bicyclic lactones **1–3** and tricyclic lactones **4** and **5**. None of these



lactones have been previously reported in optically active form. In addition to attesting to the scope of the general approach, lactones **1–5** might themselves be further elaborated to afford more complex systems.

Central to our overall synthetic approach is the multigram chromatographic separation of rationally selected diastereomeric derivatives of a racemic intermediate. The benefits of the chromatographic resolutions discussed herein (i.e., high yields, multigram capability, the obtention of both enantiomers with known absolute configuration and enantiomeric purity) are not always realized with classical resolution methods employing fractional crystallization. These benefits, coupled with the rapidly increasing generality of chromatographic resolution, are causing the latter to become the method of choice for a great many optical resolutions. For example, chromato-

(1) (a) For paper 1 in this series, see: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Presented in part at the Third Biennial Carl S. Marvel Symposium, Tucson, AZ, Mar 1979, No. 16.

(2) On sabbatical leave from the Lubrizol Corp., 1976–1979. Mobil Oil Corp. Predoctoral Fellow, 1976–1977.

(3) For reviews, see: Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625; Grieco, P. A. *Synthesis* **1975**, 67; Gammil, R. B.; Wilson, C. A. *Synth. Commun.* **1975**, *5*, 245; Yoshioka, H.; Mobry, T. J.; Timmermann, B. N. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973; Newaz, S. S. *Aldrichimica Acta* **1977**, *4*, 10.

(4) See for example: Herz, W.; Bhat, S. V. *J. Org. Chem.* **1972**, *37*, 906; Grieco, P. A.; Noguez, J. A.; Masaki, Y. *Ibid.* **1977**, *42*, 495; Martin, J.; Watts, P. C.; Johnson, F. *Chem. Commun.* **1970**, 27; Pettit, G. R.; Budzinski, J. C.; Gragg, G. M.; Brown, P.; Johnston, L. R. D. *J. Med. Chem.* **1974**, *17*, 1013; Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A. *J. Org. Chem.* **1969**, *34*, 3903, 3908; Herz, W.; Sharma, R. P. *Ibid.* **1975**, *40*, 3118; Weinheimer, A. J.; Schmitz, F. J.; Ciereszko, L. S. "Drugs from the Sea"; Marine Technology Society: Washington, DC, 1968; Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 7208.

0022-3263/80/1945-4111$01.00/0