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(21) We thank Mr. Steve Feiner and Mr. Peter Marshall for performing great numbers of these rather tedious experiments.
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# Perhydroindan Derivatives. 17. Application of the Reduction–Methylation Sequence to 7-Methoxyhexahydrofluorene Derivatives[1]

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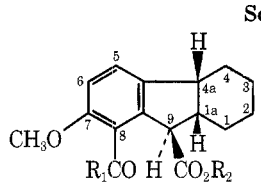
*Received February 6, 1976*

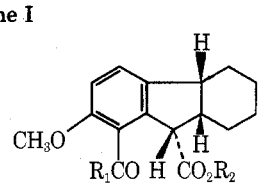
The reductive methylation of each epimeric diacid **1a** and **2a** was studied by successive reaction with Li in THF–liquid $NH_3$ followed by $CH_3I$. In each case, the diacid product (**18** from **1a** and **22** from **2a**) was formed by introduction of the C-8 methyl group into the intermediate **6** from the side of the molecule opposite to the carboxylate group at C-9. Thus, the stereochemistry of the C-9 carboxyl group may be used to control the stereochemistry of methylation at C-8. Each of the syn-diacid products **18** or **22** formed an anhydride **21** or **25** with infrared absorption typical for an unstrained cyclic anhydride.

In earlier publications[2] we have described the synthesis of the epimeric acid derivatives **1** and **2** (Scheme I) which we wished to use as models to explore the preparation of the acid lactone **3**, a model for certain of the gibberellins. To accomplish this objective we wished to introduce a methyl group at C-8 by the scheme of Lowenthal[3] in which the aromatic acid **1a** or **2a** would be reduced with lithium in ammonia to form an enolate anion **6** which could be methylated. For this reaction to be useful, it is apparent that the new methyl group must be introduced at C-8 from above the plane of the polycyclic system of the enolate anion **6** to produce one of the epimeric products **4** or **5**. In this paper we report our study of the stereochemistry of the reduction–methylation sequence with the epimeric acids **1a** and **2a**.

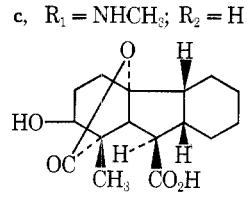
Scheme I



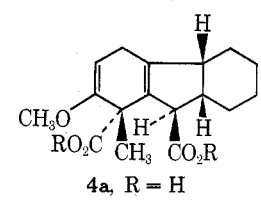
**1a**, $R_1 = OH$; $R_2 = H$
**b**, $R_1 = OCH_3$; $R_2 = CH_3$
**c**, $R_1 = NHCH_3$; $R_2 = H$



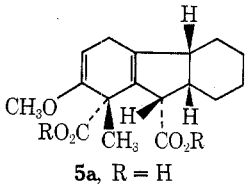
**2a**, $R_1 = OH$; $R_2 = H$
**b**, $R_1 = OCH_3$; $R_2 = CH_3$
**c**, $R_1 = NHCH_3$; $R_2 = H$



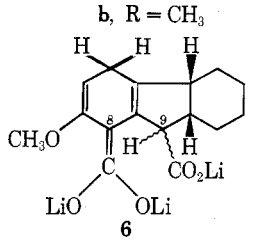
**3**



**4a**, R = H
**b**, R = $CH_3$



**5a**, R = H
**b**, R = $CH_3$

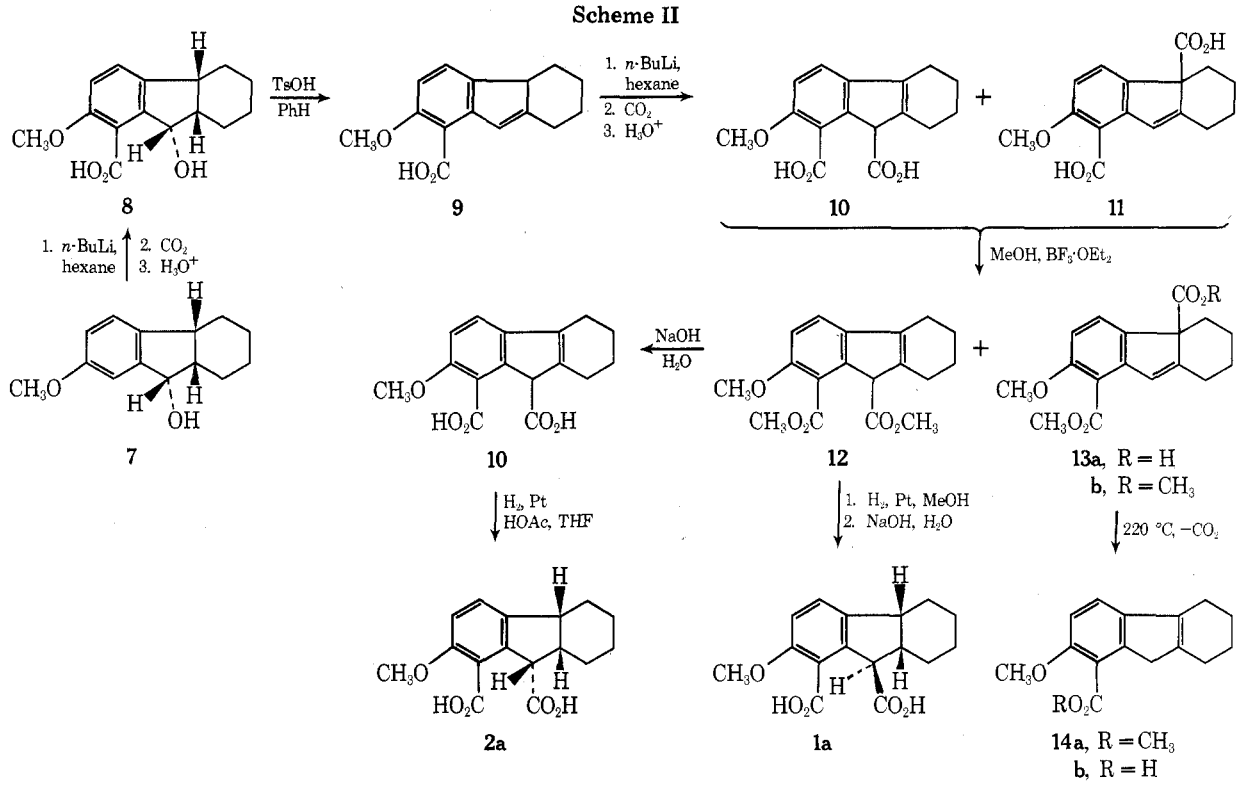


**6**

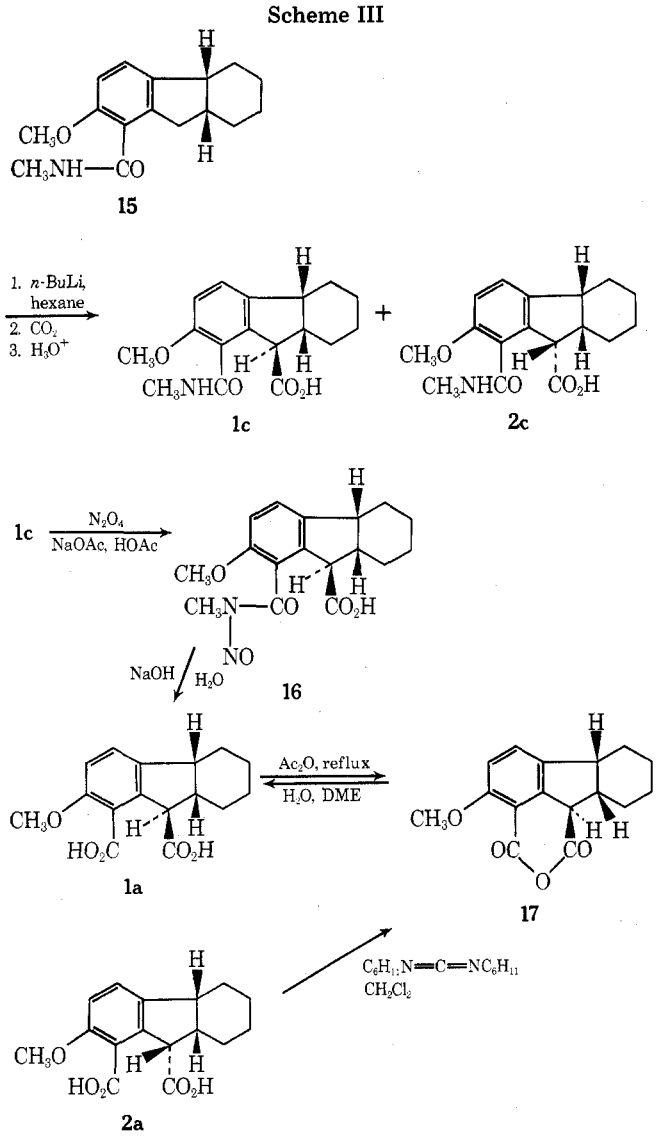
The less stable[2] diacid **2a** was obtained from the alcohol **7** as indicated in Scheme II. In this procedure, a modification of an earlier sequence,[2a] *n*-BuLi rather than *n*-BuLi and *t*-BuONa was used in the initial regiospecific metalation of the alcohol **7**,[4] selective esterification of the isomeric diacids **10** and **11** was used to facilitate separation of the diester **12** from the acid ester **13a**, and *n*-BuLi in hexane rather than MeLi in $Et_2O$–THF was used to metalate the unsaturated ester **9**. The intermediate diester **12** in this sequence could also be used to obtain more stable diacid **1a** by hydrogenation (to form diester **2b**) followed by saponification with accompanying epimerization.

An alternative route to the more stable diacid **1a** is summarized in Scheme III. In this sequence, also a modification of an earlier procedure,[2b] the amide **15**, obtained from hydroxy acid **8**,[2b] was converted to an easily separable mixture of amide acids **1c** and **2c**. Although the diacid **1a** could be converted to the corresponding cyclic anhydride **17**, examination of molecular models suggested that significant distortion of the five-membered B ring was required in this transformation. Evidence for this conformational change is provided by a change in the NMR coupling constant between protons at C-9 and C-1a from $J = 4$ Hz in the acid **1a** to $J \sim 11$ Hz in the anhydride **17**. Presumably because of the distortion required to

Scheme II



Scheme III



form a cyclic anhydride, reaction of the more rigid diacid **10** with $Ac_2O$ failed to form a cyclic anhydride; the crude reaction product appeared to contain (NMR analysis) one or more mixed anhydrides from HOAc and the diacid **10**. Interestingly, an attempt to convert the less stable diacid **2a** to the corresponding cyclic anhydride by reaction with dicyclohexylcarbodiimide in $CH_2Cl_2$ solution resulted in accompanying epimerization at C-9 to form the same anhydride **17** obtained from the more stable diacid **1a**.

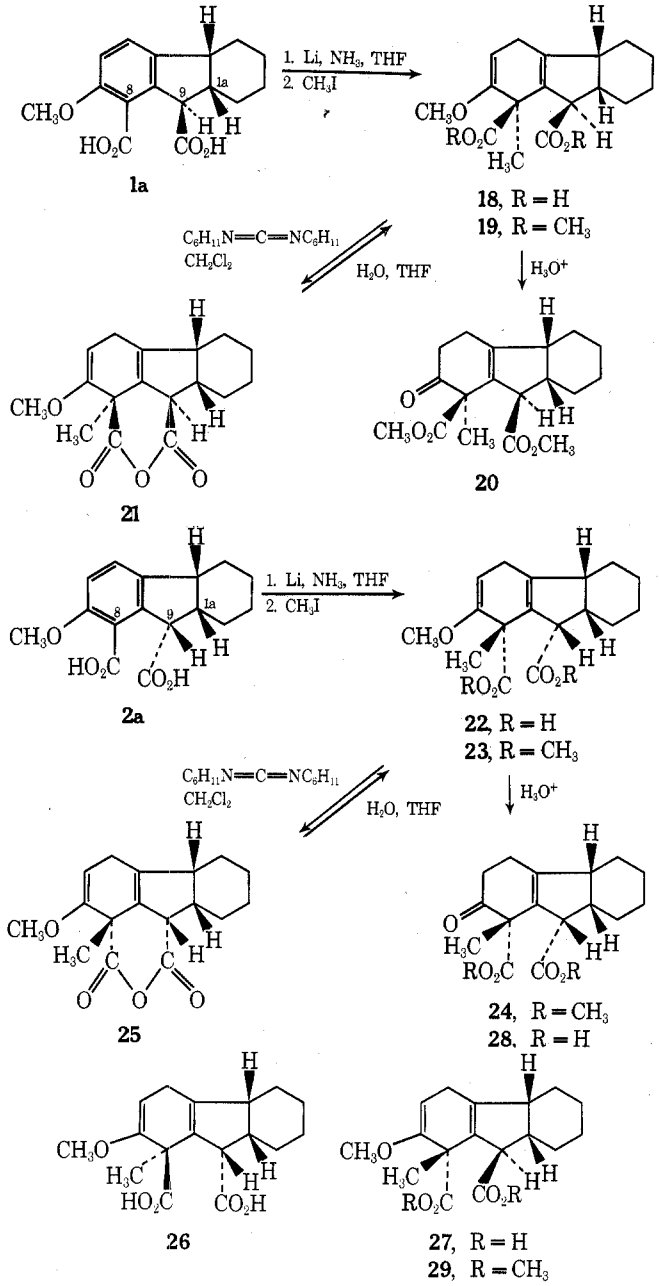
Reductive methylation of the diacid **1a** (Scheme IV) produced a single methylated methoxy diacid **18** accompanied by a crude by-product apparently formed by cleavage of the methoxyl group. The thermally unstable enol ether diacid **18** was characterized as its diester **19** which could be hydrolyzed with dilute acid to the keto diester **20**. Reaction of the diacid **18** with dicyclohexylcarbodiimide under mild conditions produced the cyclic anhydride **21** that could be hydrolyzed to the starting diacid **18**.

Similarly, the reductive methylation of the diacid **2a** produced a single methylated methoxy diacid **22** that was characterized as its diester **23** and keto diester **24**. The diacid **22** could also be easily converted to its cyclic anhydride **25** by treatment with dicyclohexylcarbodiimide.

Since each of the epimeric diacids **1a** and **2a** give a different product in the reductive methylation sequence, it was apparent that epimerization of these diacids **1a** and **2a** at C-9 before reduction was not occurring. Treatment of the diester **23** with NaOMe in MeOH produced a mixture containing **23** and a new product, believed to be diester **29**; however, the mixture from this epimerization lacked NMR absorption characteristic of diester **19**. Furthermore, the NMR coupling constants between protons at C-9 and C-1a in the aromatic acids ($J$ = 4 Hz for **1a** and $J$ = 7 Hz for **2a**) were unchanged in the reduced products ($J$ = 4 Hz in **19** and $J$ = 7 Hz in **22**). Consequently, it was clear that the two diacid products **18** and **22** have the same configuration at C-9 as the starting diacids **1a** and **2a**.

It was apparent from examination of molecular models that while each of the syn diacids **18** and **22** could form a relatively strain-free cyclic anhydride (**21** and **25**), the formation of a

Scheme IV

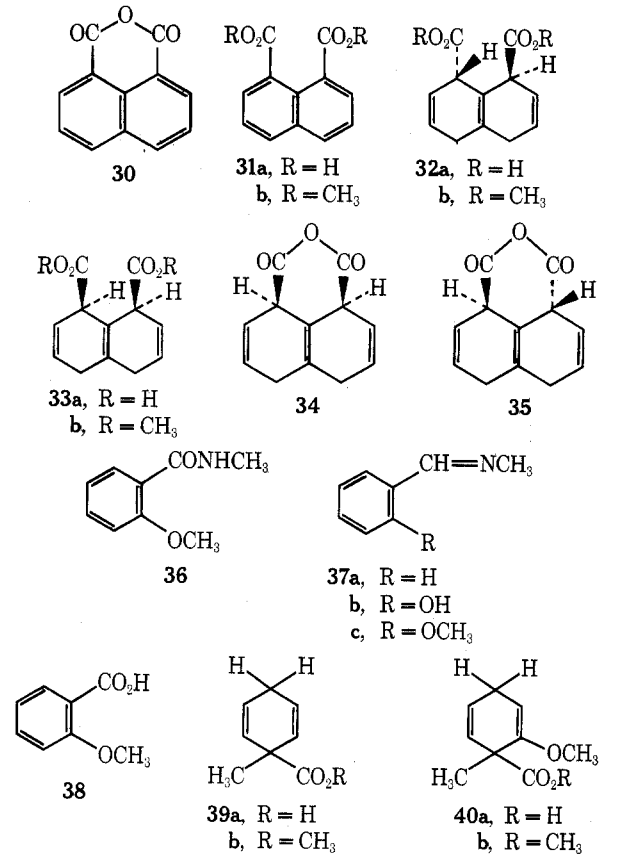



cyclic anhydride from either anti diacid **26** or **27** would be accompanied by introduction of substantial strain into the molecules. The fact that each diacid **18** or **22** could be converted to its anhydride **21** or **25** without epimerization while the same reaction conditions converted the diacid **2a** to anhydride **17** with epimerization strongly suggested that the carboxyl groups are syn in both diacids **18** and **22.**

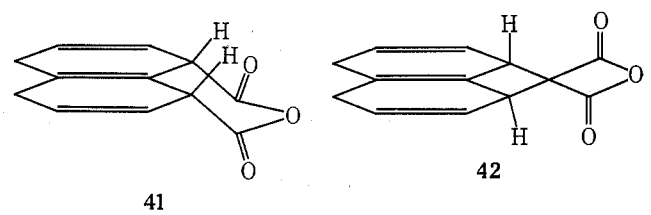
Previous studies of the infrared spectra of cyclic anhydrides derived from dicarboxylic acids[5] have shown that for unstrained six-membered cyclic anhydrides, the ratio of absorbances for the lower frequency (asymmetrical stretching) and higher frequency (symmetrical stretching) carbonyl bonds is 2–3. For acyclic anhydrides this absorbance ratio was approximately 1 and an absorbance ratio of 7–11 was observed for five-membered cyclic anhydrides. The absorbance ratios, $A_{1760}/A_{1800}$, observed for $CHCl_3$ solutions of the anhydrides **17, 21,** and **25** prepared in this study all had values in the range 1.4–1.6 indicating these materials to have the geometry of normal, unstrained six-membered anhydrides.

To obtain further evidence concerning the possibility of forming anhydrides from anti diacids such as **26** and **27,** the diacid **31a** (Scheme V) was reduced with Li in liquid $NH_3$ to

Scheme V



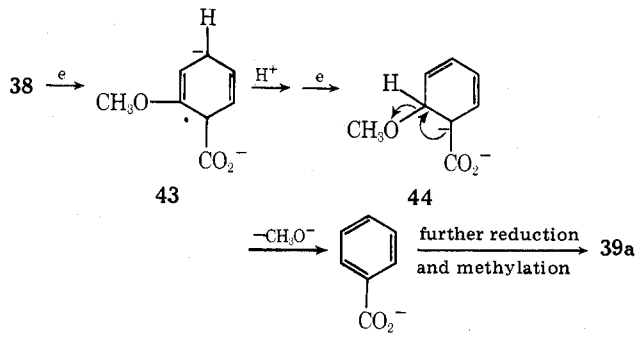

yield the anti diacid **32a** (favored in a kinetically controlled reduction) and the syn diacid **33a** (favored after equilibration of the diacids **32a** and **33a**). Reaction of either diacid with dicyclohexylcarbodiimide in $CH_2Cl_2$ formed the same anhydride **34** that could be hydrolyzed and esterified to yield the syn diester **33b.** The absorbance ratio, $A_{1762}/A_{1804}$ = 1.69, observed in the infrared spectrum of this anhydride **34** was normal for an unstrained six-membered anhydride as would be expected for the syn anhydride **34** in its more stable conformation **41.** By contrast, in the reasonable conformation **42**



41 42

for the anti anhydride **35,** the dipoles of the two carbonyl groups are approximately opposed and the shorter wavelength symmetrical stretching vibration should have significantly diminished intensity analogous to the situation observed with five-membered cyclic anhydrides. Thus, we conclude that the anti diacid, **32a,** is isomerized during reaction with dicyclohexylcarbodiimide to form the more stable syn anhydride **34.** Since comparable behavior would be expected for the geometrically similar anti diacids **26** and **27,** the foregoing stereochemical assignments are substantiated.

Since several attempts to apply the reduction–methylation sequence to the amide acids **1c** and **2c** produced complex mixtures of products, we examined this reaction briefly with the model methoxy amide **36.** After reduction of the amide **36** with Li in THF–$NH_3$ and addition of $CH_3I$, the resulting crude product was a mixture of imines **37** containing primarily the imine **37a** of benzaldehyde. We also examined briefly the reduction–methylation sequence with the model methoxy acid **38.** In addition to the expected product **40a** (characterized as




the ester **40b**), the product mixture (after esterification) also contained the product **39b** that no longer contained an aryl-$OCH_3$ function. Interestingly, this side reaction, presumably resulting from initial protonation of anion radical **43** to form intermediate **44**, was significantly more serious when the acid **38** was reduced with Li in $NH_3$ rather than Na in $NH_3$.

## Experimental Section[6]

**Preparation of the Unsaturated Acid 9.** To a cold (0 °C) suspension of 44.4 g (0.204 mol) of the alcohol **7** in 250 ml of hexane was added, dropwise and with stirring during 30 min, 320 ml of a hexane solution containing 0.525 mol of *n*-BuLi. The resulting orange solution was stirred at 25 °C for 28 h. Then the resulting suspension was cooled to −78 °C and $CO_2$ was passed through the solution with vigorous stirring for 45 min. The reaction mixture was treated with $CH_2Cl_2$ and aqueous $Na_2CO_3$ and the precipitate, the Na salt of the acid **8**, was collected by filtration. This Na salt was stirred with aqueous HCl and then the mixture was extracted with $CH_2Cl_2$. After the $CH_2Cl_2$ extract had been dried, concentration left 43.9 g (82%) of the hydroxy acid **8** as a white solid, mp 133–135 °C (lit. mp 136–137,[2a] 134–135 °C[2b]), identified with previously described samples by comparison of ir spectra. A solution of 20.0 g (76 mmol) of this acid **8** and 1.9 g (10 mmol) of TsOH in 450 ml of benzene was refluxed with continuous separation of $H_2O$ for 1 h and then washed with $H_2O$, dried, and concentrated to leave 17.5 g of the crude acid **9** as a yellow solid, mp 145–154 °C. Fractional recrystallization ($CH_2Cl_2$–hexane) separated 12.7 g of early fractions of white prisms, mp 151–157 °C (lit.[2a] mp 161.5–162.5 °C), containing (ir analysis) mainly the acid **9**. Later fractions (4.1 g, mp 125–145 °C) contained (NMR analysis) the acid **9** accompanied by increasing amounts of the isomeric acid **14b**. The total yield of the mixture of isomeric acids **9** and **14b** (suitable for further reaction with *n*-BuLi) was 16.8 g (90%).

**Preparation of the Diacid 2a.** To a cold (0 °C) suspension of 16.5 g (67.6 mmol) of the unsaturated acid **9** (containing some of the isomeric acid **14b**) in 180 ml of $Et_2O$ and 180 ml of THF was added, dropwise and with stirring, 100 ml of a hexane solution containing 156 mmol of *n*-BuLi. The resulting red solution was stirred at 25 °C for 1 h and then siphoned onto crushed dry ice. The reaction mixture was partitioned between $Et_2O$ and aqueous $Na_2CO_3$ and the aqueous phase was acidified. The precipitate of crude diacids **10** and **11** was collected, combined with the $CH_2Cl_2$ extract of the aqueous filtrate, and concentrated to leave 13.9 g of a light brown solid containing (NMR analysis, $CH_3O$ peaks at δ 3.75 and 3.80) an approximately equal mixture of the diacids **10** and **11**. A solution of this mixture of diacids and 5.0 ml of $BF_3$·$Et_2O$ in 400 ml of MeOH[7] was refluxed for 23 h and then concentrated and partitioned between aqueous $Na_2CO_3$ and $CH_2Cl_2$. The organic layer was dried and concentrated to leave 9.7 g of orange liquid containing [liquid chromatography, C-18 Corasil column with a $H_2O$–$CH_3CN$ (3:2 v/v) eluent] the diester **12** (ca. 70%, retention time 2.0 min), the diester **13b** (ca. 30%, 1.5 min), and two minor unidentified impurities (4.1 and 8.2 min). Fractional crystallization from $Et_2O$ separated 4.53 g of the crude diester **12**, mp 86–86.5 °C, that was recrystallized from MeOH to give 3.98 g of diester **12** as white needles, mp 88–89 °C (lit.[2a] 91–91.5 °C). The remaining materials from the mother liquors were chromatographed on silica gel (eluent PhH–$Et_2O$, 99:1 v/v) and subsequently crystallized to separate an additional 1.08 g (total yield 5.06 g or 26%) of the diester **12**, mp 88–89.5 °C. A mixture of 3.98 g (12.6 mmol) of the diester **12**, 1.90 g (47.4 mmol) of NaOH, and 75 ml of $H_2O$ was refluxed for 45 min and the resulting orange solution was acidified. The crude product, collected on a filter, was recrystallized from aqueous MeOH to separate 3.117 g (86%) of the diacid **10** as a pale yellow solid, mp 197 °C dec (lit.[2a] mp 200 °C dec), that was identified with a previously described sample by comparison of ir spectra.

A solution of 3.102 g (10.8 mmol) of the diacid **10** in 50 ml of THF and 50 ml of HOAc was hydrogenated at 1 atm and 27 °C over 573 mg of 5% Pt on C catalyst until the hydrogen uptake (9.74 mmol or 0.90 equiv) ceased. The mixture was filtered and concentrated to leave 3.053 g of crude product, mp 185–203 °C dec, that was recrystallized from an acetone–hexane mixture. The yield of the diacid **2a** was 2.647 g (85%) of white needles, mp 198–206 °C dec (lit.[2a] mp 201–203 °C dec), identified with a previously described[2a] sample by comparison of NMR spectra.

In another experiment, 1.52 g of a mixture of approximately equal amounts of diacids **10** and **11** in 45 ml of MeOH containing 0.8 ml of $BF_3$·$Et_2O$[7] was refluxed for 14 h and then concentrated and partitioned between aqueous $NaHCO_3$ and $Et_2O$. The $Et_2O$ solution was dried and concentrated to leave 645 mg of orange liquid that contained (NMR analysis) mainly the diester **12** (ca. 80% of product). Chromatography on silica gel ($Et_2O$–PhH eluent) separated 489 mg of the diester **12** as white needles, mp 88–90 °C. Recrystallization from MeOH afforded the pure diester **12** as white needles, mp 88.5–90.5 °C (lit.[2a] 91–91.5 °C). The aqueous phase from the reaction was acidified and extracted with $CH_2Cl_2$ and the organic extract was dried and concentrated to leave 751 mg of the crude acid ester **13a** as a pale yellow solid, mp 191–197 °C dec. Recrystallization from an acetone–hexane mixture afforded a sample of the acid ester **13a** as white prisms: mp 202.5–205.5 °C dec; ir (KBr pellet) 2940 (broad, carboxyl OH), 1725 (ester C=O), and 1685 $cm^{-1}$ (carboxyl C=O); NMR (pyridine-$d_5$) δ 7.78 (1 H, d, $J$ = 8.5 Hz, aryl CH), 6.97 (1 H, partially resolved multiplet, vinyl CH), 6.77 (1 H, d, $J$ = 8.5 Hz, aryl CH), 3.93 and 3.73 (singlets, $CO_2CH_3$ and $OCH_3$), and 0.8–3.4 (multiplet, aliphatic CH). A 910-mg sample of the acid ester **13a** was heated to 220° under a $N_2$ atmosphere for 15 min at which time gas evolution ceased. Chromatography of the crude product on silica gel with a PhH–$Et_2O$ eluent separated 642 mg (78%) of the unsaturated ester **14a**, mp 98–100 °C. Recrystallization from hexane afforded the ester **14a** as pale yellow plates: mp 100–101.5 °C; ir ($CCl_4$) 1730 (ester C=O) and 1640 $cm^{-1}$ (weak, C=C); uv maxima (95% EtOH) 268 nm (ε 14 800), 275 (inflection, 12 000), and 329 (1890); NMR ($CCl_4$) δ 7.03 (1 H, d, $J$ = 8 Hz, aryl CH), 6.70 (1 H, d, $J$ = 8 Hz, aryl CH), 3.85, 3.80 (two 3 H singlets, $OCH_3$ and $CO_2CH_3$), 3.30 (2 H, broad, benzylic $CH_2$), 2.1–2.6 (4 H, m, allylic $CH_2$), and 1.5–2.0 (4 H, m, aliphatic $CH_2$); mass spectrum *m/e* (rel intensity) 258 ($M^+$, 56), 227 (35), 226 (46), 225 (31), 211 (25), 199 (36), 198 (93), 185 (35), 183 (32), 165 (50), 155 (60), 153 (66), 152 (72), 141 (83), 140 (73), 139 (80), 128 (100), 127 (78), 115 (84), and 63 (40).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.21; H, 7.04.

**Preparation of the Diacid 1a. A. From the Diester 12.** A solution of 1.84 g (5.82 mmol) of the diester **12** in 43 ml of MeOH was hydrogenated over 360 mg of 5% Pt on C catalyst at 27 °C and 1 atm of $H_2$ to yield 1.93 g of the crude saturated diester **2b** as pale yellow oil identified with a previously described[2a] sample by comparison of ir and NMR spectra. A 1.76-g (5.5 mmol) sample of the crude diester **2b** was epimerized and saponified by treatment with 1.55 g (38.8 mmol) of NaOH in 55 ml of boiling $H_2O$ for 2 h. The crude acidic product was recrystallized from a PhH–hexane mixture to separate 1.41 g (88%) of the diacid **1a** as white needles, mp 187–189.5 °C dec (lit.[2a] mp 189.5–190.5 °C dec), which was identified with an authentic sample by comparison of ir spectra.

**B. From the Amide 15.** Following a previous procedure,[2b] a cold (0 °C) suspension of 2.692 g (10.4 mmol) of the amide **15** in 30 ml of THF was treated with 20 ml of a hexane solution containing 31.2 mmol of *n*-BuLi and the resulting mixture was stirred at 0 °C for 1 h and at reflux for 30 min. After the resulting orange suspension had been diluted with 30 ml of THF, it was poured onto crushed dry ice. The crude acidic product, isolated in the usual way, amounted to 1.659 g of an $Et_2O$-soluble fraction and 1.020 g of a less soluble fraction containing (TLC, silica gel with a $CHCl_3$–EtOAc–$HCO_2H$ eluent, 10:10:3 v/v/v) the amide acids **1c** ($R_f$ 0.51) and **2c** ($R_f$ 0.41). Repeated extraction with $Et_2O$ left 497 mg of the less soluble amide acid **2c**, mp 212–214 °C dec, that was triturated with acetone to leave 434 mg (14%) of the pure (TLC) amide acid **2c**, mp 212 °C dec (lit.[2b] mp 213–215 °C). This material was identified with a previously described sample by comparison of ir spectra. The combined $Et_2O$-soluble portions of the crude acidic product were concentrated to leave 2.179 g (70%) of the crude acid amide **1c** (TLC analysis). Recrystallization from EtOH afforded 1.70 g (55%) of the pure acid amide **1c** as white needles, mp 150–152 °C (lit.[2b] 152–153 °C), identified with a previously described sample by comparison of ir spectra. In the present studies, the mixture of amide acids **1c** and **2c** obtained from this metalation–carbonation procedure has consistently contained a greater amount of the amide acid **1c** whereas the stereoisomer **2c** was the predominant product in earlier work.[2b] The reason for this difference is not apparent.

A cold (ca. 15 °C) solution of 515 mg (1.70 mmol) of the amide acid **1c** and 220 mg (2.68 mmol) of NaOAc in 15 ml of HOAc was treated with 0.5 ml (ca. 7 mmol) of $N_2O_4$ and the resulting green solution was stirred for 15 min during which time a yellow solid separated. After the mixture had been partitioned between $H_2O$ and $CH_2Cl_2$, the $CH_2Cl_2$ layer was dried and concentrated to leave 617 mg of the crude nitroso compound **16** as an orange liquid containing (TLC, silica gel with a $CHCl_3$–EtOAc–$HCO_2H$ eluent, 10:10:3 v/v/v) one major component ($R_f$ 0.68) and lacking the starting amide **1c** ($R_f$ 0.43). The crude product was added to 25 ml of cold (0 °C) aqueous 10% NaOH and then stirred at 0 °C for 15 min and at reflux for 15 min. Gas evolution was apparent as the solution was warmed above 0 °C. The resulting dark brown solution was acidified (HCl) and extracted with $CH_2Cl_2$. After the $CH_2Cl_2$ solution had been dried and concentrated, trituration with ether left 364 mg of the crude diacid **1a** as a brown solid, mp 184–185 °C. After an acetone solution of the product had been decolorized with carbon, crystallization from acetone–hexane mixtures separated 222 mg (45%) of the diacid **1a** as a tan solid, mp 188–190 °C (lit.[2a] 189.5–190.5 °C), that was identified with a previously described sample by comparison of NMR spectra.

A mixture of 478 mg (1.65 mmol) of the diacid **1a** and 6.0 ml of $Ac_2O$ was refluxed for 1 h and then concentrated under reduced pressure. The residue was triturated with pentane to leave 393 mg of the crude anhydride **17** as a yellow solid, mp 142–155 °C. Recrystallization from acetone–hexane separated 205 mg (46%) of the anhydride **17** as white plates: mp 159–161 °C; ir ($CHCl_3$) 1802 and 1760 $cm^{-1}$ (anhydride C=O, absorbance ratio $A_{1760}/A_{1802}$ = 1.50); NMR ($CDCl_3$) $\delta$ 7.47 (1 H, d, $J$ = 8 Hz, aryl CH), 6.90 (1 H, d, $J$ = 8 Hz, aryl CH), 3.8–4.3 [4 H, m, benzylic CH doublet ($J \sim 11$ Hz) at 4.13 partially resolved from a $CH_3O$ singlet at 3.97], and 0.9–3.3 (10 H, m, aliphatic CH); uv max ($Et_2O$) 321 nm ($\epsilon$ 4900) with intense end absorption; mass spectrum *m/e* (rel intensity) 272 ($M^+$, 34), 229 (20), 228 (100), 185 (75), 171 (24), 129 (25), 128 (29), and 115 (29).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.50; H, 5.92.

After a solution of 36 mg of this anhydride **17** and 1.3 ml of $H_2O$ in 2.0 ml of DME had been heated on a steam bath for 30 min, concentration left 36 mg of the solid acid **1a**, identified with an authentic sample by comparison of ir spectra.

In an attempt to form the anhydride from the less stable diacid **2a**, 109 mg (0.376 mmol) of the diacid **2a** was added to a solution of 97 mg (0.47 mmol) of dicyclohexylcarbodiimide in 5 ml of $CH_2Cl_2$. After the resulting suspension had been stirred at 25 °C for 2.5 h, it was filtered and the filtrate was concentrated to leave a yellow semisolid. The crude product was washed with pentane, dissolved in PhH and filtered (to remove dicyclohexylurea), and again concentrated to leave 62 mg (60%) of the anhydride **17** as colorless prisms, mp 156–158 °C. Recrystallization (PhH–pentane) raised the melting point of the anhydride **17** to 159–161 °C. This product was identified with the previously described sample by a mixture melting point determination and by comparison of ir and NMR spectra.

**Reductive Methylation of the Diacid 1a.** To a refluxing (−33 °C) solution of 758 mg (108 mg-atoms) of Li in 100 ml of liquid $NH_3$ was added, dropwise and with stirring during 20 min, a solution of 659 mg (2.27 mmol) of the diacid **1a** in 20 ml of THF.[8] After the addition was complete, the resulting blue reaction mixture was stirred for 5 min and then 8.0 ml (18.4 g, 128 mmol) of $CH_3I$ was added. As the $CH_3I$ was added the blue reaction mixture changed progressively to a white suspension, a colorless solution, and finally a green solution. After the addition was complete, the reaction mixture was stirred for 30 min and then 5 ml of $CH_3OH$ was added followed by 5 ml of $H_2O$ and the $NH_3$ was allowed to evaporate. The remaining mixture was concentrated under reduced pressure, diluted with 50 ml of cold water, acidified to pH 4 with aqueous 1 M HCl, and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extract was dried and concentrated to leave 733 mg of crude yellow semisolid. Trituration of this residue with $Et_2O$ left 351 mg (50.5%) of the crude diacid **18** as a white solid, mp 175–176 °C dec. The $Et_2O$-soluble material from this separation contained (NMR analysis) little, if any, of either methylated diacid **18** or **22**. Recrystallization from MeOH separated the diacid **18** as white prisms: mp 180–181.5 °C dec; ir (KBr pellet) 2920 (broad, associated OH), 1710 (broad, carboxyl C=O), and 1660 $cm^{-1}$ (C=C); uv (95% EtOH), end absorption with $\epsilon$ 3900 at 210 nm; NMR (pyridine) $\delta$ 4.90 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.3–3.8 (4 H, m, $CHCO_2R$ and $CH_3O$ singlet at 3.56), and 1.0–3.3 (15 H, m, aliphatic CH including a $CH_3$ singlet at 1.90); mass spectrum *m/e* (rel intensity) 262 (33), 247 (20), 218 (100), 203 (87), and 91 (97). Reaction of 622 mg (2.04 mmol) of the crude diacid **18** with excess ethereal $CH_2N_2$ yielded 678 mg (99%) of the crude diester **19**. Recrystallization from $Et_2O$–hexane afforded 580 mg (85%) of the pure diester **19** as white prisms: mp 145.5–147 °C; ir ($CCl_4$) 1740 (ester C=O), 1690 (enol ether C=C), and 1655 $cm^{-1}$ (C=C); uv (95% EtOH) end absorption with $\epsilon$ 3900 at 210 nm; NMR ($CDCl_3$) $\delta$ 4.82 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.63, 3.60, 3.56 (three 3 H, s, $OCH_3$ and $CO_2CH_3$), 3.1–3.3 (1 H, m, $CHCO_2R$), 2.2–3.0 (4 H, m, allylic and aliphatic CH), and 1.0–2.0 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.47); mass spectrum *m/e* (rel intensity) 334 ($M^+$, 0.5), 275 (11), 274 (11), 216 (47), 215 (100), 173 (70), 159 (68), 141 (62), 129 (65), 128 (68), 115 (68), 91 (56), and 59 (43). Measurement of the NMR spectrum ($CDCl_3$) of the diester **19** with irradiation at $\delta$ 2.8 to decouple the allylic CH and $CH_2$ protons from the C-9 proton left the signal for this C-9 proton as a doublet ($J$ = 4 Hz) at $\delta$ 3.18 corresponding to the coupling constant between protons at C-9 and C-1a.

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.99; H, 7.71.

**Preparation of the Keto Diester 20.** Following the general procedure of Lowenthal and co-workers,[3a] 89 mg (0.27 mmol) of the enol ether **19** was dissolved in a warm mixture of 0.5 ml of MeOH, 0.3 ml of THF, and 0.08 ml of $H_2O$ and the solution was treated with 0.2 ml of aqueous 12 M HCl. The resulting solution was allowed to stand for 3 h and then concentrated under reduced pressure and partitioned between aqueous $NaHCO_3$ and $CH_2Cl_2$. The organic phase was dried and concentrated to leave 94 mg of pale yellow liquid that was chromatographed on acid-washed silica gel with a PhH–$Et_2O$ (9:1 v/v) eluent. The chromatographic fractions (76 mg, 89%) containing (TLC) the keto diester **20** crystallized as a white solid, mp 63.5–65.5 °C. Recrystallization from $Et_2O$–pentane separated the pure keto diester **20** as white prisms: mp 66–67 °C; ir ($CCl_4$) 1740 (ester C=O) and 1720 $cm^{-1}$ (C=O); uv (95% EtOH) end absorption with $\epsilon$ 3800 at 210 nm and a maximum at 310 nm ($\epsilon$ 69); NMR ($CDCl_3$) $\delta$ 3.65 (6 H, s, $CO_2CH_3$), 2.2–3.7 (7 H, m, $CH_2CO$, allylic CH and $CH_2$, bridgehead CH, and $CHCO_2R$), and 1.0–2.0 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.44); mass spectrum *m/e* (rel intensity) 320 ($M^+$, 9), 305 (12), 273 (18), 261 (100), 260 (95), 201 (82), 159 (33), 91 (18), and 43 (42).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.31; H, 7.60.

In an alternative procedure, a solution of 235 mg (0.703 mmol) of the enol ether **19** and 0.2 ml of $H_2O$ in 10 ml of trifluoroacetic acid was allowed to stand for 16 h and then concentrated under reduced pressure. After following the previously described isolation procedure, the crude product (251 mg of yellow solid) was recrystallized from $Et_2O$–pentane to separate 107 mg (48%) of the keto diester **20** as white prisms, mp 63.5–64.5 °C. An attempt to effect this hydrolysis with a mixture of 10 ml of DME and 5 ml of aqueous 50% HOAc at 25 °C for 40 h resulted in recovery of the starting enol ether **19**. Attempts to form a lactone by reaction of the enol ether **19** with trifluoroacetic acid at 25 °C for 16 h or with a refluxing mixture of 1 ml of THF and 0.1 ml of aqueous 50% $H_2SO_4$ converted the enol ether **19** to the keto diester **20**. Although ir absorption at 1780 $cm^{-1}$ was observed in the THF–$H_2SO_4$ reaction, the lactone band apparently arose from degradation of the THF. Attempts to form a lactone from the keto diester **20** by reaction with TsOH in refluxing PhH or by reaction with refluxing trifluoroacetic acid resulted in recovery of the starting material (ir and TLC analyses) with no ir evidence for the formation of a $\gamma$-lactone.

**Preparation of the Anhydride 21.** A solution of 204 mg (0.668 mmol) of the diacid **18** and 162 mg (0.787 mmol) of dicyclohexylcarbodiimide in 7.0 ml of $CH_2Cl_2$ was stirred at 25 °C for 2 h during which time a white precipitate of dicyclohexylurea separated. The mixture was filtered and the filtrate was concentrated and triturated with pentane to leave 218 mg of a pale yellow solid. A solution of this material in PhH was centrifuged to remove additional insoluble dicyclohexylurea and then diluted with pentane and cooled to crystallize 143 mg (74.5%) of the anhydride **21** as white needles, mp 145–147 °c dec. The semisolid residue (15 mg) recovered from the mother liquors contained (ir analysis) the same anhydride **21**. Recrystallization from EtOAc gave the anhydride **21** as white needles: mp 148–150 °C dec (dependent on rate of heating); ir ($CHCl_3$) 1808 and 1765 $cm^{-1}$ (anhydride C=O, absorbance ratio $A_{1765}/A_{1808}$ = 1.43); NMR ($CDCl_3$) $\delta$ 4.88 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.4–3.8 (4 H, m, $CHCO_2R$ and a $CH_3O$ singlet at 3.66), 2.3–3.0 (4 H, m, CH and allylic $CH_2$), and 0.8–2.3 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.58); mass spectrum *m/e* (rel intensity) 288 ($M^+$, 1), 260 (38), 217 (31), 216 (100), 215 (31), 201 (48), 185 (38), 174 (50), and 173 (68).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.83, H, 7.02.

A solution of 62 mg (0.22 mmol) of the anhydride **21** in 2.0 ml of THF and 1 ml of $H_2O$ was stirred at 25 °C for 8.5 h during which time a white solid separated. After the mixture had been concentrated and extracted with $CH_2Cl_2$, the $CH_2Cl_2$ extract was dried and concentrated to leave 66 mg (100%) of the diacid **1a**, mp 178 °C dec, that was identified with an authentic sample by comparison of ir and NMR spectra.

**Reductive Methylation of the Diacid 2a.** The same procedure

used with the diacid **1a** was followed with a solution of 862 mg (2.98 mmol) of the diacid **2a** in 20 ml of THF being added during 20 min[8] to a solution of 949 mg (135 mg-atoms) of Li in 100 ml of liquid $NH_3$. After reaction with 10.0 ml (22.8 g, 161 mmol) of $CH_3I$ and the previously described isolation procedure, the crude acidic product was obtained as 884 mg of yellow semisolid. Trituration with $Et_2O$ left 360 mg of the diacid **22** as a white solid, mp 180–190 °C dec. The $Et_2O$-soluble material from this separation contained (NMR analyses) little, if any, of either of the methylated diacids **18** or **22.** The crude diacid was recrystallized from EtOH to separate the diacid **22** as white prisms: mp 199–201 °C dec; ir (KBr pellet) 2920 (broad, associated OH), 1700 (broad, carboxyl C=O), 1660 and 1655 $cm^{-1}$ (shoulder) (C=C); uv (95% EtOH) end absorption with $\epsilon$ 4200 at 210 nm; NMR (pyridine) $\delta$ 4.86 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.93 (1 H, doublet, $J$ = 7 Hz, of multiplets, $CHCO_2R$), 3.55 (3 H, s, $OCH_3$), 1.82 (3 H, s, $CH_3$), and 1.1–3.1 (12 H, m, aliphatic CH); mass spectrum $m/e$ (rel intensity) 262 (100), 247 (33), 219 (45), 217 (31), 91 (34), and 44 (55). Because of the thermal instability of the diacid **22,** it was converted to the diester **23** for further characterization. Reaction of 270 mg (0.88 mmol) of the diacid **22** with excess ethereal $CH_2N_2$ yielded 284 mg (97%) of the crude diester **23.** Recrystallization from ether–hexane afforded 225 mg (77%) of the pure diester **23** as white prisms: mp 126–128 °C; ir ($CCl_4$) 1738 (ester C=O), 1690 (enol ether C=C), and 1658 $cm^{-1}$ (C=C); uv (95% EtOH) end absorption with $\epsilon$ 4000 at 210 nm; NMR ($CDCl_3$), $\delta$ 4.83 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.66, 3.63, 3.56, (three 3 H, s, $OCH_3$ and $CO_2CH_3$), 3.4–3.7 (1 H, m, $CHCO_2R$), 2.3–3.0 (4 H, m, allylic and aliphatic CH), and 1.1–1.9 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.39); mass spectrum $m/e$ (rel intensity) 334 ($M^+$, 1), 275 (15), 274 (15), 216 (31), 215 (100), and 59 (30).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.19; H, 7.79.

A mixture of 52 mg (0.17 mmol) of the diacid **22,** 0.5 ml of HOAc, 0.5 ml of $H_2O$, 0.3 ml of aqueous 1 M HCl, and 2 ml of DME was stirred at 25 °C for 5.5 h and then concentrated under reduced pressure. The crude keto acid **28,** 48 mg of tan semisolid, had the following spectral properties: ir (liquid film) 2500–3500 (broad, associated OH), 1725 (C=O), and 1705 $cm^{-1}$ (carboxyl C=O); uv (95% EtOH), end absorption.

To a solution of NaOMe, prepared from 55 mg (2.4 mg-atoms) of Na and 4 ml of MeOH, was added a solution of 50 mg (0.15 mmol) of the enol ether **23** in 1.5 ml of MeOH. The resulting solution was allowed to stand for 3 days and then concentrated under reduced pressure and extracted with $Et_2O$. The $Et_2O$ extract was concentrated and the residual semisolid (61 mg) was chromatographed on acid-washed silica gel with a PhH–$Et_2O$ (93:7 v/v) eluent. The crude epimeric diester **29** (TLC analysis) was eluted as 24 mg of a pale yellow oil: ir ($CCl_4$) 1740 (ester C=O), 1694 (enol C=C), and 1660 $cm^{-1}$ (C=C); uv (95% EtOH) end absorption with $\epsilon$ 4000 at 210 nm; NMR ($CDCl_3$) $\delta$ 4.84 (1 H, t, $J$ = 3 Hz, vinyl CH), three 3 H singlets at 3.69, 3.66, 3.57 ($CO_2CH_3$ and $OCH_3$), 2.1–3.2 (5 H, m, $CHCO_2R$, allylic CH and $CH_2$, and bridgehead CH), and 1.0–2.0 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.32). The NMR spectrum of the crude reaction product before chromatography indicated the presence of the starting diester **23** and the epimer **29** but lacked absorption at $\delta$ 1.47 corresponding to the $CH_3$ singlet of the isomeric diester **19.**

**Preparation of the Keto Diester 24.** The previously described hydrolysis and isolation procedures were followed with 79 mg (0.24 mmol) of the enol ether **23,** 0.45 ml of MeOH, 0.25 ml of THF, 0.06 ml of $H_2O$, and 0.2 ml of aqueous 12 M HCl. Chromatography of the crude product (80 mg of yellow liquid) on silica gel separated 56 mg (73%) of the keto diester **24** as a pale yellow liquid: ir ($CCl_4$) 1740 (ester C=O) and 1720 $cm^{-1}$ (C=O); uv (95% EtOH) end absorption with $\epsilon$ 3900 at 210 nm and a maximum at 295 nm ($\epsilon$ 92); NMR ($CDCl_3$) $\delta$ 3.70 (3 H, s, $CO_2CH_3$), 3.65 (3 H, s, $CO_2CH_3$), 3.3–3.7 (1 H, m, $CHCO_2R$), 2.2–3.3 (6 H, m, allylic CH and $CH_2$, $COCH_2$, and bridgehead CH), and 1.1–1.9 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.35); mass spectrum $m/e$ (rel (rel intensity) 320 ($M^+$, 6), 288 (30), 261 (51), 260 (100), 202 (18), 201 (99), 173 (20), 159 (22), 91 (16), and 43 (46).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.34; H, 7.55.

Hydrolysis of 190 mg (0.568 mmol) of the enol ether **23** with 3 ml of trifluoroacetic acid containing 0.2 ml of $H_2O$ followed by chromatography of the crude product (192 mg) afforded 156 mg (86%) of the keto diester **24** as a pale yellow liquid.

**Preparation of the Anhydride 25.** A mixture of 159 mg (0.52 mmol) of the diacid **22,** 129 mg (0.627 mmol) of dicycylohexylcarbodiimide, and 7.0 ml of $CH_2Cl_2$ was stirred at 25 °C for 2.5 h. After the resulting suspension had been filtered, the filtrate was concentrated, dissolved in PhH, filtered, and diluted with pentane. The anhydride **25** separated as 96 mg (64%) of white needles, mp 127–130 °C. Recrystallization from PhH–pentane gave the pure anhydride **25:** mp 128–130 °C; ir ($CHCl_3$) 1805 and 1764 $cm^{-1}$ (anhydride C=O, absorbance ratio $A_{1764}/A_{1805}$ = 1.55); NMR ($CDCl_3$) $\delta$ 4.90 (1 H, t, $J$ = 3.5 Hz, vinyl CH), 3.6–4.1 (4 H, m, $CHCO_2R$ and a $CH_3O$ singlet at 3.67), 2.7–3.1 (4 H, m, CH and allylic $CH_2$), and 0.8–1.9 (11 H, m, aliphatic CH including a $CH_3$ singlet at 1.50); mass spectrum $m/e$ (rel intensity) 288 ($M^+$, 2), 260 (70), 242 (45), 217 (51), 216 (100), 215 (38), 201 (41), 199 (39), 185 (42), 174 (48), and 173 (80).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.53: H, 7.06.

A solution of 33 mg (0.12 mmol) of the anhydride **25** and 0.2 ml of $H_2O$ in 1.0 ml of THF was stirred at 25 °C for 6 h and then concentrated under reduced pressure. The residual diacid **22** (35 mg or 100% of white solid, mp 190 °C dec) was identified with the previously described sample by comparison of ir and NMR spectra.

**Other Reduction and Reduction–Methylation Reactions. A. Amide 36.** The $N$-methyl amide **36** of $o$-methoxybenzoic acid was prepared from the corresponding acid chloride in 77% yield as a colorless liquid: bp 128–129 °C (0.9 mm); $n^{25}D$ 1.5638 [lit. bp 175 °C (14 mm),[9a] 127–129 °C (1 mm)[9b]]; ir (liquid film) 3410 (NH) and 1645 $cm^{-1}$ (amide C=O); NMR ($CDCl_3$) $\delta$ 8.17 (1 H, d of d, $J$ = 7.5 and 2.5 Hz, aryl CH), 7.82 (1 H, broad, NH), 6.8–7.6 (3 H, m, aryl CH), 3.85 (3 H, s, $OCH_3$), and 2.95 (3 H, d, $J$ = 5 Hz, $NCH_3$).

To a solution of 3.00 g (18.2 mmol) of the amide **36** in 45 ml of THF and 200 ml of liquid $NH_3$ was added 565 mg (81.5 mg-atoms) of Li. The resulting dark blue solution was stirred under reflux for 2 h and then 5.0 ml of $CH_3I$ was added. The resulting yellow suspension was stirred under reflux for 30 min and then diluted successively with 25 ml of MeOH and with 25 ml of $H_2O$. After the $NH_3$ had evaporated, the remaining mixture was concentrated and partitioned between $H_2O$ and $CH_2Cl_2$. The organic solution was dried and concentrated under reduced pressure to leave 2.195 g of yellow-brown liquid with NMR and ir absorption indicating the major products to be a mixture of the $N$-methylimines **37.** A 1.00-g portion of the crude product was distilled to separate 213 mg of bright yellow liquid, bp 37–65 °C (0.7–1.0 mm), $n^{25}D$ 1.5434–1.5534, containing (NMR and ir analysis) primarily the imine **37a:**[10] ir ($CCl_4$) 1655 (s) and 1640 $cm^{-1}$ (w) (C=N of both isomers); uv (95% EtOH) end absorption with $\epsilon$ 15 300 at 210 nm and a maximum at 245 nm ($\epsilon$ 14 400); NMR ($CDCl_3$) $\delta$ 8.1–8.3 (1 H, m, CH=N), 6.6–7.7 (5 H, m, aryl CH), and 3.48 (3 H, d, $J$ = 1.5 Hz, $NCH_3$) with a weak doublet ($J$ = 1.5 Hz) at $\delta$ 3.42 corresponding to a second imine isomer; mass spectrum $m/e$ (rel intensity) 119 ($M^+$, 87), 118 (100), 91 (29), 78 (25), 77 (36), 51 (21), and 42 (30). Reaction of a sample of this crude imine **37a** with 2,4-dinitrophenylhydrazine and HCl in EtOH gave a sample of benzaldehyde 2,4-dinitrophenylhydrazone as orange needles from EtOH, mp 238–239 °C. This material was identified with an authentic sample (mp 238–239 °C) by a mixture melting point. The later fraction from the distillation, 553 mg of yellow liquid, bp 65–69 °C (0.7 mm), contained (ir and NMR analysis) mainly the second component believed to be the imine **37b** accompanied by a minor amount of the imine **37c.** Reaction with 2,4-dinitrophenylhydrazine yielded a crude 2,4-dinitrophenylhydrazone as orange-red needles, mp 251–254 °C. This material appears to be a mixture of the 2,4-dinitrophenylhydrazones of salicylaldehyde and $o$-methoxybenzaldehyde. When the reduction was repeated with the amide anion, formed from reaction of the amide **36** with $n$-BuLi before reaction with Li in liquid $NH_3$, the major reduction product (ir and NMR analysis) was again a mixture of the imines **37.**

**B. Acid 38.** After a solution of 1.036 g (6.82 mmol) of the acid **38** in 10 ml of THF had been added to 50 ml of liquid $NH_3$, the resulting white suspension was treated, portionwise and with stirring, with 167 mg (24.1 mg-atoms) of Li. The reaction mixture changed successively from a white suspension to a colorless solution, then to a yellow solution, and finally to a blue solution. This cold (−33 °C) blue solution was treated with 4.56 g (32.1 mmol) of MeI and the resulting pale yellow solution was stirred at −33 °C for 90 min and then treated with 2 ml of $H_2O$. After the $NH_3$ had evaporated, the residue was partitioned between cold (0 °C) dilute aqueous HCl and $CH_2Cl_2$ and the organic phase was washed with aqueous NaCl, dried, and concentrated. The residual yellow oil (a mixture of acids **39a** and **40a**) was esterified with excess ethereal $CH_2N_2$ and this resulting solution was washed with aqueous $NaHCO_3$, dried, and concentrated. An aliquot of the residual neutral product (1.078 g of pale orange liquid) was mixed with a known weight of internal standard (naphthalene) and analyzed by GLC (LAC-728 on Chromosorb P). The product contained ester **39b** (retention time 8.0 min, 47% yield), naphthalene (19.0 min), and ester **40b** (25.2 min, 27% yield). The same general procedure was repeated with 1.059 g (7.02 mmol) of acid **38,** 10 ml of THF, 50 ml of liquid $NH_3$, 528 mg (23.0 mg-atoms) of Na, and 4.56 g (32.1 mmol) of MeI. After following the same isolation and analysis procedures,

the yields of esters **39b** and **40b** were 31 and 41%, respectively. Thus, the demethoxylation side reaction leading to by-product **39** is less serious when the reduction is effected with Na rather than Li.

To identify the reaction products, the reduction was repeated with 10.0 g (69.7 mmol) of acid **38**, 300 ml of liquid $NH_3$, 75 ml of THF, 1.584 g (226 mg-atoms) of Li, and 34.2 g (240 mmol) of MeI. After esterification with $CH_2N_2$, the crude neutral product (11.62 g) was fractionally distilled through a 15-cm Vigreux column. From the early fractions [3.49 g, bp 85–86 °C (18 mm)] containing (GLC) mainly the ester **39b**, a pure sample of the ester **39b** was collected as a colorless liquid: $n^{25}$D 1.4732; ir ($CCl_4$) 1734 $cm^{-1}$ (ester C=O); uv (95% EtOH) end absorption with $\epsilon$ 1400 at 210 nm; NMR ($CCl_4$) $\delta$ 5.5–6.0 (4 H, m, vinyl CH), 3.60 (3 H, s, $OCH_3$), 2.4–2.8 (2 H, m, allylic $CH_2$), 1.26 (3 H, s, $CH_3$); mass spectrum *m/e* (rel intensity) 152 ($M^+$, 4), 93 (100), 92 (27), 91 (38), 77 (41), and 39 (14).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.00; H, 7.95.

After separation of an intermediate distillation fraction [1.35 g, bp 86–121 °C (18 min), a mixture of **39b** and **40b**], the final distillation fraction [4.09 g, bp 121–143 °C (18 min)] contained (GLC) mainly the ester **40b** accompanied (ir and NMR analysis) by some of the acid **39a.** This fraction was reextracted with aqueous $NaHCO_3$ and redistilled to separate 1.945 (15%) of the ester **40b** as a colorless liquid, bp 113–116 °C (16 min).[11] A collected (GLC) sample of the ester **40b** was obtained as a colorless liquid: $n^{25}$D 1.4829; ir ($CCl_4$) 1740 (ester C=O), 1690 (enol ether C=C), and 1650 $cm^{-1}$ (C=C); NMR ($CCl_4$) $\delta$ 5.2–5.9 (2 H, m, vinyl CH), 4.64 (1 H, t, $J$ = 3 Hz, enol ether vinyl CH), 3.59 (3 H, s, $OCH_3$), 3.52 (3 H, s, $OCH_3$), 2.6–2.9 (2 H, m, allylic $CH_2$), and 1.33 (3 H, s, $CH_3C$); uv max (95% EtOH) 272 nm ($\epsilon$ 53) with intense end absorption ($\epsilon$ 2360 at 210 nm); mass spectrum *m/e* (rel intensity) 182 ($M^+$, 8), 123 (100), 108 (25), and 91 (18).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.65; H, 7.64.

**C. Diacid 31.** To a cold (−33 °C) suspension of 10.0 g (47.7 mmol) of the diacid **31a** in 600 ml of liquid $NH_3$ containing 10 ml of $H_2O$ was added, portionwise and with stirring during 60 min, 2.701 g (386 mg-atoms) of Li. An additional 10 ml of $H_2O$ was added and this mixture was stirred overnight while the $NH_3$ was allowed to evaporate. A solution of the residue in $H_2O$ was filtered, cooled in ice, and acidified with aqueous 12 M HCl. The resulting cold suspension (total volume 200 ml) was filtered to separate 9.6 g of the crude acids **32a** and **33a** as a tan solid. To analyze this mixture of acids **32a** and **33a,** an aliquot was esterified with excess ethereal $CH_2N_2$; the crude neutral product, a mixture of esters **32b** and **33b,** exhibited NMR peaks ($CCl_4$) at $\delta$ 3.67 ($CH_3O$ of ester **32b**) and 3.57 ($CH_3O$ of ester **33b**).

A commercial sample of the anhydride **30** was recrystallized from concentrated aqueous $HNO_3$ to separate the pure anhydride **30** as white needles: mp 273–274 °C (lit.[12] mp 274 °C); ir ($CHCl_3$) 1775 and 1737 $cm^{-1}$ (anhydride C=O, absorbance ratio $A_{1737}/A_{1775}$ = 0.86). Following a previously described procedure,[13] the anhydride **30** was dissolved in methanolic KOH and this solution was treated simultaneously with MeOH solutions of $(MeO)_2SO_2$ and of KOH. The neutral product was crystallized from MeOH to separate the diester **31b** as white needles: mp 100–101 °C (lit.[13] mp 102 °C) ir ($CCl_4$), 1728 $cm^{-1}$ (ester C=O); uv max (95% EtOH) 299 nm ($\epsilon$ 3500); NMR ($CCl_4$), $\delta$ 7.2–8.0 (6 H, m, aryl CH) and 3.81 (6 H, s, $OCH_3$).

Alternatively, mixtures of the esters could be analyzed by GLC (Silicone, fluid, No. 710, on Chromosorb P) with the following retention times being observed for the esters: **32b,** 13.8 min; **33b,** 15.0 min; and **31b,** 31.8 min.

The crude product from the reduction contained (NMR analysis of the diesters) ca. 90% of acid **32a** and ca. 10% of acid **33a.** A 1.289-g aliquot of this mixture was fractionally recrystallized from MeOH to separate 451 mg of the pure (NMR analysis of diester) acid **32a** as white prisms: mp 218–223 °C dec (dependent on rate of heating); ir (KBr pellet) 1720, 1695 (carboxyl C=O), 1665, and 1630 $cm^{-1}$ (C=C); uv (95% EtOH) end absorption with $\epsilon$ 1330 at 210 nm; NMR (pyridine-$d_5$) $\delta$ 13.0 (2 H, s, OH), 5.7–6.4 (4 H, m, vinyl CH), 4.4–4.9 (2 H, m, $CHCO_2R$), and 2.5–2.8 (4 H, m, allylic $CH_2$).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.53; H, 5.53.

To a cold (−33 °C) solution of $NaNH_2$, from 430 mg (18.7 mg-atoms) of Na and 180 ml of liquid $NH_3$, was added 1.54 g (7.00 mmol) of a mixture of diacids (ca. 80% of **32a** and 20% of **33a**). After the resulting gray-green suspension had been stirred at −33 °C for 1.5 h, a solution of 100 mg (5.6 mmol) of $H_2O$ in THF was added, dropwise and with stirring during 1.5 h. Then 5 ml of $H_2O$ was added, the $NH_3$ was allowed to evaporate, and a solution of the residue in 50 ml of cold (0 °C) $H_2O$ was filtered and acidified with cold aqueous 12 M HCl. The crystalline acid that separated was collected as 1.252 g of tan solid containing (NMR analysis of diesters) ca. 67% of diacid **33a** and ca. 33% of diacid **32a.** Fractional recrystallization of an 836-mg aliquot of this mixture from MeOH separated 230 mg of the pure (NMR analysis of the diester) diacid **33a** as white prisms: mp 211–215 °C dec (dependent on rate of heating); ir (KBr pellet) 1710 and 1685 $cm^{-1}$ (carboxyl C=O); uv (95% EtOH) end absorption with $\epsilon$ 1320 at 210 nm; NMR (pyridine-$d_5$) $\delta$ 11.9 (2 H, broad, OH), 5.8–6.5 (4 H, m, vinyl CH), 3.9–4.3 (2 H, m, $CHCO_2R$), and 2.5–2.9 (4 H, m, allylic $CH_2$).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.46; H, 5.49.

A mixture of approximately equal amounts of the diacids **32a** and **33a** was esterified with excess ethereal $CH_2N_2$ and this crude neutral product was chromatographed on silica gel with an $Et_2O$–PhH eluent (1:49 v/v). The initial chromatographic fractions were recrystallized from $Et_2O$–hexane mixtures to separate the pure diester **32b** as white needles: mp 71–72.5 °C; ir ($CCl_4$) 1740 (ester C=O) and 1665 $cm^{-1}$ (weak, C=C); uv (95% EtOH) end absorption with $\epsilon$ 1090 at 210 nm; NMR ($CCl_4$) $\delta$ 5.5–6.1 (4 H, m, vinyl CH), 3.5–3.9 (8 H, m, $CHCO_2R$ with a $CH_3O$ singlet at 3.67), and 2.5–2.8 (4 H, m, allylic $CH_2$); mass spectrum *m/e* (rel intensity) 248 ($M^+$, 4), 216 (28), 188 (26), 156 (10), 129 (100), and 128 (25).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.49; H, 6.56.

The later chromatographic fractions were recrystallized from $Et_2O$–hexane to separate the pure diester **33b** as white prisms: mp 124–126 °C; ir ($CCl_4$) 1740 (ester C=O) and 1665 $cm^{-1}$ (C=C); uv (95% EtOH) end absorption with $\epsilon$ 1050 at 210 nm; NMR ($CCl_4$) $\delta$ 5.5–6.1 (4 H, m, vinyl CH), 3.4–3.8 (8 H, m, $CHCO_2R$ with a $CH_3O$ singlet at 3.57), and 2.5–3.0 (4 H, m, allylic $CH_2$); mass spectrum *m/e* (rel intensity) 248 ($M^+$, 5), 216 (7), 189 (16), 188 (14), 129 (100), and 128 (21).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73: H, 6.50. Found: C, 67.65; H, 6.58.

After a suspension of 162 mg (0.74 mmol) of the anti diacid **32a** in 5 ml of $CH_2Cl_2$ containing 163 mg (0.79 mmol) of dicyclohexylcarbodiimide had been stirred at 25°C for 75 min, the mixture was filtered to remove dicyclohexylurea. The yellow filtrate was concentrated under reduced pressure and triturated with pentane to leave 163 mg of the crude syn anhydride **34** as a yellow solid, ir ($CHCl_3$) 1804 and 1762 $cm^{-1}$ (anhydride C=O). This crude product was stirred at 25 °C with 2 ml of DME and 1 ml of aqueous 3 M HCl for 10 h and the concentrated under reduced pressure and washed with $H_2O$. The residual red-brown solid (134 mg) was combined with additional material obtained from extraction of the aqueous washings with $CH_2Cl_2$ and the total crude product (154 mg) was esterified with excess ethereal $CH_2N_2$. After this mixture had been filtered and concentrated, the residue amounted to 121 mg of yellow solid with ir and NMR absorption corresponding to the syn diester **33b.** Analysis (GLC, Silicone, fluid, No. 710, on Chromosorb P) indicated the presence of the syn diester **33b** (retention time 13.3 min) accompanied by four minor, unidentified impurities (7.8, 12.1, 15.6, and 24.2 min). After an aliquot of the crude esterified product had been mixed with a known amount of internal standard ($n$-$C_{24}H_{50}$, retention time 29.5 min), the calculated (GLC) yield of the syn diester **33b** was 31%.[14] A collected (GLC) sample of the peak corresponding in retention time to the syn diester **33b** was identified with an authentic sample by comparison of ir spectra. In another comparable experiment, the crude syn anhydride **34** was partially purified by adding pentane to a $CHCl_3$ solution of the crude anhydride and by sublimation under reduced pressure at 85 °C. This partially purified solid anhydride **34** exhibited NMR Peaks ($CDCl_3$) at $\delta$ 6.0–6.3 (ca. 4 H, m, vinyl CH), 3.7–4.2 (ca. 2 H, m, allylic CHCO), and 2.5–2.9 (ca. 4 H, m, allylic $CH_2$) with ir absorption ($CHCl_3$) at 1804 and 1762 $cm^{-1}$ (anhydride C=O, absorbance ratio, $A_{1762}/A_{1804}$ = 1.69). As a control experiment to demonstrate that the anti acid **32a** was not epimerized by the hydrolysis conditions, a suspension of 105 mg (0.48 mmol) of the anti acid **32a** in 2 ml of DME and 1 ml of aqueous 3 M HCl was stirred for 10 h at 25 °C and then subjected to the previously described isolation and esterification procedures. The final neutral product obtained was 101 mg (85%) of the anti diester **32b,** mp 71–71.5 °C, that was identified with an authentic sample by GLC analysis and comparison of ir spectra.

A suspension of 119 mg (0.54 mmol) of the syn diacid **33a** in 5 ml of $CH_2Cl_2$ containing 125 mg (0.61 mmol) of dicyclohexylcarbodiimide was stirred at 25 °C for 75 min and then subjected to the previously described isolation procedure. The crude syn anhydride **34** (121 mg of yellow solid with ir absorption corresponding to the previously described sample) was hydrolyzed at 25 °C for 10 h with 2 ml of DME and 1 ml of aqueous 3 M HCl and subjected to the previously described isolation and esterification procedure. The crude neutral product (95 mg of yellow solid) contained (GLC) the syn diester **33b** accompanied by the same minor impurities noted in the preparation from the anti-acid. After an aliquot of this neutral product had been mixed with a known amount of internal standard ($n$-$C_{24}H_{50}$), the calculated (GLC) yield of the syn diester **33b** was 25%.[14]

**Registry No.**—**1a,** 19765-82-3; **2a,** 19765-81-2; **7,** 19765-84-5; **9,** 19766-22-4; **12,** 19766-24-6; **13a,** 59034-37-6; **14a,** 59034-38-7; **15,** 33495-51-1; **17,** 59034-39-8; **18,** 59034-40-1; **19,** 59034-41-2; **20,** 59034-42-3; **21,** 59034-43-4; **22,** 59034-44-5; **23,** 59034-45-6; **24,** 59034-46-7; **25,** 59091-69-9; **28,** 59034-47-8; **29,** 59034-48-9; **30,** 81-84-5; **31a,** 518-05-8; **31b,** 10060-33-0; **32a,** 59034-49-0; **32b,** 59034-50-3; **33a,** 59034-51-4; **33b,** 59034-52-5; **34,** 59034-53-6; **36,** 3400-35-9; **37a,** 622-29-7; **38,** 579-75-9; **39b,** 59034-54-7; **40b,** 21173-69-3.

## References and Notes


(1) This research has been supported by Public Health Service Grant RO1-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institution Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

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(6) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The $^1H$ NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the $^{13}C$ NMR spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in $\delta$ values (ppm) relative to a $Me_4Si$ internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(7) The esterification procedure of J. L. Marshall, K. C. Erickson, and T. K. Folsom [*Tetrahedron Lett.*, 4011 (1970)] was used.

(8) This slow addition of a solution of the diacid was necessary to minimize formation of a by-product resulting from protonation of the initially formed carbanion before the $CH_3I$ was added.

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(10) (a) R. B. Moffett [*Org. Synth.*, **34,** 65 (1954)] reports bp 92–93 °C (34 mm) and $n^{25}D$ 1.5497 for the imine **37a.** (b) The imine **37a** is reported to have NMR peaks ($CCl_4$) at $\delta$ 8.24 (CH=N) and 3.45 ($CH_3$) by D. Y. Curtin, E. J. Grubbs, and C. J. McCarty, *J. Am. Chem. Soc.*, **88,** 2775 (1966). (c) This imine **37a** has an ir band at 1645 $cm^{-1}$ [F. H. Suydam, *Anal. Chem.*, **35,** 193 (1963)] with a uv maximum (EtOH) at 246 nm ($\epsilon$ 19 400) [P. Brocklehurst, *Tetrahedron,* **18,** 299 (1962)].

(11) The initial characterization of this ester was performed in our laboratories by Dr. Thomas M. Bare.

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(14) Since both esters **32b** and **33b** undergo partial decomposition under the conditions of our GLC analysis, we regard these yields as minimum values.


# Crown Ether Catalyzed Synthesis of Dialkylvinylidenecyclopropane Derivatives[1]


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*Received January 20, 1976*


In the phase-transfer catalyzed synthesis of dimethylvinylidenecyclopropanes from 3-chloro-3-methyl-1-butyne (**1a**) and olefins in the presence of 51% aqueous potassium hydroxide, the effect of crown ethers as the catalyst was examined in comparison with quaternary ammonium salts such as benzyltriethylammonium chloride. Crown ethers such as dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and 18-crown-6 were found to be more effective catalysts than quaternary ammonium salts. Application of this method to the synthesis of some new dimethyl- and pentamethylenevinylidenecyclopropane derivatives has been described.


Recently it has been reported that the phase-transfer catalyzed generation of dimethylvinylidenecarbene can be carried out effectively by using appropriate quaternary ammonium salts such as benzyltriethylammonium chloride (BTAC)[2,3] and tricaprylylmethylammonium chloride (Aliquat-336)[4,5] as the catalyst. This method provides a facile synthesis of dimethylvinylidenecyclopropanes from 3-chloro-3-methyl-1-butyne (**1a**)[2-4] or 1-bromo-3-methyl-1,2-butadiene[5] and appropriate olefins compared to the noncatalyzed method.[6] However, quaternary ammonium salts are not always satisfactory catalysts. For example, the yields of dimethylvinylidenecyclopropanes are much lower for olefinic substrates having hydrophilic or potentially hydrophilic functions such as hydroxyl, ester, and pyridyl groups.[2a] As shown in this paper, certain crown ethers, which are powerful complexing agents for alkali metal cations, and provide highly reactive and unsolvated anions,[7,8] may be more effective or at least as effective catalysts as quaternary ammonium salts in the phase-transfer catalyzed synthesis of dialkylvinylidenecyclopropanes.[9,10]

## Results and Discussion

**The Catalytic Effect of Crown Ethers on Dimethylvinylidenecyclopropanation of Styrene.** In order to compare the catalytic effect of crown ethers with quaternary ammonium salts, dimethylvinylidenecyclopropanation of styrene was investigated under two-phase reaction conditions by using 18-crown-6 and BTAC as the catalyst. The reaction was carried out by slow addition of **1a** (10 mmol) in benzene (5 ml) to a vigorously stirred mixture of 51% aqueous potassium hydroxide (30 ml), benzene (5 ml), and styrene (30 mmol) in the presence of the catalyst (0.7 mmol). The product **2**[6] was analyzed on GLC at appropriate times.[11] The results are shown in Figure 1. From these data it is clear that 18-crown-6 is a more effective catalyst than BTAC at all temperatures examined. Even at 45 °C, 18-crown-6 was effective, in contrast to BTAC,[2a] although the product **2** decomposed rapidly at this temperature. Hence, it seems most convenient to carry out the reaction at 25 °C (i.e., around room temperature), at which temperature the optimum yield of **2** was obtained after 5–7 h.

The catalytic effect of several other crown ethers was examined at 20–25 °C as summarized in Table I. Except for 15-crown-5 and dibenzo-24-crown-8, the three 18-crown-6 ethers gave better results than BTAC. Such ring-size effect of crown ethers as the catalyst may be attributable to the stability difference of metal–polyether complexes.[7b]