Comparative Study of the Reactions of Dilithiated Vicinal Diesters and Dilithiated 1,2-Dicarboximides with Methyl Iodide, α,ω-Dihalides, α,ω-Ditosylates, and ω-Bromo Esters

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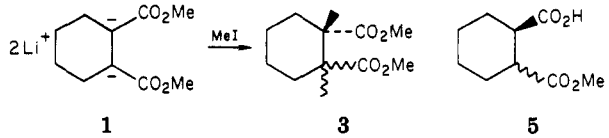
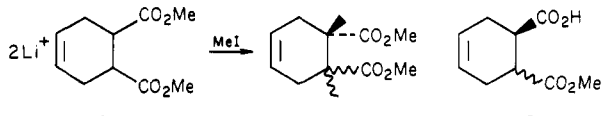
The reactions of dilithiated dimethyl cyclohexane-1,2-dicarboxylate (1), dimethyl 4-cyclohexene-1,2-dicarboxylate (2), *N*-substituted cyclohexane-1,2-dicarboximides **11a–c**, and *N*-phenyl-4-cyclohexene-1,2-dicarboximides 18 with a variety of substrates have been investigated and the results compared. Intramolecular reactions of the monolithiated esters prevent complete conversion to the dilithiated species, but this problem is circumvented in the case of the carboximides which form the dilithiated species quantitatively. The dilithiated species 1 undergoes equilibrium with ethanal or propanone to give monoacylated products formed by intramolecular reactions. Annelation of both 2 and 18 occurs with ethyl 4-bromobutyrate under the appropriate conditions, but in the latter case the carboximide ring undergoes considerable cleavage, presumably in a release of strain. Equilibration of 2 and the ω-bromo ester occurs at higher temperatures, and rearranged products result. The conditions necessary for successful annelation of a 1,2-disubstituted dianion are described. The ^{13}C NMR spectrum of dilithiated *N-tert*-butylcyclohexane-1,2-dicarboximide is reported and adduced as evidence for the pyrrole-like structure **11a**.

We have earlier shown that the treatment of vicinal diesters with lithium diisopropylamide (LDA) gives species which react as dianions and which can be annelated with diethyl phthalate[2] and with α,ω-dihalides and -ditosylates.[3] The yields in these reactions seldom exceeded 60% although little or no other ether-soluble product could be detected. Since the yields were also nonquantitative in the simple dialkylation of these lithiated species with methyl iodide, it was decided to investigate this anomoly by conducting a careful product balance on the reaction of the dilithiated esters 1 and 2 with methyl iodide. Be-



1 3 5



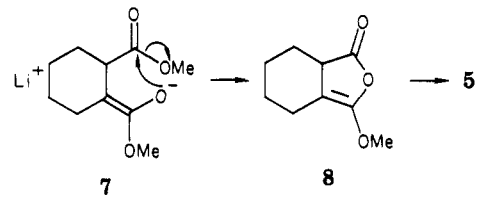
2 4 6

sides the dimethylated derivatives 3 and 4, isolated in 55% and 65% yields, respectively, the half esters 5 and 6 were obtained from the aqueous phase in yields of 28% and 22%.

The formation of 5 and 6 could be most readily accounted for by the elimination of methoxide ion from the dianion to give a ketene intermediate which would then hydrate to the acid during isolation. However, if this were the case, then the dianion should be unstable, decomposing with the loss of lithium methoxide. In fact, the dilithiated species, once formed, are extremely stable, and the yields of methylated product remain unchanged even when solutions of the dianions are stored at ambient temperatures for a number of hours. The half-ester may be formed from the monolithiated diester 7: attack by the oxygen of the enolate anion on the adjacent ester group with elimination of methoxide would give the methoxy lactone 8, which would be susceptible to ready hydrolysis (Scheme I).

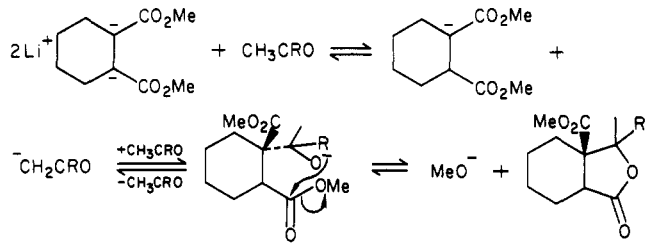
An attempt to substantiate the mechanism outlined in Scheme I by preparation of the monolithiated species was

Scheme I



7 8

Scheme II



9a, R = H
b, R = CH_3

unsuccessful, since reaction of the diester with LDA followed by methylation gave a complex mixture of dimethylated and monomethylated derivatives and acidic products. Some support for Scheme I is afforded by the reaction of 1 with ethanal and propanone, in which the lactones **9a,b** are the major products. We presume that **9a,b** arise by the sequence of reactions shown in Scheme II.

Clearly, if the half-ester is formed by the mechanism outlined in Scheme I, then its formation should be suppressed if the two ester groups were linked together in such a way that intramolecular attack by the monolithiated precursor is precluded. Anhydrides and cyclic carboximides are the two obvious substrates which might have the desired properties of anion stabilization without the possibility of intramolecular interaction. All attempts to generate dilithiated *cis*-cyclohexane-1,2-dicarboxylic anhydride were unsuccessful, a complex mixture of products being obtained, but some corresponding N-substituted carboximides readily formed dilithiated species.[4]

Formation of Dilithiated 1,2-Carboximides and Their Reaction with Methyl Iodide. Treatment of

(1) Smith, Kline and French Research Ltd., The Frythe, Welwyn, Herts AL6 9AR, United Kingdom.
(2) Garratt, P. J.; Zahler, R. *Tetrahedron Lett.* **1979**, 73.
(3) Bilyard, K. G.; Garratt, P. J.; Zahler, R. *Synthesis* **1980**, 389.
(4) For related work on 1,2-carboximides see: Garratt, P. J.; Hollowood, F. *J. Org. Chem.* **1982**, *47*, 68.

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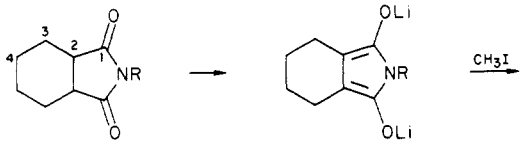
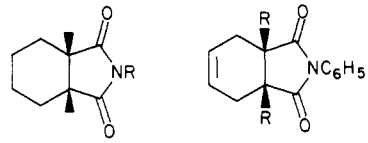
N-*tert*-butyl-*cis*-cyclohexane-1,2-dicarboximide (**10a**) with 2 equiv of LDA gave the dilithiated species **11a**. The



10a, R = $C^5(C^6H_3)_3$
b, R = CH_3
c, R = C_6H_5

11a, R = $C^5(C^6H_3)_3$
b, R = CH_3
c, R = C_6H_5



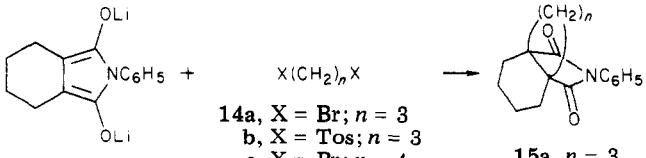
12a, R = $C^5(C^6H_3)_3$
b, R = CH_3
c, R = C_6H_5

13a, R = H
b, R = CH_3

dilithiated nature of **11a** is substantiated by its chemical reactions and by its ^{13}C NMR spectrum. Reaction of **11a** with methyl iodide gave the dimethylated derivative **12a** in 90% isolated yield. The ^{13}C NMR spectrum of **11a** in hexamethylphosphoric triamide (HMPA) showed signals at 156.7, 70.0, 54.0, 39.3, 31.7, and 30.7 ppm, assigned respectively to C-1, C-2, C-5, C-3, C-4, and C-6, consistent with a symmetrical dilithiated species. By comparison with the ^{13}C NMR spectrum of the imide **10a**, C-1 (24.9 ppm) and C-5 (3.3 ppm) have moved upfield in the dilithiated species and C-2 (29.5 ppm), C-3 (14.8 ppm), C-4 (9.4 ppm), and C-6 (2.0 ppm) have moved downfield. These results are best accommodated by structure **11a**, a lithium O-enolate with a pyrrole type ring, the change in hybridization leading to a large *downfield* shift of C-2 (rather than the upfield shift expected because of the negative charge).[5] Some evidence for the existence of the related phthalimide dianion, prepared by reduction of *N*-methylphthalimide with lithium in liquid NH_3, has recently been reported.[6]

The carboximides **10b,c** and **13a** could also be readily converted into the corresponding dilithiated species, and on reaction with MeI these gave the corresponding dimethylated products **12b,c** and **13b** in high yield (>90%). Reaction of **11b** with deuterium oxide also gave 1,2-dideuterio-substituted **10b** in 95% yield with a deuterium incorporation of ca. 75% by ^1H NMR spectroscopy.[7]

Annelation Studies with Dilithiated 1,2-Dicarboximides and α,ω-Dibromides and -Ditosylates. The reaction of the dilithiated species **11c** with α,ω-dibromoalkanes and -ditosylates was investigated in order to compare the results obtained in these reactions with those obtained for the corresponding dilithiated diesters.[3] Results from both series are collected in Table I.



11c

14a, X = Br; *n* = 3
b, X = Tos; *n* = 3
c, X = Br; *n* = 4
d, X = Br; *n* = 5

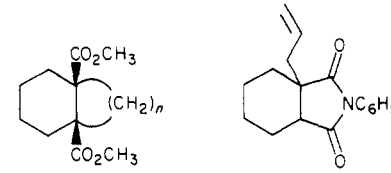
15a, *n* = 3
c, *n* = 4
d, *n* = 5

Table I. Reaction of Dilithiated Cyclohexane-1,2-dicarboximides and Dilithiated Dimethyl Cyclohexane-1,2-dicarboxylate with α,ω-Dihalides and α,ω-Ditosylates

dilithiated species	substrate	product	yield,[a] %	ref
11c	14a	15a	47	
11c	14b	15a	59	
1	14a	16a	71	3
11c	14c	15c	52	
1	14c	16c	53	3
11c	14d	15d	27	
1	14d	16d	35	3

[a] Yields refer to isolated material.

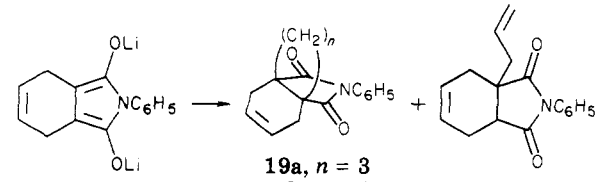
As can be seen from Table I, the substitution of the 1,2-dicarboximides for the 1,2-diester did not lead to an increase in yield of the annelated product, although compounds **15** are more readily isolated than **1b**, being crystalline. As is clear from the last section, the low yields with the carboximides cannot be due to the nonformation of the dilithiated species, and the problem now appears to arise from the strain engendered in forming the tricyclo[4.3.*n*] system. This is borne out by the isolation of monoalkylated products in these reactions. Thus in the reaction of **11c** and **14a**, compound **17** was also isolated in 13% yield. This product presumably arises from monoalkylation of the dianion followed by dehydrobromination, via either inter- or intramolecular anion exchange (dehydrohalogenation to give 3-bromopropene followed by alkylation is also possible but appears less likely).



16a, *n* = 3
c, *n* = 4
d, *n* = 5

17

Very similar results were observed when the dilithiated 4-cyclohexene-1,2-dicarboximide **18** was reacted with α,ω-dibromides. Besides the corresponding annelated products **19a,b**, a monoalkylated analogue of **17** was also obtained with 1,3-dibromopropane which was tentatively identified as **20**.



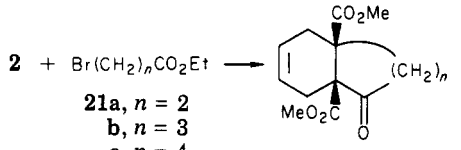
18

19a, *n* = 3
b, *n* = 4

20

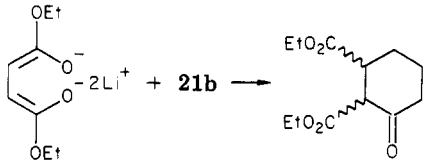
Annelation Studies of Dilithiated 1,2-Dicarboximides and 1,2-Diesters with ω-Bromo Esters. The Dilithiated diester **2** has been shown to react with ethyl 4-bromobutyrate (**21b**) at −78 °C to give the keto diester **22b**.[8] The reactions of **2** with ethyl 3-bromopropionate (**21a**) and ethyl 5-bromopentoate (**21c**) were investigated under similar conditions, and the results are shown in Table II. The reaction of a dilithiated acyclic diester, dilithiated diethyl succinate **23**, with **21b** was also examined and found to give the monocyclic diethyl cyclo-

(5) See: House, H. O.; Prabhu, A. V.; Philips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.
(6) Flynn, G. A. *J. Chem. Soc., Chem. Commun.* **1980**, 862.
(7) Relatively low deuterium incorporation is not uncommon when enolate anions are quenched. See: Creger, P. L. *J. Am. Chem. Soc.* **1976**, *92*, 1396.
(8) Bilyard, K. G.; Garratt, P. J. *Tetrahedron Lett.* **1981**, *22*, 1755. See also Noire, P. D.; Franck, R. W. *Ibid.* **1982**, *23*, 1031.



21a, $n = 2$
b, $n = 3$
c, $n = 4$

22a, $n = 2$
b, $n = 3$
c, $n = 4$



23 24

hexan-3-one-1,2-dicarboxylate (24) as a mixture of diastereomers in 55% yield (Table II).[9]

The same series of reactions were carried out by using the dilithiated carboximide 18 with 21a and 21b. These results are also reported in Table II.

As can be seen from Table II, the most successful annelations occurred between ethyl 4-bromobutyrate (21b) and the dilithiated diesters 2 and 23 to give the bicyclo[4.4.0] system 22b and the monocyclic ketone 24. The annelation of the dilithiated carboximide 18 gave a much lower yield of the tricyclo[4.4.3] derivative 25b, but this was accompanied by a larger amount of the annelated but ring-opened compound 26 (Scheme III). Thus it appears that 25b is unstable under the reaction conditions and that partial opening of the carboximide ring occurs by attack of the ethoxide ion formed in the initial reaction. The ^1H NMR spectrum of 26 has a double doublet at δ 3.05 attributable to the ring junction proton vicinal to the carbonyl group. This proton is coupled to the adjacent methylene protons with apparent coupling constants of J = 7 and 2 Hz, but it is not possible to assign the stereochemistry of 26 on this basis since models indicate that in both the cis and trans isomers these couplings should be unequal. The product derived from monoalkylation of 18 was also obtained in 19% yield in this reaction.

With ethyl 3-bromopropionate (21a) the dilithiated ester 2 gave a low yield of the annelated compound 22a whereas the dilithiated carboximide 18 gave only monoalkylated products (15%).

In the case of ethyl 5-bromopentoate (21c), no annelated products could be identified in the reaction with 2.

The conditions used for the reaction of 2 with 21a,c are based on the optimized conditions for the reaction of 2 and 21b, and it is possible that conditions could be found to increase the yield of annelated products in these reactions. It is unlikely that a significant yield of 25a could be obtained from the reaction of 18 with 21a as this product is very seriously strained.

The reaction of 2 with 21b at ca. 20 °C produced, as was reported briefly elsewhere,[8] a different product which was identified as 31. We suppose that this product occurs because of equilibrium between the dianion and ethyl 4-bromobutyrate to give the corresponding monoanions (Scheme IV). Displacement of bromide ion from the anion of 21b should be facile and lead to ethyl cyclopropanecarboxylate (28). Reaction of the monoanion 27 with 28 with loss of ethoxide gives the β-keto ester 29 which can react with ethoxide to give the enolate anion 30. Intramolecular displacement of methoxide and a protropic shift then gives 31. These reactions follow a pattern similar to those between 1 and ethanal or propanone. Compound 31 is readily dehydrogenated to the aromatic lactone 32.

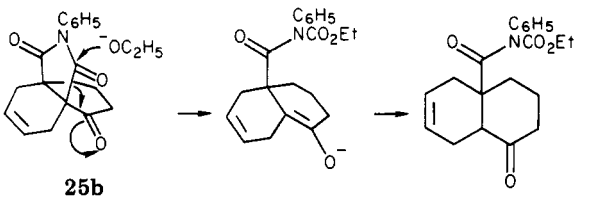
(9) Interestingly, the ^1H NMR spectrum of the 2,4-dinitrophenylhydrazone of 26 suggests that this is largely one stereomer, possibly because of equilibration under the strongly acid conditions of its formation.

Table II. Reaction of Dilithiated 4-Cyclohexene-1,2-dicarboximide (18), Dilithiated Diethyl Succinate (23), and Dilithiated Dimethyl 4-Cyclohexene-1,2-dicarboxylate (2) with ω-Bromo Esters

dilithiated species	substrate	product	yield, %
2	21a	22a	20[a]
18	21a	25a	trace
2	21b	22b	61
23	21b	24	55
18	21b	25b	13[b]
2	21c	22c	0[c]

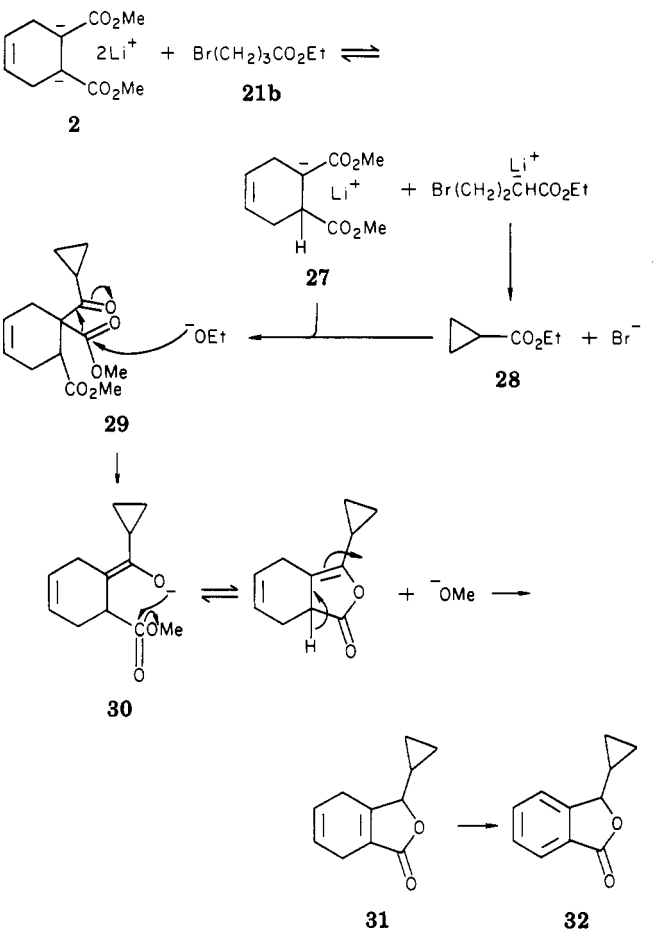
[a] Based on isolated 2,4-dinitrophenylhydrazone. [b] Total annelated product ca. 40% (see Discussion). [c] Based on nondetection of 2,4-dinitrophenylhydrazone.

Scheme III



25b 26

Scheme IV



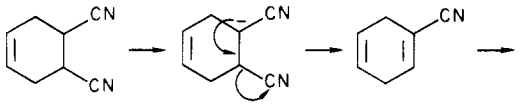
2 21b 27 28 29 30 31 32

Discussion

The carboximides have a clear advantage over the 1,2-diesters in that a clean reaction to the dilithiated species

can be accomplished without alternative intramolecular reactions of the monolithiated species. However, the carboximides provide their own problems in that the cyclic imide introduces a degree of strain not present in the diesters, and, consequently, a greater proportion of monoalkylated products is formed with the carboximides. Further, in the case of the reaction with ω-bromo esters either little reaction occurs or the polycyclic system formed is susceptible to opening of the carboximide ring. In the reaction of the dilithiated esters with aldehydes, ketones, and esters having acidic α-protons, equilibrium can occur. This seems impossible to circumvent in the case of the aldehydes and ketones, condensation appearing to be slower than equilibration at −75 °C. With ethyl 4-bromobutyrate equilibration is sufficiently slow at −75 °C for acylation to be observed, but at higher temperatures equilibrium does lead to the formation of other products.

We have examined a number of other difunctional compounds as possible precursors in annelation reactions. For these to be useful, lithiation must be reasonably facile and the dilithiated species stable at the temperature at which alkylation or acylation will occur. If the electrophilic reagent contains any sufficiently acidic protons, then the dianion may react as a base rather than as a nucleophile. We have shown in at least one case that the occurrence of such an undesired side reaction may be attenuated by conducting the annelation over a prolonged period at a lower temperature. The anion-stabilizing substituents must also not be too efficient as leaving groups; thus we were unable to dilithiate 1,2-dicyano-4-cyclohexene (**33**),



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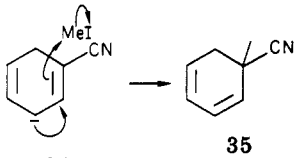

34 **35**

which instead underwent a loss of cyanide to give presumably the anion of 1-cyano-1,4-cyclohexadiene (**34**), which methylated to give 5-cyano-5-methyl-1,3-cyclohexadiene (**35**). *N,N'*-Dimethyl-*N,N'*-diphenyl-4-cyclohexene-1,2-dicarboxamide also failed to dilithiate in the desired manner.

A problem with both the 1,2-diesters and the carboximides is that they provide products containing carboxylic functions which are not readily transformed in high yield into other groups. We continue to explore other anion stabilizing groups which would both allow annelation and provide substituents more susceptible to functional group manipulation.

Experimental Section

^{1}H NMR spectra were obtained on either a Varian T-60 or XL-200 spectrometer in $CDCl_3$ as the solvent and are reported in δ units with Me_4Si as an internal standard. ^{13}C NMR spectra were obtained on either a Varian CFT-20 or XL-200 spectrometer in $CDCl_3$ as the solvent and are reported in δ units with Me_4Si as an internal standard. Mass spectra were obtained on a VG-7070F spectrometer and IR spectra on a Perkin-Elmer 177 spectrometer. Melting points were taken on a Kofler hot-stage melting point apparatus and are uncorrected. Unless otherwise stated, reactions were worked up by addition of water and extraction with ether. The ethereal layer was washed with water and saturated $NaHCO_3$ solution and dried. Solutions of *i*-Pr_2NLi were prepared under N_2 by the addition of the appropriate amount of *n*-BuLi in *n*-hexane to a 10% excess of *i*-Pr_2NH in THF or THF–HMPA at or below 0 °C. Solvents were purified by standard methods, and those used for lithiation reactions were scrupulously dried.

Reaction of the Dilithiated Esters 1 and 2 with MeI. The diester (1 mmol) was dissolved in THF (1 mL) and the solution added dropwise to a stirred solution of *i*-Pr_2NLi (2.1 mmol) in THF (5 mL) at −75 °C under N_2. The resultant deep yellow solution was stirred for a further 25 min at −75 °C, and then MeI (0.2 mL, ca 3.2 mmol) was added by using a syringe. Stirring was continued at −75 °C for a further 30 min, and the reaction was allowed to warm to 20 °C and stirred for a further 2 h, by which time the solution had become pale yellow. The solution was cooled to −75 °C, aqueous acetic acid (33%, 1.5 mL) was added, and the reaction mixture was worked up. Removal of the ether gave a yellow oil which on short-path chromatography on silica gel, eluting with Et_2O/hexane, gave the dimethyl derivative as a colorless oil.

3: 126 mg (55%); mass spectrum, *m/e* (relative intensity) 229 (M^+ + 1, 88), 197 (M^+ − 31, 100), 168 (M^+ − 60, 43); ^{1}H NMR δ 3.59 (s, 6 H), 2.23–1.15 (s, 14 H); ^{13}C NMR δ 176.3, 52.0, 50.7, 47.2, 31.3, 20.3, 19.0.

4: 147 mg (65%); mass spectrum, *m/e* (relative intensity) 226 (M^+, 1), 194 (M^+ − 32, 3), 166 (M^+ − 60, 32); ^{1}H NMR 5.62 (m, 2 H), 3.68 (s, 6 H), 2.73–1.67 (m, 4 H), 1.23 (s, 6 H); ^{13}C NMR δ 175.8, 123.3, 51.4, 46.0, 33.0, 19.5.

The combined aqueous solutions from the workup were acidified to pH 1 (10 M HCl) and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a pale yellow oil.

5: 52 mg (28%); mass spectrum, *m/e* (relative intensity) 168 (M^+ − 18, 3), 155 (M^+ − 31, 10), 140 (M^+ − 46, 33), 126 (M^+ − 60, 27), 81 (100); ^{1}H NMR [$(CD_3)_2CO$] δ 9.39 (br s, 1 H), 3.67 (s, 3 H), 3.10–2.67 (m, 2 H), 2.34–1.24 (m, 8 H); ^{13}C NMR δ 179.8, 173.8, 51.3, 42.3, 42.0, 26.0, 25.6, 23.4, 23.3.

6: 41 mg (22%); mass spectrum, *m/e* (relative intensity) 166 (M^+ − 18, 2), 153 (M^+ − 31, 5), 138 (M^+ − 46, 14), 124 (M^+ − 60, 19), 79 (100), ^{1}H NMR [$(CD_3)_2CO$] δ 10.48 (br s, 1 H), 5.73 (br s, 2 H), 3.70 (s, 3 H), 3.35–2.88 (m, 2 H), 2.75–2.22 (m, 4 H); ^{13}C NMR δ 179.0, 173.2, 124.5, 51.3, 39.0, 38.9, 25.1, 24.9.

Reaction of the Dilithiated Diester 1 with Ethanal. A solution of ethanal (176 mg, 4 mmol) in THF (5 mL) was cooled to −75 °C under N_2. To the stirred solution was added by syringe over 5 min a solution of the dilithiated ester 1 [prepared by adding the diester (200 mg, 1 mmol) in dry THF (1 mL) to a stirred solution of *i*-Pr_2NLi (2.1 mmol) in dry THF (3 mL) containing HMPA (0.5 mL) at −75 °C under N_2, stirring for 30 min, and then allowing the red solution to warm to 20 °C]. The reaction mixture was allowed to warm to 0 °C and was stirred at that temperature for 1 h. The mixture was cooled to −75 °C, aqueous acetic acid (33%, 1.5 mL) was added, and the mixture was worked up. Removal of the solvent under reduced pressure gave a yellow oil which was chromatographed on silica to give some starting diester (ca. 25 mg) and the lactone **9a** (150 mg, 71%) as a mixture of stereomers: mass spectrum, *m/e* (relative intensity) 212 (M^+, 12), 197 (M^+ − 15, 20), 181 (M^+ − 31, 35), 169 (M^+ − 43, 100); ^{1}H NMR (CCl_4) δ 4.28, 4.15 (q, 1 H, *J* = 7 Hz), 3.73 (s, 3 H), 3.17–2.95 (m, 1 H), 2.33–1.00 (m, 1 H); IR, $CHCl_3$, 1770, 1735 cm^{-1}.

When the reaction was carried out at 0 °C, mainly starting diester was isolated (55%), and at −30 °C the ratio of ester to lactone was ca. 1:1.

Reaction of the Dilithiated Diester 1 with Propanone. Dry propanone (174 mg, 3 mmol) in THF (1 mL) was added rapidly to a solution of the diester dianion [prepared from the diester (200 mg, 1 mmol) in THF (1 mL) and *i*-Pr_2NLi (2.0 mmol) in THF (8 mL) at −75 °C] at −75 °C under N_2. The mixture was stirred for 1 h at −75 °C, aqueous acetic acid (33%, 1.5 mL) was added, and the mixture was worked up to give a pale yellow oil (195 mg). Separation on a Harrison Chromatotron (silica gel, Et_2O/hexane) gave the starting diester (52 mg, 26%) and the lactone **9b**: 120 mg (53%); mass spectrum, *m/e* (relative intensity) 226 (M^+, 10), 211 (M^+ − 15, 25), 195 (M^+ − 31, 20), 182 (M^+ − 44, 30), 168 (M^+ − 58, 100); ^{1}H NMR (CCl_4) δ 3.77 (s, 3 H), 3.40–3.13 (m, 1 H), 2.40–0.80 (m, 14 H); IR ($CHCl_3$) 1775, 1735 cm^{-1}.

Synthesis of Carboximide 10a. A mixture of *cis*-cyclohexane-1,2-dicarboxylic anhydride (10.0 g, 0.065 mol) and *tert*-butylamine (5.33 g, 0.073 mol) in glacial acetic acid (100 mL) was heated to reflux for 40 h. After the mixture cooled, water (100 mL) was added and the resulting solution extracted with Et_2O (2 × 50 mL). The combined organic layers were worked with aqueous HCl (2 M, 50 mL) and Na_2CO_3 (saturated, 50 mL) and dried. The solvent was removed under reduced pressure and the resulting white solid recrystallized from pentane as **10a**: 10.20 g (75%); mp 54–55 °C; mass spectrum, *m/e* (relative intensity) 209 (M^+, 10), 194 ($M^+ - 15$, 14), 154 ($M^+ - 55$, 100); ^1H NMR δ 2.80–2.52 (m, 2 H), 1.95–1.18 (m, 17 H); ^{13}C NMR δ 179.5, 56.6, 39.3, 27.5, 23.1, 21.1; ^{13}C NMR (HMPA) δ 181.6, 57.3, 40.5, 28.7, 24.5, 22.3. Anal. Calcd for $C_{12}H_{19}O_2N$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.59; H, 9.19; N, 6.58.

Synthesis of Carboximide 10b. A mixture of *cis*-cyclohexane-1,2-dicarboxylic anhydride (5.0 g, 0.0325 mol) and methylammonium hydrochloride (5.0 g, 74 mmol) in glacial acetic acid (50 mL) containing NaOAc (10.0 g) was heated to reflux for 24 h. After cooling, sufficient aqueous Na_2CO_3 (saturated) was added to adjust the pH to 8.5, and the reaction was then worked up as for **10a** to give **10b**: 5.10 g (94%); mp 50–51 °C; mass spectrum, *m/e* (mass spectrum) 167 (M^+, 75), 152 ($M^+ - 15$, 2), 138 ($M^+ - 29$, 18), 67 (100); ^1H NMR δ 2.97 (s, 3 H), 2.86 (t, 2 H, *J* = 5 Hz), 2.00–1.62 (m, 4 H), 1.44 (t, 4 H, *J* = 5 Hz); ^{13}C NMR δ 178.7, 38.7, 23.5, 22.7, 20.6. Anal. Calcd for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.23; H, 7.96; N, 8.23.

Synthesis of Carboximides 13a and 10c. A warm solution of *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride (15.2 g, 0.1 mol) in glacial acetic acid (50 mL) was added to a solutioin of aniline (9.95 g, 0.107 mol) in glacial acetic acid (50 mL). The mixture was heated to reflux for 18 h, the solution cooled, and water (50 mL) added. A white precipitate was formed which was removed by filtration. The filtrate was treated with water (50 mL), and further precipitation occurred, the precipitate again being collected. This procedure was continued until no more precipitate was obtained. The collected precipitates were combined and dissolved in $CHCl_3$ (ca. 150 mL), and the resulting solution was washed with aqueous HCl (4 M, 50 mL) and NaOH (10%, 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting solid recrystallized from CCl_4/hexane as **13a**: white needles; 17.3 g (76%); mp 115–116 °C; mass spectrum, *m/e* (relative intensity) 227 (M^+, 100), 198 ($M^+ - 29$, 20); ^1H NMR δ 7.67–7.13 (m, 5 H), 6.10–5.92 (m, 2 H), 3.4–3.13 (m, 2 H), 3.00–2.03 (m, 4 H); ^{13}C NMR δ 178.8, 131.8, 128.6, 128.1, 127.4, 126.0, 38.8, 23.3. Anal. Calcd for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.86; H, 5.74; N, 5.93.

Compound **13a** (2.0 g) was dissolved in EtOAc/MeOH (3:1) and Pd/C (5%, 0.50 g) was added and the mixture stirred under a H_2 atmosphere. Removal of the catalyst and evaporation of the solvent gave **10c**: white crystals; 2.0 g (ca. 100%); mp 129–130 °C; mass spectrum, *m/e* (relative intensity) 229 (M^+, 100), 119 ($M^+ - 110$, 99); ^1H NMR δ 7.35 (m, 5 H), 3.0 (m, 2 H), 2.15–1.70 (m, 4 H), 1.70–1.35 (m, 4 H).

Lithiation of the Carboximides 10a–c and 13a. The carboximide (1 mmol) was dissolved in dry THF (1 mL) and added dropwise to a stirred solution of *i*-Pr_2NLi (2.1 mmol) in THF (3 mL) at −75 °C under N_2. The resulting yellow solutions were stirred at −75 °C for 20 min. In the preparation of dilithiated **13a**, HMPA (0.5 mL) was added to the *i*-Pr_2NLi solution.

Methylation of the Dilithiated Carboximides. MeI (0.2 mL, ca. 3.2 mmol) was added to the dilithiated carboximide solution (1 mmol) at −75 °C from a syringe. The solution was stirred for 30 min at −75 °C and then for 1.5 h at 20 °C, by which time the yellow color was largely discharged. Aqueous acetic acid (33%, 1.5 mL) was added and the mixture worked up to give the dimethylated carboximides **12a–c** and **13b**.

12a: 205 mg (90%); bp 103–105 °C (0.2 mmHg); mp 32.5–35 °C; mass spectrum, *m/e* (relative intensity) 237 (M^+, 13), 222 ($M^+ - 15$, 8), 182 ($M^+ - 55$, 100); ^1H NMR δ 1.95–1.2 (m), 1.53 (s, 17 H), 1.07 (s, 6 H); ^{13}C NMR δ 183.4, 57.1, 46.7, 32.6, 28.1, 21.5, 19.7. Anal. Calcd for $C_{14}H_{23}O_2N$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.61; H, 9.55; N, 6.15.

12b: 181 mg (93%); bp 82–84 °C (0.2 mmHg); mp 29–30.5 °C; mass spectrum, *m/e* (relative intensity) 195 (M^+, 81), 180 ($M^+ - 15$, 31), 110 (100); ^1H NMR δ 3.00 (s, 3 H), 2.03–1.33 (m, 8 H), 1.17 (s, 6 H); ^{13}C NMR δ 182.6, 47.0, 32.7, 24.5, 21.2, 20.0. Anal. Calcd for $C_{11}H_{17}O_2N$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.32; H, 8.66; N, 7.01.

12c: 223 mg (87%); mp 74–75 °C; mass spectrum, *m/e* (relative intensity) 257 (M^+, 97), 243 ($M^+ - 14$, 13), 110 (77); ^1H NMR δ 7.25 (m, 5 H), 2.0–1.3 (m, 8 H), 1.24 (s, 6 H). Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.54; H, 7.45; N, 5.49.

13b: 220 mg (86%); mp 83–85 °C; mass spectrum, *m/e* (relative intensity) 255 (M^+, 100), 240 ($M^+ - 15$, 50), 226 ($M^+ - 29$, 10); ^1H NMR δ 7.60–7.10 (m, 5 H), 6.08–5.85 (m, 2 H), 3.05–2.00 (m, 4 H), 1.35 (s, 6 H); ^{13}C NMR δ 181.6, 132.0, 128.8, 128.3, 126.2, 47.2, 34.0, 20.4. Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.99; H, 6.73; N, 5.72.

Deuteration of Dilithiated Carboximide 11b. A mixture of D_2O (99.8% D, 1.0 mL) and CH_3CO_2D (99.8% D, 1.0 mL) in THF (3 mL) was added to a stirred solution of **11b** (1 mmol) at −75 °C by using a syringe. The mixture was allowed to warm to 20 °C and was stirred for 1.5 h. The workup gave a pale yellow oil which crystallized on standing: 167 mg (99%); mass spectrum, *m/e* (relative intensity) 169 (M^+, $C_9H_{11}D_2NO_2$, 67), 168 (M^+, $C_9H_{12}DNO_2$, 53); ^1H NMR δ 3.02 (s, 3 H), 2.88 (br t, 0.5 H, *J* = 6 Hz), 2.13–1.27 (m, 8 H).

Reaction of the Dilithiated Carboximides 11c and 18 with α,ω-Dibromides and -Ditosylates. A solution of the dibromide or ditosylate (1.2 mmol) was added to a stirred solution of **11c** [1.0 mmol; prepared from **10c** (229 mg, 1 mmol) and *i*-Pr_2NLi (1 mmol) in THF (5 mL) containing HMPA (0.5 mL)] or **18** at −75 °C under N_2. The mixture was stirred at −75 °C for 2 h, allowed to warm to 20 °C, and stirred for a further 14 h. Saturated ammonium chloride (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel.

15a: 127 mg (47% from **14a**); 160 mg (59% from **14b**); mp 62–63 °C; mass spectrum, *m/e* 269 (M^+, 82), 122 ($M^+ - 147$, 100); ^1H NMR δ 7.3 (m, 5 H), 2.4–1.2 (m, 14 H). Anal. Calcd for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.84; H, 6.92; N, 5.21.

17: 35 mg (13% from **14a**); 32 mg (12% from **14b**); mass spectrum, *m/e* (relative intensity) 269 (100).

15c: 148 mg (52%); mp 144–145 °C; mass spectrum, *m/e* (relative intensity) 283 (M^+, 19), 299 ($M^+ - 54$, 4), 136 ($M^+ - 147$, 23), 83 (100); ^1H NMR δ 7.3 (m, 5 H), 1.9–1.2 (m, 16 H). Anal. Calcd for $C_{18}H_{21}O_2N$: C, 76.30; H, 7.47; N, 4.94. Found: C, 75.94, H, 7.50; N, 4.89.

15d: 80 mg (27%); mp 88–89 °C; mass spectrum, *m/e* (relative intensity) 297 (M^+, 57), 229 ($M^+ - 68$, 100); ^1H NMR δ 7.3 (m, 5 H), 2.4–1.0 (m, 18 H). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 75.97; H, 7.65; N, 4.78.

19a: 73 mg (27%); mp 66–67 °C; mass spectrum, *m/e* (relative intensity) 267 (M^+, 90), 224 ($M^+ - 43$, 21), 91 (100); ^1H NMR δ 7.4 (m, 5 H), 6.03 (m, 2 H), 3.13–1.33 (m, 10 H).

20: 37 mg (14%); mp 186–188 °C; mass spectrum, *m/e* (relative intensity) 267 (M^+, 94), 148 (100); ^1H NMR δ 7.42 (m, 2 H), 7.18 (m, 5 H), 6.50 (m, 1 H), 5.96 (m, 2 H), 2.62 (d, 1 H), 2.2–1.4 (m, 6 H).

19b: 123 mg (43%); mp 130–131 °C; mass spectrum, *m/e* (relative intensity) 281 (M^+, 100), 91 (53); ^1H NMR δ 7.4 (m, 5 H), 5.90 (m, 2 H), 2.93–1.40 (m, 12 H).

Reaction of the Dilithiated Diester 2 with ω-Bromo Esters. The bromo ester (5 mmol) in THF (10 mL) was added by a motorized syringe pump over 18 h to a stirred solution of **2** (5 mmol) in THF (15 mL) containing HMPA (2.5 mL) at −75 °C under N_2. The mixture was then stirred between −60 and −80 °C for 120 h, quenched with aqueous acetic acid (33%, 7.5 mL), and worked up to give an orange oil, **22a**. This oil was dissolved in methanol (2 mL) and treated with 2,4-dinitrophenylhydrazine (1.0 g, 5.1 mmol) in methanol (15 mL) containing concentrated HCl (2 mL). The solution was heated to just boiling and cooled to give an orange precipitate which was recrystallized from ethanol as the 2,4-dinitrophenylhydrazone of **22a**: 0.43 g (20%); mp 181–182 °C; mass spectra, *m/e* (relative intensity) 434.1438 ($C_{19}H_{22}O_8N_4$ requires *m/e* 434.1438), 434 (M^+, 11), 433 ($M^+ - 1$, 55), 401 ($M^+ - 33$, 8), 373 ($M^+ - 61$, 56), 91 (100); ^1H NMR δ 9.12 (d, 1 H, *J* = 3 Hz), 8.34 (dd, 1 H, *J* = 10, 3 Hz), 7.94 (d, 1 H, *J*

= 10 Hz), 5.82–5.50 (m, 2 H), 3.89 (s, 3 H), 3.79 (s, 3 H), 3.44–3.36 (m, 1 H), 2.91–2.22 (m, 6 H), 1.74–1.53 (m, 2 H). Anal. Calcd for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.49; H, 5.18; N, 12.78.

For **22c** the procedure reported above was carried out on the oil derived from this experiment, but no hydrazone could be isolated.

For 22b[5] trituration of the oil with ether/pentane (1:1 v/v, 20 mL) gave a white crystalline precipitate which was removed by filtration and recrystallized from CCl_4: 0.81 g (61%); mp 103–105 °C; mass spectrum, *m/e* (relative intensity) 266 (M^+, 3), 234 (M^+ – 32, 5), 206 (M^+ – 60, 5), 147 (100); ^1H NMR δ 5.58 (br s, 2 H), 3.68 (s, 3 H), 3.66 (s, 3 H), 2.90–1.68 (m, 10 H); ^{13}C NMR δ 204.9, 174.7, 170.4, 124.2, 62.0, 52.1, 51.5, 48.6, 35.1, 31.0, 29.0, 28.7, 20.3. Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.48; H, 6.92.

Reaction of Dilithiated Diethyl Succinate (23) with Ethyl 4-Bromobutyrate (21b). *n*-BuLi (35 mL, 1.57 M, 55 mmol) was added slowly by syringe to a stirred mixture of diisopropylamine (8 mL, 65 mmol) in dry THF (200 mL) containing HMPA (25 mL) under N_2 at –78 °C. After completion of this addition, diethyl succinate (4.35 g, 25 mmol) in THF (10 mL) was added and the stirred mixture maintained at –78 °C for 30 min. Ethyl 4-bromobutyrate (5.50 g, 28 mmol) in THF (10 mL) was then added via a syringe pump over 1 h and the mixture maintained at –78 °C for 6 days. Saturated NH_4Cl solution was then added, the mixture allowed to warm to room temperature, and the organic solvent removed under reduced pressure. The residue was extracted with ether (3 × 200 mL), the combined extracts were washed with water (5 × 50 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give the crude ketone (4.40 g, 75%). Chromatography on silica gel, eluting with CH_2Cl_2, gave the ketone **24** as a mixture of diastereomers: 3.25 g (55%); mass spectrum, *m/e* (relative intensity) 242 (M^+, 1), 197 (M^+ – 45, 11), 123 (M^+ – 119, 100); ^1H NMR δ 4.20 (q, 4 H), 3.75 (m, 1 H), 3.50 (m, 1 H), 2.30 (m, 2 H), 1.80 (m, 4 H), 1.25 (t, 6 H). A sample of **24** was treated with 2,4-dinitrophenylhydrazine in MeOH containing H_2SO_4 to give the 2,4-dinitrophenylhydrazone: mp 137–138 °C; mass spectrum, *m/e* (relative intensity) 422 (M^+, 8), 376 (M – 46, 26), 349 (M^+ – 73, 48), 303 (M^+ – 119, 100); ^1H NMR δ 11.05 (s, 1 H), 9.08 (d, 1 H, *J* = 3 Hz), 8.27 (dd, 1 H, *J* = 10, 3 Hz), 7.80 (d, 1 H, *J* = 10 Hz), 4.30 (q), 4.18 (q) (4 H), 3.74 (d, 1 H, *J* = 9.6 Hz), 3.15 (dt, 1 H, *J* = 9.6 Hz) 2.84 (m, 1 H), 1.61–2.34 (m, 5 H), 1.30 (dt, 6 H). Anal. Calcd for $C_{18}H_{22}N_4O_8$: C, 51.19; H, 5.25; N, 13.27. Found: C, 50.95, H, 5.20; N, 13.26.

Reaction of Dilithiated Carboximide 18 with ω-Bromo Esters. A solution of the bromo ester (1 mmol) in THF (5.0 mL) was added by syringe over 50 min to a stirred solution of **18** (1 mmol) in THF (5 mL) containing HMPA (0.5 mL) at –78 °C under N_2. The solution was stirred for 96 h at –78 °C, saturated NH_4Cl (20 mL) was added, and the mixture was worked up. The resulting solid was chromatographed on silica by eluting with EtOAc/pentane (2:8 to 3:7) to give the separate products which were recrystallized.

With Ethyl 3-Bromopropionate. A trace (TLC) of annelated product was formed, and two stereoisomeric monoalkylated compounds isolated: 51 mg (15%); ^1H NMR δ 7.45 (m, 5 H), 6.05 (t, 2 H), 4.20 (q, 2 H), 3.15–2.0 (m, 9 H) 1.25 (t, 3 H).

With Ethyl 4-Bromobutyrate. 25b: 45 mg (13%); mp 118–119 °C (MeOH); mass spectrum, *m/e* (relative intensity) 295 (M^+, 91), 120 (100); ^1H NMR δ 7.5 (m, 5 H), 6.1 (m, 2 H), 3.0–1.5 (m, 10 H). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 74. Found: C, 72.45; H, 5.72; N, 4.63.

26: 90 mg (26%); oil; mass spectrum, *m/e* (relative intensity) 341 (M^+, 18), 295 (M^+ – 46, 100); ^1H NMR δ 7.50–7.14 (m, 5 H), 6.05 (m, 2 H), 4.15 (q, 2 H), 3.05 (dd, 1 H, *J* = 7, 2 Hz), 2.88–2.56 (d, dd, 2 H, *J* = 16 Hz), 2.4–1.5 (m, 8 H), 1.25 (t, 3 H).

A monoalkylated, noncyclized fraction was also isolated: 64 mg (19%); mass spectrum, *m/e* (relative intensity) 341 (26), 226 (100); ^1H NMR δ 7.4 (5 H, m), 5.80 (s), 5.94 (m, 2 H), 4.0 (2 H, q), 3.0–1.85 (7 H, m), 1.74 (2 H, t), 1.14 (2 H, m), 1.12 (3 H, t).

Reaction of 2 with Ethyl 4-Bromobutyrate at ~20 °C. A solution of **2** (20 mmol) in THF (100 mL) containing HMPA (10 mL) at –75 °C was added over 20 min to a stirred solution of **21b** (3.92 g, 20 mmol) in THF (75 mL) at 20 °C under N_2. The resulting red solution was stirred at 20 °C for 18 h, aqueous HCl (10 M, 30 mL) was added, and the reaction mixture was worked up. The resulting orange oil (ca. 5.0 g) was distilled through a short-path apparatus under reduced pressure to give a fraction with a boiling point of 125–135 °C (0.07 mmHg). This solidified and was recrystallized from CCl_4 as **31**: 1.01 g (28%); white needles; mp 122–123 °C; mass spectrum, *m/e* (relative intensity) 176.0836 (calcd for $C_{11}H_{12}O_2$ *m/e* 176.0837), 176 (M^+, 32), 148 (M^+ – 28, 7) 107 (M^+ – 69, 100); ^1H NMR δ 6.00–5.76 (m, 2 H), 4.17 (br d, 1 H, *J* = 8 Hz), 3.34–2.82 (m, 4 H), 1.00–0.44 (m, 5 H); ^{13}C NMR δ 172.6, 160.4, 123.9, 123.6, 121.8, 86.6, 24.8, 21.6, 12.3, 1.93; IR, $CHCl_3$, 1745 cm^{-1}.

Dehydrogenation of 31. Dichlorodicyanoquinone (48.4 mg, 0.213 mmol) was added to a solution of the lactone **31** (25 mg, 0.143 mmol) in dry benzene (2 × 5 mL), and the resulting mixture was stirred and heated under reflux for 8 h. The solvent was removed under reduced pressure, the residue was extracted with ether (2 × 5 mL), and the ethereal extracts were passed through a short column of Florisil. The solvent was removed under reduced pressure from the colorless eluent, and the residue crystallized (Et_2O/hexane) as **32**: 24.5 mg (99%); mp 97–99 °C; mass spectrum, *m/e* (relative intensity) 174.0681 (calcd for $C_{11}H_{10}O_2$ *m/e* 174.0681), 174 (M^+, 17), 146 (M^+ – 28, 51), 133 (M^+ – 41, 62), 105 (M^+ – 69, 100); ^1H NMR δ 7.90 (dd, 1 H, *J* = 8, 2.5 Hz), 7.75–7.48 (m, 3 H), 4.85 (d, 1 H, *J* = 9 Hz), 1.20–1.00 (m, 1 H), 0.85–0.58 (m, 4 H). Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.52; H, 6.01.

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Registry No. **1**, 4336-20-3; **1**·2Li, 72039-99-7; **2**, 7500-55-2; **2**·2Li, 83248-47-9; **3**, 83248-48-0; **4**, 83248-49-1; **5**, 7719-08-6; **6**, 56124-48-2; **9a**, 83248-50-4; **9b**, 83248-51-5; **10a**, 83248-52-6; **10b**, 83248-53-7; **10c**, 26491-47-4; **11a**, 83248-54-8; **11b**, 83248-55-9; **11c**, 83248-56-0; **12a**, 83248-57-1; **12b**, 83248-58-2; **12c**, 83248-59-3; **13a**, 20141-47-3; **13b**, 83248-60-6; **14a**, 109-64-8; **14b**, 40230-73-7; **14c**, 110-52-1; **14d**, 111-24-0; **15a**, 83248-61-7; **15c**, 83248-62-8; **15d**, 83248-63-9; **17**, 83248-64-0; **18**·2Li, 83248-65-1; **19a**, 83248-66-2; **19b**, 83248-67-3; **20**, 83248-68-4; **21a**, 539-74-2; **21b**, 2969-81-5; **21c**, 14660-52-7; **22a**, 83248-69-5; **22a**·DNP, 83248-70-8; **22b**, 78813-04-4; *cis*-**24**, 83248-71-9; *trans*-**24**, 83248-72-0; **24**·DNP, 83248-76-4; **25a**, 83248-73-1; **25b**, 83248-74-2; **26**, 83248-75-3; **31**, 78813-02-2; **32**, 78813-03-3; *cis*-cyclohexane-1,2-dicarboxylic anhydride, 13149-00-3; methylammonium hydrochloride, 593-51-1; *cis*-cyclohex-4-ene-1,2-dicarboxylic anhydride, 935-79-5; aniline, 62-53-3; ethyl 3-[*cis*-*N*-phenyl-3a,4,7,7a-tetrahydro-7a-phthalimido]propionate, 83248-77-5; ethyl 3-[*trans*-*N*-phenyl-3a,4,7,7a-tetrahydro-7a-phthalimido]propionate, 83248-78-6; ethyl [*N*-phenyl-3a,4,7,7a-tetrahydro-7a-phthalimido]propionate, 83248-79-7; ethanal, 75-07-0; propanone, 67-64-1; *tert*-butylamine, 75-64-9; diethyl succinate, 123-25-1; MeI, 74-88-4; $(i\text{-Pr})_2NLi$, 4111-54-0.