acetate as the eluent. Extraction of the main band gave pure **15** (0.090 g) as a vitreous product: IR ($CHBr_3$) ν 1796.0 cm^{-1}; ^1H NMR δ 1.66 (s, 3, 2β-CH_3), 2.13 (s, 3, $OCOCH_3$), 2.96 (s, 3, $CHOCH_3$), 5.15 (d, 1, J = 4.5 Hz, CHS), 6.04 (q, 1, J = 4.5 and 10.5 Hz, NHCH); MS m/e 574 (M^+). Anal. Calcd for $C_{27}H_{30}N_2O_{10}S$: C, 56.43; H, 5.26; N, 4.88. Found: C, 56.23; H, 5.05; N, 4.60.

When a solution of **13** in benzene was refluxed for a shorter time (1 h) some starting material was detected (^1H NMR, TLC) in the reaction mixture.

When the (*S*)-sulfoxide **14** was heated as described above for **13** or for longer times, it was recovered completely unchanged (^1H NMR, TLC).

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Registry No. **1**, 58747-45-8; **2**, 58747-43-6; **3**, 70942-89-1; **4**, 73156-59-9; **5**, 73156-60-2; **6**, 73156-61-3; **10**, 73156-62-4; **11**, 73156-63-5; **12**, 73156-64-6; **13**, 73156-65-7; **14**, 73156-66-8; **15**, 73156-67-9; **17**, 73156-68-0.

Approaches to Anthracyclines. 1. Conjugate Aroylation of α,β-Unsaturated Esters[1a,b]

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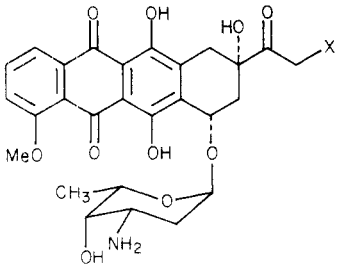
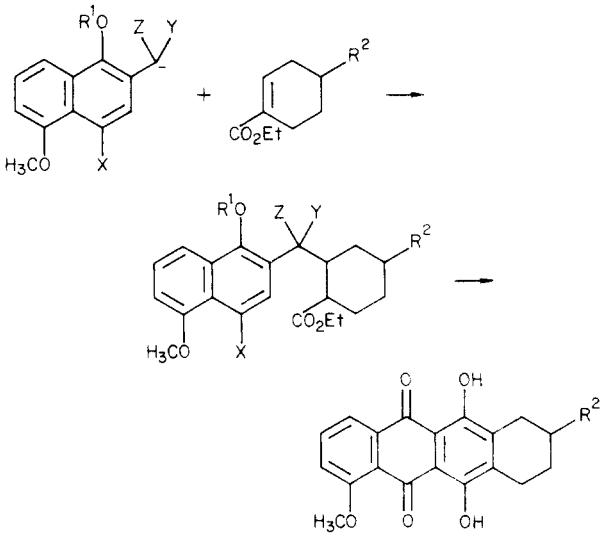
A scheme for the two-step nucleophilic aroylation of α,β-unsaturated esters has been developed. The Michael reaction of an arylacetonitrile enolate with an α,β-unsaturated ester generally proceeds in good yield. Oxidative decyanation of the adduct affords clean γ-keto esters when the aryl substituent is not electron rich.

The anthracycline antibiotics daunomycin (**1**) and adriamycin (**2**) exhibit impressively potent and broad-spectrum antitumor activity.[2] The lack of an efficient biosynthetic process, the desirabililty of analogues with improved therapeutic indices, and the challenging regio- and stereochemical features have made the anthracyclines the focus of an intense synthetic effort.[3] Accordingly, there has been a resurgence of interest in synthetic approaches to the quinone moiety and especially to the regiocontrolled elaboration of linear quinone systems.[4]



1, X = H
2, X = OH

The use of masked functionality to reverse the normal mode of reactivity of functional groups has been an area of vigorous research in recent years; the carbonyl group, because of its dominant role in organic synthesis, has received particular attention with respect to inversion of its usual electrophilic character.[5] We hoped to employ the concept of nucleophilic acylation in a construction of the anthracycline skeleton by utilizing a masked aryl aldehyde as the nucleophilic partner in a Michael-type condensation with a suitably functionalized α,β-unsaturated ester (eq 1).



(1)

While the conjugate nucleophilic acylation of enones has been extensively investigated,[6,7] the corresponding reaction

(1) (a) Abstracted from the doctoral dissertation of J.L.K., Brown University, Oct 1979. (b) For a preliminary report of this work, see K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 4557 (1977). (c) Camille and Henry Dreyfus Teacher-Scholar award recipient.

(2) Several excellent reviews of the chemistry and pharmacology of the antitumor anthracyclines have appeared recently: R. K. Blum and S. K. Carter, *Ann. Intern. Med.*, **80**, 249 (1974); W. A. Remers, "The Chemistry of Antitumor Antibiotics", Vol. I, Wiley, New York, 1979, pp 63-132; F. Arcamone, *Top. Antibiot. Chem.*, **2**, 99-239 (1978).

(3) A recent review concerned with approaches to the synthesis of anthracyclines is given by T. R. Kelly, *Annu. Rep. Med. Chem.*, **14**, 288-298 (1979).

(4) For a review of quinone synthesis, see R. H. Thomas, "The Chemistry of Quinonoid Compounds", S. Patai, Ed., Wiley, New York, 1974, pp 111-61. Since we began this work, a number of methods for the regiospecific construction of the quinone moiety of fused quinone systems have been developed: (a) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **101**, 1628 (1979); *J. Org. Chem.*, **43**, 178 (1978); F. M. Hauser and S. Prasanna, *J. Org. Chem.*, **44**, 2596 (1979); (b) G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 2263 (1978); (c) J. E. Baldwin and K. W. Bair, *ibid.*, 2559 (1978); I. Forbes, R. A. Pratt, and R. A. Raphael, *ibid.*, 3965 (1978); S. O. deSilva and V. Snieckus, *ibid.*, 5103 (1978); (d) K. S. Kim, E. Vanotti, A. Suaroto, and F. Johnson, *J. Am. Chem. Soc.*, **101**, 2483 (1979); (e) J. S. Swenton and P. W. Raynolds, *ibid.*, **100**, 6188 (1978). Also, a potentially regiospecific method is reported: D. K. Jackson, L. Narasimhan, and J. S. Swenton, *ibid.*, **101**, 3989 (1979).

(5) For reviews of nucleophilic acylation, see: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); O. W. Lever, *Tetrahedron* **32**, 1943 (1976).

(6) (a) G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **96**, 5272 (1974); (b) J. L. Herrman, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3275 (1973); (c) R. K. Boeckman and K. J. Bruza, *ibid.*, 3365 (1974); (d) J. E. McMurry and J. Melton, *J. Am. Chem. Soc.*, **93**, 5309 (1971); (e) T. Mukaiyama, K. Narasaka, and M. Furusato, *ibid.*, **94**, 8641 (1972). See also ref 16 and references therein.

(7) J. L. Herrman, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973).

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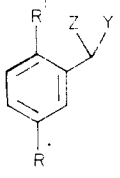
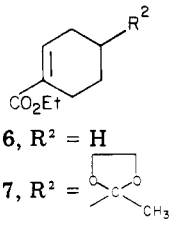
of α,β-unsaturated esters has received only scattered attention. Stetter[8] reported the benzoin-like condensation of aldehydes and alicyclic unsaturated esters catalyzed by cyanide ion. More recently, Schlessinger and co-workers[7] successfully added the anion of thioacetal monosulfoxide to acrylate, crotonate, and butenolides; hydrolysis gave the γ-formyl esters. Other isolated examples of conjugate nucleophilic acylation of α,β-unsaturated esters have appeared.[9]

Results and Discussion

Initially, attempts to employ available methodology to effect the proposed conjugate addition were made. The lithium enolate of protected cyanohydrin **3** adds in Michael



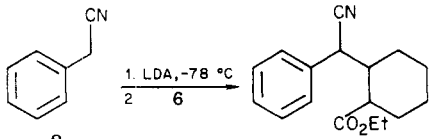
3, Z = CN; Y = $OCH(CH_3)OEt$; R^1 = H
4, Z = Y = $SCH_2CH_2CH_2S$; R^1 = H
5, Z = Y = O; R^1 = OCH_3



6, R^2 = H
7, R^2 =

fashion to cyclohexenone;[6a] however, all attempts to add this reagent to ester **6** resulted in recovery of starting materials. Similarly, dithane **4**[10] was recovered unchanged after treatment with *n*-butyllithium, followed by ester **6**.[11] An attempt to effect directly the desired condensation between aldehyde **5** and ester **7**[12] by using the Stetter procedure likewise led to recovery of starting materials.

The simplicity and mildness of the Watt oxidative decyanation[13] led us to consider nitrile enolates as acyl anion equivalents. Initial investigations focused on addition of phenylacetonitrile **8** to the ester **6** (eq 2). Thus, when the



(2)

8 9

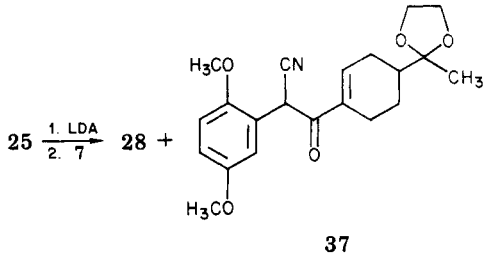
lithium enolate of phenylacetonitrile was treated at −78 °C with ester **6**, the Michael adduct **9** was obtained in 70% yield. The product of successful conjugate addition is typified by a characteristic carbonyl shift in the infrared spectrum (1715 cm^{-1} for **6** to 1735 cm^{-1} for **9**) and the disappearance of the vinyl resonance from the NMR spectrum. A broad signal for the proton α to the nitrile and the presence of several overlapping quartets at 4.1 pm (OCH_2CH_3) indicate that the adduct **9** is obtained as a mixture of diastereomers.

The results of further investigation of the conjugate addition using functionalized esters and arylacetonitriles are summarized in Table I. Higher temperatures and longer reaction times are required to effect the addition of the enolates of arylacetonitriles substituted with one or more methoxy groups, possibly because of their decreased solubility in THF at low temperatures. Attempts to isolate Michael adducts in cases where the lithium enolates were insoluble at −78 °C invariably resulted in total recovery of starting materials, even with extended reaction times. The addition of HMPA to the reaction mixture effectively solubilizes the enolates but fails to improve yields. In practice, solubility problems were circumvented by warming the solution of lithium enolate to obtain a homogenous mixture, rapidly recooling it to −78 °C, and immediately adding ester to the reaction mixture.

The effect of the metal counterion on the course of the addition was briefly examined with the expectation that an increase in cation size would result in an increased reactivity of the nitrile enolate, as is observed for the corresponding ketone enolates.[14] Table II shows that both sodium and potassium enolates afford yields of conjugate adducts comparable to those with lithium enolates; these additions are best carried out at higher temperatures, however. Sodium enolates, generated from sodium hydride, are more convenient to prepare than lithium enolates; however, an excessive period of time is required for enolate generation in some cases.[15] In contrast, the potassium enolates of arylacetonitriles are generated quantitatively in 5 min at room temperature by potassium hydride.

As shown in Table I, acylic esters are efficient Michael acceptors (entries 1–4, 10). The exceptions are the β-unsubstituted esters, acrylate and methacrylate (entries 1, 4), which give poor yields of conjugate adducts. Similar difficulties with acrylates as Michael acceptors have been encountered by others,[16] and the suggestion has been made that, for these highly reactive esters, the intermediate adduct may function as a competing nucleophile, scavenging unreacted ester and leading to complicated product mixtures. Alicyclic esters undergo conjugate addition (entries 5–9, 11–16); more vigorous reaction conditions are required, and yields are slightly reduced. Yields are further lowered in cyclohexene esters with substitution at C-4.

In one set of experiments, we investigated the formation of 1,2-adducts. In this study, the reaction of nitrile **25** with



37

ester **7**, 1,4-addition (leading to **28**) was favored over 1,2-addition (leading to **37**) by a lower temperature. This behavior (Table III) is unlike that of nitrile enolates with cyclohexenone in which 1,2-addition is favored by lower temperatures, as expected for a kinetic process.[17]

(8) H. Stetter and M. Schreckenberg, *Angew Chem., Int. Ed. Engl.*, **12**, 81 (1973); H. Stetter, M. Schreckenberg, and K. Wiemann, *Chem. Ber.*, **109**, 541 (1976); H. Stetter and M. Schreckenberg, *Tetrahedron Lett.*, 1461 (1973).
(9) E. J. Corey, K. Narasaka, and M. Shibasaki, *J. Am. Chem. Soc.*, **98**, 6417 (1976); M. P. Cooke and R. M. Parlman, **99**, 5222 (1977).
(10) D. Seebach, B. W. Erickson, and G. Singh. *J. Org. Chem.*, **31**, 4303 (1966).
(11) Recently the successful conjugate addition of acyldithiane enolates (but not the corresponding protected cyanohydrin) to butenolide, methyl cinnamate, and methyl crotonate was reported: F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, **43**, 985 (1978).
(12) K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 1197 (1979).
(13) (a) S. J. Selikson and D. S. Watt, *J. Org. Chem.*, **40**, 267 (1975); (b) R. R. Wroble and D. S. Watt, *ibid.*, **41**, 2939 (1976).
(14) H. D. Zook and W. L. Gumby, *J. Am. Chem. Soc.*, **82**, 1386 (1960).
(15) For nitriles such as **24** in which the aryl group bears two methoxyl substituents, enolate formation with sodium hydride requires up to 72 h at 35 °C.
(16) J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczykowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **101**, 1541 (1979).

Table I. Conjugate Addition of Arylacetonitriles to Unsaturated Esters and Oxidation of 1,4-Adducts

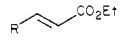
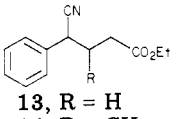
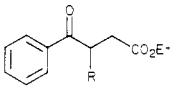
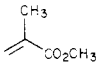
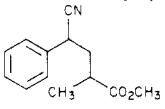
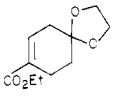
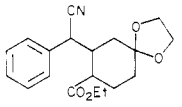
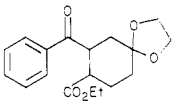
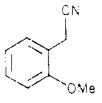
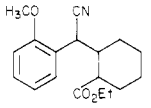
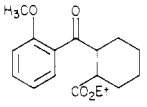
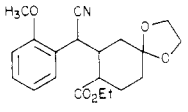
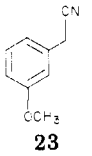
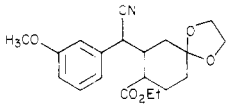
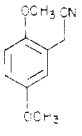
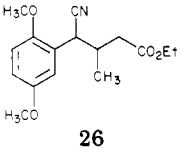
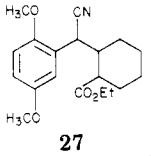
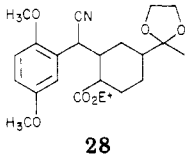
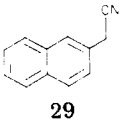
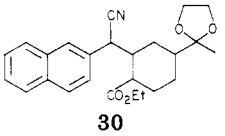
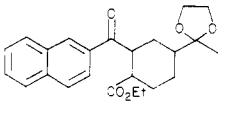
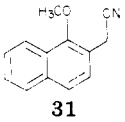
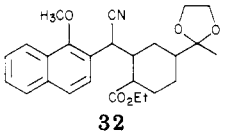
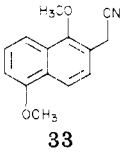
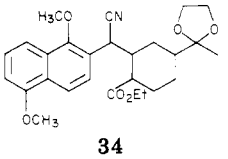
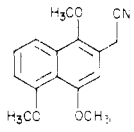
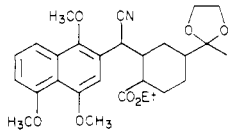
entry	nitrile	ester	adduct	yield,[a] %	conds[b]	keto ester	yield,[a] %
							
1	**8**	**10**, R = H	**13**, R = H	50	A	**39**, R = H	42
2		**11**, R = CH_3	**14**, R = CH_3	90	A	**40**, R = CH_3	72
3		**12**, R = C_6H_5	**15**, R = C_6H_5	74	A	**41**, R = C_6H_5	74
4	**8**	 **16**	 **17**	40[c]	A		
5	**8**	**6**	**9**	73	A	**38**	69
6	**8**	 **18**	 **19**	73[c]	A	 **42**	84
7	 **20**	**6**	 **21**	76	A	 **43**	85
8	**20**	**18**	 **22**	73	B		
9	 **23**	**18**	 **24**	68	B		
10	 **25**	**11**	 **26**	89	A		
11	**25**	**6**	 **27**	52	A		
12	**25**	**7**	 **28**	64	A		
13	 **29**	**7**	 **30**	65	A	 **44**	69
14	 **31**	**7**	 **32**	19	B		
15	 **33**	**7**	 **34**	79[c]	C		

Table I (*Continued*)

entry	nitrile	ester	adduct	yield,[a] %	conds[b]	keto ester	yield,[a] %
16	 35	7	 36	72[c]	C		

[a] All yields refer to chromatographed material. [b] A, LDA, −78 °C; B, NaH, −45 °C; C, KH, −20 °C; see Experimental Section for details. [c] Based on recovered nitrile.

Table II. Effect of Cation on Yields of 1,4-Adducts[a]

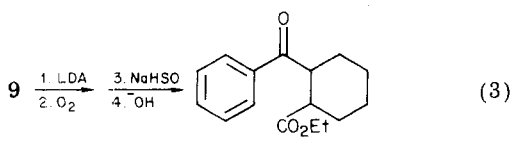
nitrile	base	yield,[b] %	nitrile	base	yield,[b] %
25	LDA	64	33	NaH	67
25	NaH	63	33	KH	60 (79)[c]
33	LDA	77			

[a] The ester was compound 7 in each case. [b] Refers to chromatographed 1,4-adducts. [c] Based on recovered nitrile 33.

Table III. Effect of Temperature on Product Ratio

temp, °C	ratio of 28 to 37	yield (28 + 37), %
0	1.2:1	96
−20	3.5:1	82

Oxidative decyanation of γ-aryl γ-cyano esters was investigated as follows. Cyano ester **9** was chosen as a model for the desired oxidative decyanation. Cyano ester **9** was treated with lithium diisopropylamide, and dry oxygen gas was rapidly bubbled through the reaction mixture (eq 3).



38 (3)

Reductive workup according to Watt[13] and chromatography gave the desired keto ester **38** in 69% yield. Assignment of structure is based on the infrared spectrum, which shows bands for aryl ketone (1680 cm^{-1}) and ester (1730 cm^{-1}) and no band for nitrile (2240 cm^{-1}), and on the NMR spectrum, which contains an aromatic multiplet identical with that of acetophenone.

A number of other cyano esters were cleanly oxidized by this procedure to the corresponding keto esters, as shown in Table I. Conspicuously absent from Table I are decyanated products derived from the adducts of the polysubstituted nitriles **25**, **33**, and **35**. We were unable to isolate keto esters from attempted oxidation of these adducts. Infrared spectra of the crude reaction products indicated some conversion to the aryl ketones; however, thin-layer chromatography revealed a complex product mixture in each case.

It appears unlikely that steric factors are responsible for the difficulties encountered in the oxidation of systems such as **27**, as structurally similar compounds such as **21** are oxidized without complication. More likely, the inductive destabilization of the nitrile enolate by two or more electron-donating groups on the aryl substituent decreases the acidity of the protons α to the cyano group; enolization α to the carboethoxy group would lead to oxidation at this position as well as α to the cyano group.[18]

Summary. The addition/oxidation sequence is an efficient procedure for the conjugate nucleophilic aroylation of α,β-unsaturated esters, provided the aryl substituent is not electron rich. This promises to be a useful procedure because the acyl anion synthons, the arylacetonitriles, are generally accessible (by homologation[19-21] or functional group transformation[22]) and because acid-sensitive functional groups are unaffected by the sequence.

For the purposes of constructing highly oxidized anthracycline intermediates this two-step sequence was not effective; a change in direction brought about by this observation is described in the following paper.

Experimental Section

Instrumentation and Materials. Infrared spectra were recorded on a Perkin-Elmer 257 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian Associates A-60A spectrometer. All chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory and Galbraith Laboratories.

Column chromatography was carried out by using the following: (A) MN-Kieselgel, 70–270 mesh; (B) Baker silica gel 60, 60–200 mesh; (C) Merck silica gel 60, 70–230 mesh. Preparative thin-layer chromatography (TLC) was carried out by using 20 × 20 cm plates, prepared with Merck silica gel PF-254.

Except where noted, reactions were carried out under nitrogen and argon. Dry tetrahydrofuran (THF) was obtained by distillation from lithium aluminum hydride. Dry benzene was distilled from calcium hydride. Dimethyl sulfoxide (Me_2SO) and hexamethylphosphoramide (HMPA) were distilled from sodium metal. Phenylacetonitrile (**8**), (*o*-methylphenyl)acetonitrile (**20**), (*m*-methoxyphenyl)acetonitrile (**23**), and β-naphthylacetonitrile (**29**)

(17) N. Wang, S. Su, and L. Tsai, *Tetrahedron Lett.*, 1121 (1979); E. M. Kaiser, P. L. Knutson and J. R. McClure, *ibid.*, 1747 (1979), and references therein.

(18) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **85**, 1655 (1963); H. R. Gersman, H. J. W. Nieuwehuis, and A. F. Bickel, *Proc. Chem. Soc., London*, 279 (1962); M. Avramoff and Y. Sprinzak, *Proc. Chem. Soc., London*, 150 (1962).

(19) Numerous examples of the displacement of halides and sulfonates by cyanide ion appear in the literature. See, for example: I. T. Harrison and S. Harrison, "Compendeum of Organic Synthetic Methods", Vol. 1, Wiley-Interscience, New York, 1971, pp 468–70; L. Friedman and H. Schecter, *J. Org. Chem.*, **25**, 877 (1960), and references therein; D. T. Mowry, *Chem. Rev.*, **42**, 189 (1948).

(20) The synthesis of substituted arylacetonitriles by direct replacement of the hydroxyl group of a benzyl alcohol has been reported: M. A. Schwartz, M. Zoda, B. Vishnuva, and I. Mami, *J. Org. Chem.*, **41**, 2502 (1976).

(21) K. A. Parker and T. Iqbal, *J. Org. Chem.*, **45**, 1149 (1980).

(22) (a) J. Streith, C. Fizet, and H. Fritz, *Helv. Chim. Acta*, **59**, 2786 (1976); (b) C. Fizet and J. Streith, *Tetrahedron Lett.*, 3187 (1974); (c) M. J. Miller and G. M. Loudon, *J. Org. Chem.*, **40**, 126 (1975); (d) P. A. Wehrli and B. Schaer, *ibid.*, **42**, 3956 (1977); (e) M. M. Rogic, J. F. VanPeppen, K. P. Klein, and T. R. Demmin, *ibid.*, **39**, 3424 (1974); (f) P. J. Foley, *ibid.*, **34**, 2805 (1969); R. S. Glass and R. C. Hoy, *Tetrahedron Lett.*, 1781 (1976); (g) T. Saraie, T. Ishiguro, K. Kawashima, and K. Morita, *ibid.*, 2121 (1973); (h) W. Lehnert, *ibid.*, 559 (1971).

were obtained from Aldrich Chemical Co.

Diisopropylamine was distilled from calcium hydride and stored over calcium oxide. *n*-Butyllithium was obtained as 2.2–2.6 M solutions in hexane from Alfa; the titer was determined by the procedure of Gilman.[23] Sodium hydride, obtained as a 50% oil dispersion (Alfa), and potassium hydride, obtained as a 20% oil dispersion (Alfa), were prepared by washing five times with pentane; the last traces of solvent were removed in vacuo.

Ethyl Cyclohexene-1-carboxylate (6). Ethyl 1-chlorocyclohexane-1-carboxylate[24] (67.0 g, 0.35 mol) was combined with triethylamine (25.0 g) in 120 mL of absolute ethanol, and the mixture was stirred at reflux for 14 h. The reaction mixture was cooled and concentrated. The crude product was dissolved in 150 mL of ether; this resulting solution was washed with 100-mL portions of 1 N HCl and H_2O and dried over $MgSO_4$. Concentration followed by distillation (58–60 °C, 1.7 mm) afforded the pure ester **6** (37.5 g, 76%) as a water-white oil.

Ethyl 2-(α-Cyanobenzyl)cyclohexene-1-carboxylate (9). Method A. To a solution of lithium diisopropylamide (20 mmol), from 2.7 mL of diisopropylamine and 75 mL of 2.2 M *n*-butyllithium in 70 mL of dry THF at −78 °C, was added 1.87 g (16 mmol) of phenylacetonitrile in 4 mL of THF, and the resulting pale yellow solution stirred at −78 °C for 1 h. Then 2.49 g (16 mmol) of ethyl cyclohexene-1-carboxylate (**6**) in 10 mL of THF was added dropwise. The reaction mixture was stirred 3 h at −78 °C, warmed slowly (ca. 1 h) to 0 °C, and stirred an additional 3 h, and then 2 mL of H_2O was added. The pale yellow mixture was diluted with 100 mL of ether; this solution was washed with 100-mL portions of 1 N HCl, with H_2O, and with saturated brine, dried over $MgSO_4$, and concentrated. The crude product was subjected to column chromatography (B, eluted with 3% ethyl acetate in hexane) followed by bulb-to-bulb distillation (118 °C, 0.15 mm) to afford a pale, viscous oil: 3.15 g (73%), IR (film) 2235, 1730, 1451 cm^{-1}; NMR ($CDCl_3$) δ 7.32 (s, 5 H), 4.42–3.90 (m, 3 H), 3.35–3.31 (m, 1 H), 2.41–1.64 (m, 9 H), 1.23 (m, 3 H).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.00; H, 8.08; N, 5.15. Found: C, 75.03; H, 7.98; N, 4.90.

Ethyl 4-Cyano-4-phenylbutyrate (13). A 1.17-g sample of nitrile **8** and 1.25 g of ethyl acrylate were subjected to method A. Bulb-to-bulb distillation (0.05 mm, oven temperature 150 °C) gave 1.09 g (50%) of a pale yellow, viscous oil: IR (film) 2235, 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.31 (s, 5 H), 4.35–3.90 (m, 3 H), 2.71–1.93 (m, 4 H), 1.21 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.89; H, 6.91; N, 6.45. Found: C, 71.69; H, 7.12; N, 6.39.

Ethyl 3-Methyl-4-cyano-4-phenylbutyrate (14). A 1.17-g sample of nitrile **8** and 1.20 g of ethyl crotonate were subjected to method A. Chromatography (B) gave 2.07 g (90%) of a pale viscous oil. Bulb-to-bulb distillation (0.03 mm, oven temperature 118 °C) gave analytically pure material: IR (film) 2235, 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.34 (s, 5 H), 4.45–3.90 (m, 3 H), 2.61–2.31 (m, 3 H), 1.35–0.92 (m, 6 H).

Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.87; H, 7.65; N, 6.23.

Ethyl 4-Cyano-3,4-diphenylbutyrate (15). A 1.17-g sample of nitrile **8** and 1.76 g of ethyl cinnamate were subjected to method A. Chromatography (B) gave a pale oil which solidifies on standing. Recrystallization from ether–petroleum ether (1:1) gave 2.17 g (74%) of white crystals: mp 98–99 °C; IR (KBr) 2240, 1730, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (s, 5 H), 7.18 (s, 5 H), 4.33 (d, J = 6 Hz, 1 H), 4.02 (q, J = 7.5 Hz, 2 H), 3.57 (dt, J = 6 Hz, J = 6 Hz, 1 H), 2.82 (d, J = 6 Hz, 2 H), 1.11 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.61; H, 6.57; N, 4.82.

Methyl 2-Methyl-4-cyano-4-phenylbutyrate (17). A 1.17-g sample of nitrile **8** and 1.00 g of methyl methacrylate were subjected to method A. Chromatography (B) gave 0.89 g of a pale, viscous oil: bp 90 °C (0.3 mm); IR (film) 2240, 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5 H), 3.90 (m, 1 H), 3.67 (s, 3 H), 2.71–1.92 (m, 3 H), 1.21 (br d, J = 7 Hz, 3 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.03; H, 7.13; N, 6.53.

Ethyl 1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylate (18). Ester **18** was prepared from ethyl acrylate and *trans*-1-methoxy-3-trimethylsilyloxybutadiene[25] by the procedure reported for the corresponding methyl ester.[26] Column chromatography of the crude product (B, eluted with 20:1 benzene–ether) followed by bulb-to-bulb distillation (0.2 mm, 119 °C) gave ester **18**: 84% yield; IR (film) 1705, 1649, 1370 cm^{-1}; NMR ($CDCl_3$) δ 6.81–6.65 (m, 1 H), 4.14 (q, J = 7 Hz, 2 H), 3.88 (s, 3 H), 2.70–2.25 (m, 4 H), 1.23 (t, J = 7 Hz, 3 H).

Ethyl 7-(α-Cyanobenzyl)-1,4-dioxaspiro[4.5]decane-8-carboxylate (19). An 0.80-g sample of nitrile **8** and 1.40 g of ester **18** were subjected to method A. Chromatography (B) gave 1.21 g (41%) of a viscous oil which solidified on standing. Bulb-to-bulb distillation (0.05 mm, oven temperature 125 °C) gave a clear viscous oil: IR (film) 2240, 1730 cm^{-1}; NMR ($CDCl_3$) δ 7.34 (s, 5 H), 4.44–3.90 (m, 3 H), 3.95, 3.70 (br s, 4 H), 3.35–3.10 (m, 1 H), 2.43–1.43 (m, 7 H), 1.29 (overlapping t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.03; N, 4.25. Found: C, 69.45; H, 7.24; N, 4.06.

Ethyl 2-[Cyano(2-methoxyphenyl)methyl]cyclohexane-1-carboxylate (21). A 1.16-g sample of nitrile **20** and 1.16 g of ester **6** were subjected to method A. Chromatography (B) gave 1.76 g (76%) of a clear viscous oil. An analytical sample was prepared by bulb-to-bulb distillation (0.08 mm, oven temperature 120 °C): IR (film) 2235, 1730, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.40–6.70 (m, 4 H), 4.58 (d, J = 10 Hz, 1 H), 4.23 (q, J = 7 Hz, 3 H).

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.53; H, 7.69; N, 4.50.

Ethyl 7-[Cyano(2-methoxyphenyl)methyl]-1,4-dioxaspiro[4.5]decane-8-carboxylate (22). Method B. To a suspension of sodium hydride (0.85 g, 35.4 mmol) in 60 mL of dry THF was added 5.20 g (35 mmol) of (*o*-methoxyphenyl)acetonitrile (**20**) in 10 mL of THF. The mixture was vigorously stirred at room temperature for 36 h, during whch time a deep red-brown solution is formed. The reaction mixture was cooled to −45 °C, and a solution of ester **18** (7.70 g, 35 mmol) in 10 mL of THF was added dropwise. After being stirred for 3 h at −45 °C, the reaction mixture was warmed slowly (ca. 1 h) to 0 °C and stirred an additional 2 h; then the dark brown mixture was allowed to warm to ambient temperature and quenched with 5 mL of H_2O. The reaction mixture was poured into 200 mL of ether, and this solution was washed with 150-mL portions of H_2O and saturated brine, dried over $MgSO_4$, and filtered. Concentration gave the crude adduct as a red-brown oil. Column chromatography (B, eluted with 20:1 benzene–ether) afforded 9.35 g (73%) of a waxy solid: mp 62–70 °C; NMR ($CDCl_3$) δ 7.50–6.83 (m, 4 H), 4.51 (m, 1 H), 4.16 (q, J = 7 Hz, 2 H), 3.82 (br s, 4 H), 2.60 (m, 1 H), 2.10–1.45 (m, 7 H), 1.32 (t, J = 7 Hz, 3 H); IR ($CHCl_3$) 2240, 1730 cm^{-1}.

Anal. Calcd for $C_{20}H_{25}O_5N$: C, 66.83; H, 701; N, 3.90. Found: C, 66.84; H, 6.73; N, 3.92.

Ethyl 7-[Cyano(3-methoxyphenyl)methyl]-1,4-dioxaspiro[4.5]decane-8-carboxylate (24). A 2.60-g sample of nitrile **23** and 3.90 g of ester **18** were subjected to method B. Chromatography (B) gave 4.46 g (68%) of a pale oil. An analytical sample was prepared by bulb-to-bulb distillation (0.04 mm, 170 °C): IR (film) 2240, 1730, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.81 (m, 4 H), 4.49–4.01 (m, 3 H), 3.76 (br s, 7 H), 3.52 (m, 1 H), 2.72–1.52 (m, 7 H), 1.27 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{20}H_{25}O_5N$: C, 66.83; H, 7.01; N, 3.90. Found: C, 67.25; H, 6.72; N, 3.80.

(2,5-Dimethoxyphenyl)acetonitrile (25). 2,5-Dimethoxybenzaldehyde (40.0 g, 0.24 mol) was treated with sodium borohydride (3.4 g) in absolute ethanol at 0 °C to give the corresponding benzyl alcohol, which was converted without further purification to the chloride by treatment with excess dry hydrogen chloride in benzene. The crude benzyl chloride was combined with sodium cyanide (13.4 g, 0.27 mol) and sodium iodide (2.0 g) in 100 mL of anhydrous Me_2SO and stirred 16 h at 90 °C.[27] Standard workup afforded 21.8 g of the nitrile **25** as a pale oil

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(24) N. N. Chatterjee, *J. Indian Chem. Soc.*, **14**, 417 (1937).
(25) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
(26) S. Danishefsky and T. Kitahara, *J. Org. Chem.*, **40**, 538 (1975).
(27) E. R. Shepard and J. F. Noth, *J. Am. Chem. Soc.*, **72**, 4364 (1950).

which crystallized on standing; mp 54–55 °C (lit. 56–57 °C).[28]

Ethyl 3-Methyl-4-cyano-4-(2,5-dimethoxyphenyl)butyrate (26). A 1.77-g sample of nitrile **25** and 1.20 g of ethyl crotonate were subjected to method A. Chromatography (B) gave 2.51 g (89%) of a yellow oil. An analytical sample was prepared by bulb-to-bulb distillation (0.25 mm, 155 °C): IR (film) 2235, 1730, 1590, 1500 cm^{-1}; NMR ($CDCl_3$) δ 7.15–6.71 (m, 3 H), 4.42–3.92 (m, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 2.90–2.20 (m, 3 H), 1.45–1.01 (m, 6 H).

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.17; H, 7.26; N, 4.64.

Ethyl 2-[Cyano(2,5-dimethoxyphenyl)methyl]cyclohexane-1-carboxylate (27). A 2.50-g sample of nitrile **25** and 2.14 g of ester **6** were subjected to method A. Chromatography (B) gave 4.85 g (52%) of adduct **27**. Bulb-to-bulb distillation (0.05 mm, 124 °C) gave a yellow oil which solidified on standing: mp 44–47 °C; IR (film) 2240, 1725, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.02–6.70 (m, 3 H), 4.53–4.10 (m, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 2.85–1.45 (m, 9 H), 1.31 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{26}H_{25}NO_5$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.81; H, 7.85; N, 4.36.

Effect of Temperature on Adducts 28 and 37. To a stirred solution of lithium diisopropylamide (6.5 mmol from 1.0 mL of diisopropylamine and 2.5 mL of 2.6 M *n*-butyllithium) in 20 mL of THF at −78 °C was added 953 mg (5.4 mmol) of (2,5-dimethoxyphenyl)acetonitrile (**25**) in 4 mL of THF. The resulting red-brown solution was stirred at −78 °C for 1 h, during which time a light solid precipitated. The reaction mixture was warmed to 0 °C until homoegeneous and then cooled to −78 °C, and 1.29 g (5.4 mmol) of ester **7** in 5 mL of THF was added rapidly by syringe. The reaction mixture was stirred 1 h at −78 °C, warmed to 0°, stirred for 3 h, and finally warmed to room temperature for 3 h. Then 5 mL of H_2O was added, and the reaction mixture was poured into 75 mL of ether. The ether phase was washed with two 50-mL portions of H_2O and saturated brine and dried over $MgSO_4$. Concentration gave an orange oil. Column chromatography (B, eluted with 20:1 benzene–ether) afforded 1.33 g (64%) of a pale orange oil. An analytical sample was prepared by bulb-to-bulb distillation (0.04 mm, 190 °C) to give adduct **28** a waxy semisolid: IR (film) 2240, 1730, 1503 cm^{-1}; NMR ($CDCl_3$) δ 7.11–6.80 (m, 3 H), 4.65–4.01 (m, 3 H), 4.00–3.65 (m, 10 H), 2.74–1.11 (m, 14 H).

Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.16; H, 7.49. Found: C, 66.15; H, 7.11.

The aqueous washes were acidified with 1 N HCl and extracted with three 60-mL portions of ether. The combined organic layers were washed with H_2O and saturated brine and dried over $MgSO_4$. Concentration afforded a yellow solid, which was crystallized from 10:1:1 ether–petroleum ether–methylene chloride to give 0.96 gm of **37** as tiny white needles: 110–110.8 °C; IR ($CHCl_3$) 2240, 1678, 1642 cm^{-1}; NMR ($CDCl_3$) δ 7.30–6.80 (m, 4 H), 5.84 (br s, 1 H), 3.93 (br s), 3.82 (s), 3.77 (s, 10 H), 2.75–1.60 (m, 7 H), 1.21 (br s, 3 H).

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.56; H, 6.78; N, 3.61.

Ethyl 2-[Cyano(naphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (30). A 875-mg sample of nitrile **29** and 1.26 g of ester **7** were subjected to method A. Chromatography (B) gave 680 mg (19%) of adduct **30**. Bulb-to-bulb distillation (1.1 mm, oven temperature 210 °C) gave a pale yellow glass: mp 45–50 °C; IR ($CHCl_3$) 2240, 1735 cm^{-1}; NMR ($CDCl_3$) δ 8.04–7.21 (m, 7 H), 4.48–3.90 (m, 3 H), 3.96 (s, 4 H), 3.20–2.95 (m, 1 H), 2.88–1.07 (m, 11 H), 1.33 (s, 3 H).

Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.97; H, 7.13; N, 3.21.

Ethyl 2-[Cyano(1-methoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (32). A 1.63-g sample of nitrile **31** and 2.00 g of ester **7** were subjected to method B. Chromatography (B) gave **32** in 69% yield; bulb-to-bulb distillation (1 mm, oven temperature 210 °C) gave a pale orange glass: mp 64–69 °C; IR ($CHCl_3$) 2240, 1730 cm^{-1}; NMR ($CDCl_3$) δ 8.31–7.25 (m, 6 H), 4.57 (m, 1 H), 4.17 (q, J = 7 Hz, 2 H), 4.02 (s, 3 H), 3.89 (br s, 4 H), 3.21–2.98 (m, 1 H), 2.24–1.50 (m, 8 H), 1.56 (s, 3 H), 1.27 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.82; H, 6.99; N, 3.77.

Ethyl 2-[Cyano(1,5-dimethoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexene-1-carboxylate (34). Method C. To a stirred suspension of potassium hydride (75 mg, 1.88 mmol) in 10 mL of dry THF was added 425 mg (1.87 mmol) of (1,5-dimethoxynaphth-2-yl)acetonitrile (**33**)[12,29] in 5 mL of THF; this was accompanied by a vigorous gas evolution. The resulting deep red-brown solution was stirred for 1 h at room temperature and then cooled to −20 °C. A 450-mg (1.87 mmol) sample of ester **7** in 5 mL of THF was added dropwise, following which the reaction mixture was stirred 2 h at −20 °C, warmed to room temperature, and stirred an additional 12 h. The reaction was quenched with 3 mL of H_2O and poured into 60 mL of ether. This solution was washed with H_2O and saturated brine, dried over $MgSO_4$, and concentrated to give a dark viscous oil. Chromatography (A, eluted with 5–20% ether in benzene) afforded 525 mg of adduct (60%) as well as 106 mg (25%) of recovered nitrile **33**. Bulb-to-bulb distillation (0.03 mm 210 °C) gave the analytically pure cyano ester as a pale glass: mp 75–80 °C; IR ($CHCl_3$) 2240, 1730, 1600 cm^{-1}; NMR ($CDCl_3$) δ 8.20–7.93 (m, 1 H), 7.71–7.20 (m, 3 H), 6.98–6.71 (m, 1 H), 4.77–4.45 (m, 1 H), 4.42–4.15 (m, 2 H), 3.99 (s), 3.97 (s), 3.96 (s, 10 H), 3.75–3.51 (m, 1 H), 2.62–1.50 (m, 8 H), 1.42–1.12 (m, 6 H).

Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.63; H, 7.03; N, 3.21.

Ethyl 2-[Cyano(1,4,5-trimethoxynaphth-2-yl)methyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (36). To a stirred suspension of potassium hydride (151 mg, 3.8 mmol) in 40 mL of dry THF was added 974 mg (3.79 mmol) of nitrile **35**[21,30] in 5 mL of THF. The resulting dark brown solution was stirred for 1 h at ambient temperature; during this time a light precipitate forms. Then 1 mL of HMPA was added, and the resulting homogeneous mixture was cooled to −20 °C. A solution of ester (910 mg, 3.79 mmol) in 4 mL of THF was added rapidly. The mixture was stirred for 3 h at −20 °C, warmed to 0 °C and stirred an additional 3 h. Finally, the mixture was warmed to ambient temperature and stirred for 12 h. A 1-mL aliquot of H_2O was added, and the mixture was poured into 100 mL of ether. This solution was washed with two 100-mL portions of H_2O and dried over Na_2SO_4. Concentration afforded a brown oil which was subjected to chromatography (C, eluted with 8–25% ether in benzene). Eluted first was a mixture of nitrile **35** and ester **7**, which was dissolved in 1:1 ethyl acetate–cyclohexane. When the mixture cooled, nitrile **35** separated as a beige solid (246 mg, 25%). Eluted second was the cyano ester **36** (1.02 g, 72% based on recovered **35**) as a viscous oil which solidified upon standing to give a red-brown solid: mp 73–76 °C; IR ($CHCl_3$) 2240, 1730, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.78–6.66 (m, 4 H), 4.72–3.98 (m, 3 H), 3.95 (s, 9 H), 3.90 (s, 4 H), 2.88 (m, 1 H), 2.56–1.18 (m, 11 H), 1.28 (s, 3 H).

Anal. Calcd for $C_{28}H_{35}NO_7$: C, 67.58; H, 7.09. Found: C, 67.83; H, 7.05.

Oxidation of 1,4-Adducts. General Procedure. Oxygen gas was dried by being passed through a tower of $CaSO_4$–KOH. Oxygen was delivered to the reaction mixture through a 20-gauge syringe needle at approximately 200 mL/min. The general procedure is illustrated in the following example.

Ethyl 2-Benzoylcyclohexane-1-carboxylate (38). To a solution of lithium diisopropylamide (5.3 mmol from 0.6 mL of diisopropylamine and 2.5 mL of 2.2 M *n*-butyllithium) in 10 mL of THF at −78 °C was added cyano ester **9** (1.26 g, 4.8 mmol) in 3 mL of THF–HMPA (10:1 v/v). The resulting deep purple solution was stirred 0.5 h at −78 °C, whereupon oxygen gas was rapidly bubbled through the reaction mixture for 1 h. The reaction was quenched with 6 mL of 1 M $SnCl_2$/2 M HCl and poured into 50 mL of ether. This solution was washed with 40-mL portions of 1 N NaOH, H_2O, and saturated brine and dried over $MgSO_4$. Concentration gave a pale yellow oil which was distilled (0.05 mm,

(28) V. K. Kalra, A. S. Kukla, and T. R. Seshadri, *Indian J. Chem.*, 287 (1967).

(29) Alternative and superior preparations of nitriles **33** and **35** have now been developed: see ref 21.

(30) A. S. Kende, J. Rizzi, and J. Reimer, *Tetrahedron Lett.*, 1201 (1979).

100 °C) to give analytically pure keto ester as a pale viscous oil: 0.80 g (69%); IR (film) 1730, 1682, 1445 cm^{-1}; NMR ($CDCl_3$) δ 8.01–7.76 (m, 2 H), 7.49–7.22 (m, 3 H), 4.20 (q, J = 7.5 Hz, 2 H), 2.89–2.58 (m, 1 H), 2.52–1.27 (m, 9 H), 1.10 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.81; H, 7.74. Found: C, 73.63; H, 7.80.

Ethyl 4-Phenyl-4-oxobutyrate (39). A 950-mg sample of adduct **13** was subjected to oxidation. Bulb-to-bulb distillation (0.25 mm, oven temperature 130 °C) [lit. bp 186 °C (24 mm),[31a] 120 °C (0.2 mm)[31b]] gave 380 mg of a pale orange oil (42%): IR (film) 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 8.12–7.79 (m, 2 H), 7.55–7.30 (m, 3 H), 4.03 (q, J = 7.5 Hz, 2 H), 2.79 (br t, J = 8 Hz, 2 H), 2.52 (br t, J = 8 Hz, 2 H), 1.32 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.12; H, 6.85.

Ethyl 3-Benzoylbutyrate (40). A 1.66-g sample of adduct **14** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.02 mm, 100 °C) gave 1.14 g (72%) of a clear viscous oil: lit.[32] bp 108–116 °C (0.6 mm); IR (film) 1730, 1680, 1595, 1450 cm^{-1}; NMR ($CDCl_3$) δ 8.08–7.85 (m, 2 H), 7.59–7.32 (m, 3 H), 4.12 (q, J = 7.5 Hz, 2 H), 2.84 (d, J = 8 Hz, 2 H), 2.67 (t q, J = 7 Hz, 8 Hz, 1 H), 1.23 (d, J = 7 Hz, 3 H), 1.20 (t, J = 7.5 Hz, 3 H).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 71.19; H, 7.55.

Ethyl 3,4-Diphenyl-4-oxobutyrate (41). An 840-mg sample of adduct **15** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.01 mm, 150 °C) gave 596 mg (74%) of a viscous oil: IR (film) 1730, 1680, 1601, 1453 cm^{-1}; NMR ($CDCl_3$) δ 8.16–7.92 (m, 2 H), 7.56–7.34 (m, 3 H), 7.26 (s, 5 H), 3.24 (t, J = 8 Hz, 1 H), 2.97 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.76; H, 6.55.

Ethyl 7-Benzoyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (42). A 246-mg sample of adduct **19** was subjected to oxidation. The reaction mixture was quenched with 1 N sodium bisulfite and worked up as usual. Chromatography (B) gave 200 mg (84%) of **42**: IR (film) 1730, 1685, 1595 cm^{-1}; NMR ($CDCl_3$) δ 7.91–7.68 (m, 2 H), 7.59–7.23 (m, 3 H), 4.13 (q, J = 7 Hz, 2 H), 3.89 (br s), 3.85 (br s, 4 H), 3.08–2.72 (m, 1 H), 2.34–1.48 (m, 7 H), 1.19 (t, J = 7 Hz, 3 H).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.78; H, 7.35.

Ethyl 2-(2-Methoxybenzoyl)cyclohexane-1-carboxylate (43). A 290-mg sample of adduct **21** was subjected to oxidation. Chromatography (B) and bulb-to-bulb distillation (0.03 mm, oven temperature 130 °C) gave 238 mg (85%) of **43** as a clear viscous oil: IR (film) 1730, 1682, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.59–6.72 (m, 4 H), 4.08 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 3.03–2.68 (m, 1 H).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.17; H, 7.56.

Ethyl 2-[(Naphth-2-yl)carbonyl]-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexane-1-carboxylate (44). A 709-mg sample of adduct **30** was subjected to oxidation. Preparative TLC (silica gel PF-254, eluted with chloroform) followed by bulb-to-bulb distillation (0.8 mm, 220 °C) gave 547 mg (60%) of an amber oil: IR (film) 1730, 1685, 1460 cm^{-1}; NMR ($CDCl_3$) δ 8.29–7.41 (m, 7 H), 4.38–3.92 (m, 2 H), 3.89 (br s, 4 H), 3.20–2.78 (m, 1 H), 2.74–1.48 (m, 8 H), 1.45–1.00 (m, 6 H).

Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 72.65; H, 6.95.

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Registry No. 6, 1617-22-7; **7**, 66617-28-5; **8**, 140-29-4; **9**, 66617-29-6; **10**, 140-88-5; **11**, 10544-63-5; **12**, 103-36-6; **13**, 19748-87-9; **14**, 66617-33-2; **15**, 31861-57-1; **16**, 80-62-6; **17**, 73481-50-2; **18**, 38334-82-6; **19**, 66617-34-3; **20**, 7035-03-2; **21**, 66617-35-4; **22**, 73481-51-3; **23**, 19924-43-7; **24**, 73453-62-0; **25**, 18086-24-3; **26**, 73481-52-4; **27**, 73453-53-9; **28**, 66617-31-0; **29**, 7498-57-9; **30**, 73481-53-5; **31**, 71056-95-6; **32**, 73481-54-6; **33**, 71742-31-9; **34**, 71771-25-0; **35**, 71611-77-3; **36**, 73481-55-7; **37**, 66617-32-1; **38**, 66617-36-5; **39**, 6270-17-3; **40**, 40394-84-1; **41**, 53647-50-0; **42**, 66617-37-6; **43**, 66617-38-7; **44**, 73481-56-8; ethyl 1-chlorocyclohexane-1-carboxylate, 71911-74-5; phenylacetonitrile, 140-29-4; *trans*-1-methoxy-3-[(trimethylsilyl)-oxy]butadiene, 54125-02-9; 2,5-dimethoxybenzaldehyde, 93-02-7.

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Approaches to Anthracyclines. 2. Regiospecific Annelative Quinone Synthesis[1a]

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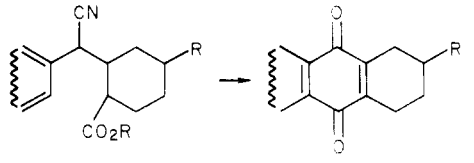
Linear polycyclic quinone systems may be assembled by an efficient regiospecific annelation procedure in which the key step is oxidative decyanation of a cyanocyclohexenone system to the quinone moiety.

The conjugate addition of arylacetonitriles to cyclohexene esters[2] rapidly and efficiently assembles the structural components of potential polycyclic systems. We hoped to convert the Michael adducts obtained in this reaction to quinones by a sequence involving cyclization and oxidation steps (eq 1).



(1)

We have shown[2b] that the conditions of oxidative decyanation lead to mixtures when applied to Michael ad-

(1) (a) Abstracted from the doctoral dissertation of James L. Kallmerten, Brown University, October, 1979. (b) Camille and Henry Dreyfus Teacher-Scholar award recipient.

(2) (a) K. A. Parker and J. L. Kallmerten, *Tetrahedron Lett.*, 4557 (1977). (b) This work is described in detail in K. A. Parker and J. Kallmerten, *J. Org. Chem.*, previous paper in this issue.

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