A Highly Stereoselective and Completely Regiospecific Method for the Dehydration of β-Hydroxy Esters *via* β-Alanoxy Enolates. Application to the Synthesis of Trisubstituted Olefins and Two Ant Mandibular Gland Secretions

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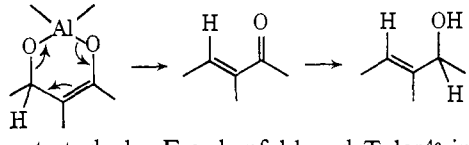
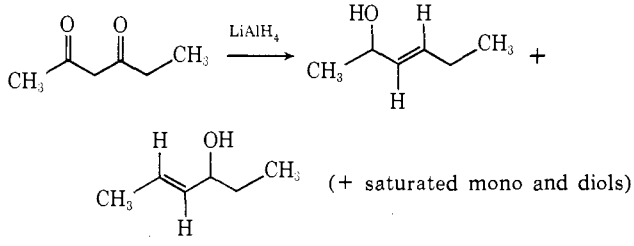
Abstract: The treatment of a β-hydroxy ester with aluminum ethoxide or diethoxyaluminum chloride, followed by warming with added lithium diisopropylamide, produces the corresponding α,β-unsaturated ester in moderate yield (44–56%). This process is completely regiospecific (no β,γ isomers formed) and in suitably substituted cases is completely stereospecific, producing only the *E* olefin isomer. It is conceived that the reaction proceeds through a β-alanoxy enolate intermediate, similar to that postulated in the lithium aluminum hydride reduction of β-dicarbonyl enolates; the stereoselectivity results from the minimization of 1,4 interactions in a boat cyclohexane-like transition state. This alanoxy enolate dehydration process has been applied in the stereo- and regiospecific syntheses of two ant mandibular gland secretions.

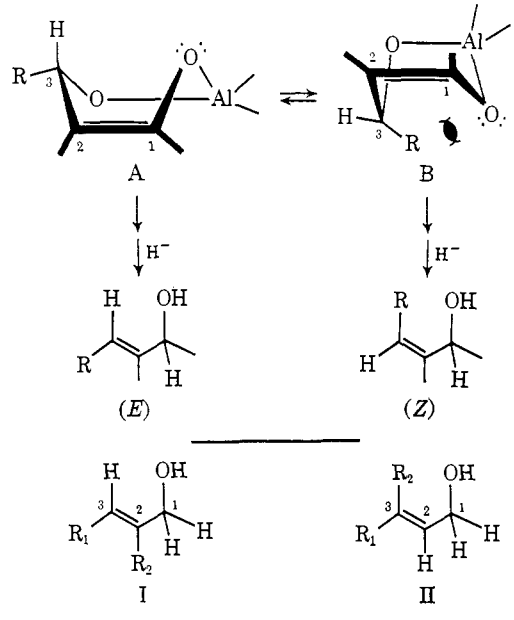
The reduction of enolates derived from β-dicarbonyl systems with lithium aluminum hydride is a well-established method for the synthesis of allylic alcohols.[1] This reaction has been investigated with β-keto esters,[2] malonic esters,[3] and β-diketones,[2a,4] and has been employed in several natural product syntheses.[5] The salient feature of this reaction involves the elimination of an aluminum alkoxide from a β-alanoxy enolate intermediate. This process is generally formulated as proceeding through a six-membered ring transition state, with subsequent hydride reduction of the carbonyl group producing the allylic alcohol.



A recent study by Frankenfeld and Tyler[4c] indicated that certain stereoelectronic features of the cyclic transition state resulted in the production of olefins with a high degree of stereoselectivity. For example, the reduction of 2,4-hexadione gave the structurally isomeric allylic alcohols both with exclusively the *E* stereochemistry. This stereoselective preference was rationalized within the context of a six-membered cyclic transition state[4c] in a fashion similar to that advanced in



the Claisen and Cope rearrangements.[6] However, the planarity of the four atoms in the enolate system makes a boat-like cyclohexane formulation more attractive than a chair-like one. According to this analysis, the stereoselectivity results from a preference of the substituent at C-3 for occupying the exo position, as in A, thus avoiding the severe 1,4-nonbonded interaction attendant with the alternative transition state conformation B. Cyclic elimination *via* A and subsequent reduction produces the *E*-olefin isomer.



(1) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1972, pp 82–85.

(2) (a) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 939 (1953); (b) V. M. Micovic and M. Lj. Mihailovic, *Bull. Soc. Chim. Belg.*, **19**, 329 (1954); (c) E. Romann, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1900 (1957); (d) J. C. Richter and R. C. Clarke, *Tetrahedron Lett.*, 935 (1964); (e) J. A. Marshall and S. B. Listas, *J. Org. Chem.*, **37**, 1840 (1972).

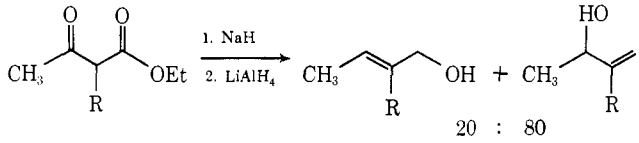
(3) (a) W. F. Gannon and E. A. Steck, *J. Org. Chem.*, **27**, 4137 (1962); (b) W. J. Bailey, M. E. Humes, and W. A. Klein, *ibid.*, **28**, 1724 (1963); (c) J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *ibid.*, **32**, 113 (1967).

(4) (a) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 3723 (1953); (b) L. A. Pohoryles, S. Sarel, and R. Ben-Shoshan, *J. Org. Chem.*, **24**, 1878 (1959); (c) J. W. Frankenfeld and W. E. Tyler III, *ibid.*, **36**, 2110 (1971).

(5) (a) G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961) [cedrol]; (b) J. A. Marshall and N. Cohen, *ibid.*, **87**, 2663 (1965) [alantolactone]; (c) *J. Org. Chem.*, **30**, 3475 (1965) [sesquiterpenoid α-methylene-γ-butyrolactones]; (d) J. A. Marshall and R. D. Carroll, *Tetrahedron Lett.*, 4223 (1965) [costol and costic acid].

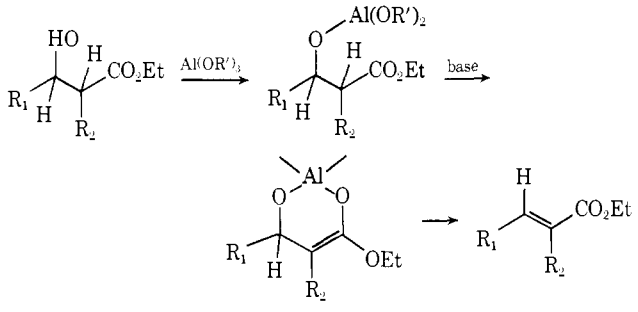
(6) C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969).

Such an analysis suggests that the reduction of β-keto ester enolates should permit the stereoselective synthesis of isoprenoid trisubstituted olefin alcohols of structural type I; in these, the second alkyl substituent (R_2) would be accommodated in the sterically "neutral" position 2. Those of type II should not be produced stereoselectively, as disubstitution at C-3 necessitates an endo substituent in each of the alternative transition states.[7]



Marshall and Listas[2e] explored some of these possibilities in their study of the reduction of 2-alkyl-3-keto ester enolates. As expected, only the *E* isomer of the 2-alken-1-ol was produced; however, this isomer was the minor component (20%) of the product mixture, which consisted mainly of the allylically related 1-alken-3-ol. This lack of regioselectivity, which results from preferential hydride attack at the ester carbonyl in the enolate (previously documented in cyclic keto esters[2b,c]), makes this reaction unattractive as a method for the stereoselective synthesis of trisubstituted olefins.

In principle, however, this lack of positional selectivity could be overcome by elaboration of the crucial β-alanoxy enolate intermediate by indirect means. For example, treatment of a β-hydroxy ester with an aluminum alkoxide, followed by the addition of a strong base, might permit enolization of the β-alanoxy ester, which should then result in an analogous elimination. As such a reaction would not be conducted in a reducing medium, the final product would be the unsaturated ester, and the overall reaction would be a dehydration, which should be highly stereoselective as well as completely regiospecific. For this process to be successful, of course, elimination must compete successfully with the retro-aldol process.

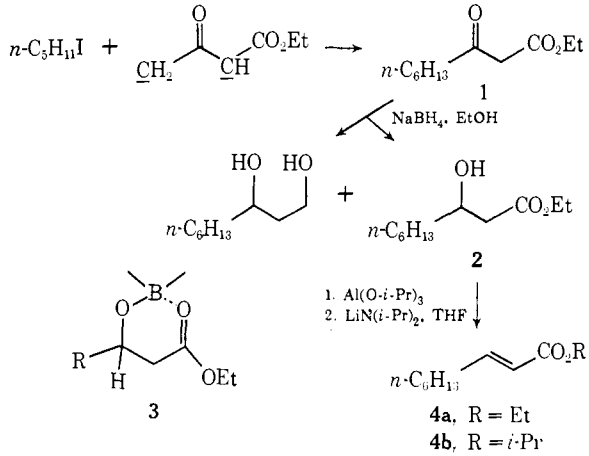


In this report, we describe the successful execution of this alanoxy dehydration procedure in model systems and its application to the synthesis of two ant mandibular gland secretions.

Results and Discussion

Studies in Model Series. Ethyl 3-oxononanoate (**1**) was prepared in 70% yield by alkylation of the dianion of ethyl acetoacetate with 1-iodopentane, according to the procedure of Weiler.[8] Selective reduction of the β-keto ester **1** to the β-hydroxy ester **2** was more problematical than anticipated, as treatment with excess ethanolic sodium borohydride for 1 hr at 25° resulted in considerable overreduction to 1,3-nonanediol. The facility with which the ester function in this molecule is reduced may indicate that the ester carbonyl is unusually reactive because of polarization by chelation with boron in the purported intermediate **3**. Subsequent experiments showed that the use of a more limited excess of borohydride resulted in the production of the hydroxy ester **2** (60% yield) to the near exclusion of the diol.

Treatment of β-hydroxy ester **2** with 2 equiv of aluminum isopropoxide in tetrahydrofuran for 15 min at 25°, followed by the addition of 2 equiv of lithium diisopropylamide and warming to 60° for 1 hr, gave, upon product isolation, the desired *E* alkenoic ester **4**. This reaction was complicated by a facile interchange of alkoxide between ester and aluminum, so that both the ethyl (**4a**) and the isopropyl esters (**4b**) were produced in varying proportions depending on the reaction time. Further, the combined yield of the two esters was only 33%, and the crude product was contaminated by several components of lower volatility (by glpc analysis on SE-30). Substitution of potassium *tert*-butoxide for lithium diisopropylamide gave the esters **4a,b** in only very low yield. However, substitution of aluminum ethoxide for aluminum isopropoxide avoided the problems associated with the ester interchange reaction and raised the yield of the (*E*)-ethyl ester **4a** to 52%. No detectable quantities of the *Z* isomer or the β,γ isomer were noted on nmr or glpc analysis.



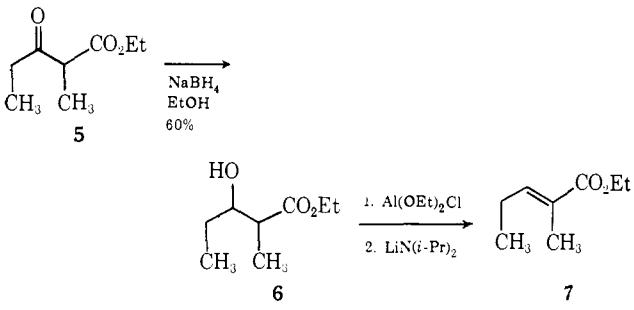
4a, R = Et
4b, R = *i*-Pr

Ethyl 2-methyl-3-oxopentanoate (**5**), synthesized by Claisen condensation of methyl propionate,[9] was selectively reduced with sodium borohydride to the hydroxy ester **6**. Dehydration of **6** by the sequential addition of 2 equiv of both aluminum ethoxide and lithium diisopropylamide, as described previously, gave the desired alkenoate **7** in less than 10% yield. The presence of more volatile products, detected by glpc analysis, suggested that retro-aldol condensation had occurred in this case. In an attempt to minimize this process by excluding alkoxide ion, diisobutylaluminum hydride was substituted for aluminum ethoxide; none of the ester **7** was formed under these conditions. However, when diethoxyaluminum chloride (prepared *in situ* by mixing one part aluminum chloride with two parts

(7) The production of an olefin alcohol of type II from a β-keto ester would require addition of a carbanion (rather than a hydride ion) to the carbonyl group; however, the stereochemical arguments are still valid.

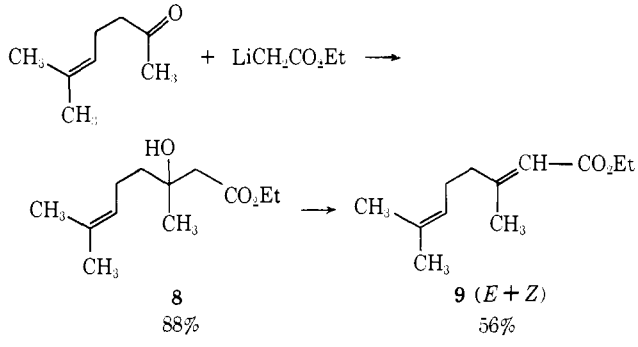
(8) L. Weiler, *J. Amer. Chem. Soc.*, **92**, 6702 (1970).

(9) C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, 1, 266 (1942).



aluminum ethoxide) was substituted for aluminum ethoxide, and 4 equiv of lithium diisopropylamide was used, the ester **7** was produced in 50% yield (glpc). None of the *Z* or β,γ isomers were evident upon nmr analysis. Somewhat more vigorous conditions (1 hr, reflux) were required to effect the elimination by this procedure.

Ethyl 3,7-dimethyl-3-hydroxy-6-octenoate (**8**), a β-hydroxy ester of the 3,3-disubstituted type, was synthesized in 88% yield by the addition of the lithium enolate of ethyl acetate with 6-methyl-5-hepten-2-one.[10] Dehydration of **8** using diethoxyaluminum chloride and lithium diisopropylamide gave a mixture of ethyl geranate esters **9** (*E*:*Z* 1:1.5) in 56% yield. The lack



of stereoselectivity in the conversion of **8** to **9** is consistent with the stereochemical analysis described earlier; however, the preponderance of the *Z* isomer is difficult to rationalize on the basis of boat-like transition states, as it implies that the larger 4-methyl-3-pentenyl group, rather than the methyl group, prefers to occupy the endo orientation.

The high stereo- and regioselectivity of this β-alanoxy elimination procedure in systems like **2** and **6** is attested to by the fact that treatment of the ester **2** with sodium hydride, followed by reduction with lithium aluminum hydride according to the procedure of Marshall and Listas,[2e] gave a product mixture which contained substantial quantities of at least five components.

Several other procedures for the dehydration of β-hydroxy esters were investigated for comparison with the alanyl enolate procedure. Treatment of the hydroxy ester **2** with refluxing acetic anhydride gave only the corresponding acetate, while reaction with phosphorus oxychloride in refluxing benzene[11a] gave the desired unsaturated ester **4a** contaminated with several other components with comparable and higher volatility (by glpc on SE-30). Although treatment of **6** with toluenesulfonyl chloride in pyridine[11b] gave substantial quantities of the ester **7**, application of this procedure to the ester **10** gave a mixture of products containing both the α,β- and β,γ-unsaturated isomers in a 40:60 ratio.

Synthesis of Two Ant Mandibular Gland Secretions. (*E*)-2,4-Dimethyl-2-hexenoic Acid and (*E*)-4,6-Dimethyl-4-octen-3-one (Manicone). The required precursor for the synthesis of (*E*)-2,4-dimethyl-2-hexenoic acid (**12**)[12] was prepared in 60% yield by ethylation of the dianion of ethyl 2-methyl-3-oxopentanoate (**5**) and subsequent selective reduction with sodium borohydride (57% yield). Dehydration by the aluminum ethoxide procedure gave, as in the case of **6**, only cleavage products; however, using diethoxyaluminum chloride, the desired ester (**11**) was formed in 44% yield.

The bulk of the byproducts in this reaction consisted of a single higher molecular weight material. Production of this species was minimized by using the shortest possible reaction times, and its identity was not pursued further.

Other bases were substituted for lithium diisopropylamide in an attempt to increase the yield in this dehydration reaction. However, neither lithium bis(trimethylsilyl)amide,[13a] lithium diisopropylamide–hexamethylphosphoramide complex,[13b] nor lithium dicyclohexylamide[13c] gave substantial yields of the desired alkenoate; only lithium tetramethylpiperidide[13c] gave a yield comparable to, though slightly lower than, that of lithium diisopropylamide.

Dehydration of **10** with toluenesulfonyl chloride–pyridine gave **11** as a 2:3 mixture with the β,γ-unsaturated ester.[14]

Hydrolysis of ester **11** with methanolic sodium hydroxide produced the desired natural acid **12**. Detailed spectroscopic and chromatographic comparison of this acid and its methyl ester established that these compounds were identical with those prepared by MacConnell by an Emmons condensation.[12,15] A previously reported comparison had shown MacConnell's synthetic acid was identical with the natural product.[12] Spectroscopic and chromatographic analysis failed to show any detectable trace of geometric or positional isomers.[16]

Reaction of lithium diethylcuprate at −78° with the acid chloride of **12**[17] gave (*E*)-4,6-dimethyl-4-octen-3-

(10) M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).

(11) (a) G. A. R. Konard and K. S. Norgund, *J. Chem. Soc.*, 2461 (1932); (b) O. W. Wintersteiner and M. Moore, *J. Amer. Chem. Soc.*, **65**, 1503, 1507 (1943).

(12) J. M. Brand, R. M. Duffield, J. G. MacConnell, M. S. Blum, and H. M. Fales, *Science*, **179**, 388 (1973).

(13) (a) E. H. Amonoo-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965); (b) J. L. Herrman, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973); (c) R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, **95**, 582 (1973).

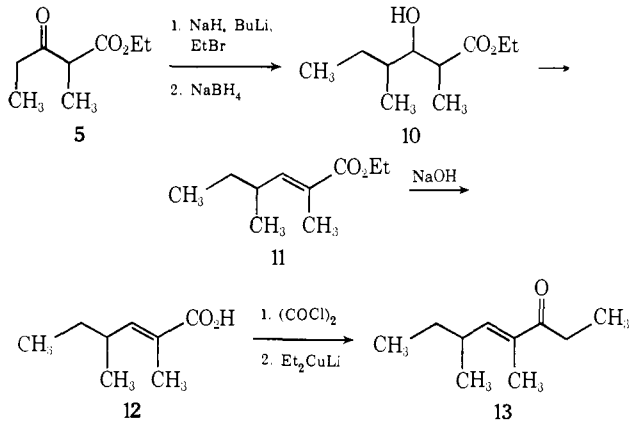
(14) (a) L. J. Dolby and G. N. Riddle, *J. Org. Chem.*, **32**, 3481 (1967); (b) K. L. Rinehart and L. J. Dolby, *ibid.*, **22**, 13 (1957).

(15) We are indebted to Dr. J. G. MacConnell for sending us samples of the acid **12** and its methyl ester.

(16) From their method of synthesis, the ester **11**, acid **12**, and ketone **13** should all be of the *E* configuration. The chemical shift of the vinyl hydrogen is a sensitive indicator of stereochemistry, particularly in **11** and **12**. A comparison of our shift values with those predicted by the empirical rules of C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966) [(our value, predicted for *E*, predicted for *Z*) **11**: δ 6.40, 6.58, 5.99; **12**: δ 6.62, 6.78, 6.17] shows that the observed shifts fall much closer to the values predicted for the *E* isomer, although they are *ca.* 0.2 ppm further upfield. The shift observed for the ketone **13** (δ 6.24), however, is closer to that predicted for the *Z* isomer (δ 6.27) than the *E* isomer (δ 6.56). The predicted chemical shift difference between *E* and *Z* ketones is much smaller (0.29 ppm) than in the esters (0.59 ppm) and acids (0.61 ppm), so that a downfield correction by 0.2 ppm (based on our values in **11** and **12**) places our resonances at δ 6.44, more in the range of the *E* isomer.

(17) G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, **94**, 5106 (1972).

one (Manicone; **13**)[18] in 92% overall yield, without



5 10 11 12 13

any detectable traces of isomeric substances. The spectroscopic properties of this material and the melting point of its 2,4-dinitrophenylhydrazone are consistent with those reported for the natural material.[18]

Conclusion

The elimination of β-alanoxy enolates is a method for dehydrating β-hydroxy esters which produces the α,β unsaturated ester completely regiospecifically and, in cases with a suitable substituent pattern, with high *E* stereoselectivity as well. Although the yields obtained so far with this reaction are only moderate (44 to 56%), the variety of new and convenient methods[8,10,19] for preparing the β-hydroxycarbonyl compound starting materials, the relatively mild conditions of the reaction, and its regio- and stereoselectivity should make it a useful synthetic method.

Experimental Section

THF was dried by distillation from sodium naphthalide. The following reagents were obtained from the sources indicated: aluminum isopropoxide (Alfa Inorganics), aluminum ethoxide (Organic-Inorganic Chemical Corp.), aluminum chloride (Baker Chemical Co.), butyllithium (Ventron), ethyllithium (Foote), diisopropylamine (Aldrich), dicyclohexylamine (Aldrich), hexamethyldisilazine (Aldrich), tetramethylpiperidide (Aldrich), sodium borohydride (Ventron), triethylphosphonoacetate (Aldrich), 6-methyl-5-hepten-2-one (Farchan). Lithium diisopropylamide was either commercial material (Organic-Inorganic Chemical Corp.) or was prepared from butyllithium and the amine. Sodium hydride was obtained as a 57% dispersion in mineral oil (Ventron).

Glassware for reactions involving the aluminum reagents and amide bases was dried by flaming under a nitrogen atmosphere; the nitrogen atmosphere was maintained during the reaction. Unless indicated otherwise, all quenched reaction mixtures were worked up by ether extraction, and the extracts were dried with Na_2SO_4 (hydroxy esters) or $MgSO_4$ (all others).

Glpc analysis was performed on a Hewlett-Packard Model 5750 instrument, equipped with a flame ionization detector, using 0.125-in. stainless steel columns with a nitrogen flow rate of 30 cm^3 min^{-1}. The following columns were used: column A, 3 ft, 5% SE-30, 80–100 mesh Gaschrom Q; column B, 10 ft, 5% SE-30, 80–100 mesh Gaschrom Q; column C, 10 ft, 4.3% Carbowax 4000, 80–100 mesh Chromosorb W DMCS; column D, 3 ft, 5% DEGS 80–100 mesh Chromosorb W DMCS. Tlc analysis was performed on glass-backed silica gel plates (Brinkman F-254).

Nmr spectra were obtained in CCl_4 solution on a Varian A-60 or HA-100 instrument; chemical shifts are reported in parts per million, downfield from internal TMS (δ scale). Infrared spectra were taken as neat films on a Perkin-Elmer Model 521 spectrometer. Mass spectra were obtained on a Varian-MAT CH-5 spectrometer, and melting points were determined on a Fisher-Johns apparatus and are corrected. Elemental analysis was provided by the microanalytical laboratory of the University of Illinois.

Ethyl 3-Oxononanoate (1). The procedure of Weiler[8] was used. Sodium hydride (4.8 g, 113 mmol) was slurried in 250 ml of THF and cooled to 0° under nitrogen. Ethyl acetoacetate (13 g, 100 mmol) was added dropwise, and the colorless solution was stirred at 0° for 10 min. Butyllithium (66 ml of a 1.6 *M* solution in hexane; 105 mmol) was added dropwise; the orange solution was stirred an additional 10 min, and then 21.8 g of 1-iodopentane (110 mmol) in 20 ml of THF was added. Stirring was continued for 3 hr at room temperature, and the reaction mixture was quenched with 70 ml of 20% H_2SO_4. Product isolation and distillation gave a fraction (14 g, 70%) boiling at 87° (0.8 Torr). As this material was somewhat discolored by a deeply colored forerun, it was further purified by passage through a silica gel column (ethyl acetate–hexane): nmr δ 0.9 (t, *J* = 5 Hz, 3 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.38 (broad, 8 H), 2.48 (t, *J* = 7 Hz, 2 H), 3.27 (s, 2 H), and 4.15 (quartet, *J* = 7 Hz, 2 H).

Ethyl 3-Hydroxynonanoate (2). Sodium borohydride (1.134 g, 30 mmol) was dissolved in 30 ml of absolute ethanol under nitrogen, and 5 g of ethyl 3-oxononanoate (25 mmol) in 25 ml of ethanol was added slowly. The solution was stirred for 1 hr at room temperature and then quenched by the cautious addition of 10% aqueous acetic acid with ice bath cooling. Product isolation gave 5.4 g of an oil. Tlc analysis (cyclohexane–ethyl acetate, 2:3) indicated the absence of starting material and the presence of a small amount of diol. Chromatography on silica gel eluted with hexane–benzene–ethyl acetate gave 3.0 g (60%) of pure hydroxy ester **2**: nmr δ 0.9 (t, *J* = 5 Hz, 3 H), 1.26 (t, *J* = 7 Hz, 3 H), 1.34 (broad s, 10 H), 2.32 (d, *J* = 7 Hz, 1 H), 2.33 (d, *J* = 5.5 Hz, 1 H), 2.95 (s, 1 H), 3.9 (m, 1 H), and 4.1 (quartet, *J* = 7 Hz, 2 H); ir 3500, 1740, and 1035 cm^{-1}; mass spectrum (70 eV) *m/e* 203 (*M* + 1) and 117 (base peak).

Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.04; H, 11.04.

Ethyl (*E*)-2-Nonenoate (4a). Ethyl 3-hydroxynonanoate (404 mg, 2 mmol) in 5 ml of THF was added to a flask containing 648 mg (4 mmol) of aluminum ethoxide in 50 ml of THF (dissolution incomplete). The mixture was stirred for 15 min; 429 mg (4 mmol) of lithium diisopropylamide in 16 ml of THF was added, and the mixture was warmed for 2 hr at 65°. Isolation of the product and column chromatography on 25 g of silica gel (hexane–ether) gave 190 mg (52%) of the desired product as a colorless oil: nmr δ 0.9 (t, *J* = 5 Hz, 3 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.34 (broad s, 8 H), 2.2 (quartet, *J* = 7 Hz, 2 H), 4.12 (quartet, *J* = 7 Hz, 2 H), 5.73 (doublet of triplets, *J* = 15 Hz, *J* = 1.5 Hz, 1 H, C(2) H), and 6.88 (doublet of triplets, *J* = 15 Hz, *J* = 7 Hz, 1 H, C(3) H); ir 1720 and 1650 cm^{-1}; mass spectrum (12 eV) *m/e* 184 (M^+) and 96 (base peak).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.33; H, 10.95.

An authentic sample of this unsaturated ester was prepared as follows. A solution of 6.75 g (30 mmol) of triethylphosphonoacetate in 5 ml of THF was added dropwise to a slurry of 1.3 g (31 mmol) of sodium hydride in 60 ml of THF, and the solution was stirred until hydrogen evolution was complete (0.5 hr). Heptanal (3.42 g, 30 mmol) in 5 ml of THF was added dropwise, and the reaction mixture was refluxed for 2 hr. Once the solution had cooled to room temperature, 30 ml of half-saturated brine was added to quench the reaction. Product isolation and distillation gave 4 g (73%) of a fraction boiling at 50–51° (0.2 Torr). Glpc analysis (column A, 120°) showed a large peak with retention time of 5.7 min and a peak *ca.* 5% of this at 4.5 min (presumed to be the *Z* isomer).

In order to prepare a sample of the β,γ-unsaturated ester, ethyl 3-nonenoate, 50 mg of the ester **4a** was dissolved in 0.8 ml of pentane and irradiated at 254 nm (Rayonet PCR 100) in a quartz test tube for 9 hr.[20] Glpc analysis (column A, 120°) indicated a 90% conversion of (*E*)-**4a** to ethyl (*E* + *Z*)-3-nonenoate: nmr δ 0.9 (t, *J* = 5 Hz, 3 H), 1.25 (t, *J* = 7 Hz, 3 H), 1.36 (broad s, 6 H), 2.04 (broad, 2 H, C(4) H_2), 2.94 (m, 2 H, C(2) H_2) 4.10 (quartet, *J* = 7 Hz, 2 H), and 5.5 (m, 2 H).

Isopropyl (*E*)-2-Nonenoate (4b). Reaction of **2** and aluminum

(18) H. M. Fales, M. S. Blum, R. M. Crewe, and J. M. Brand, *J. Insect. Physiol.*, **18**, 1077 (1972).

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isopropoxide according to the procedure described for the preparation of **4a** (1 hr, 60°) gave a crude product which showed two prominent peaks on glpc analysis (column A, 110–250°, programmed at 15° min^{-1}) corresponding to the ethyl (**4a**, 4.8 min) and isopropyl (**4b**, 5.2 min) esters. Elution from a silica gel column (hexane–benzene) gave a leading fraction consisting of pure isopropyl ester (**4b**): nmr δ 0.9 (t, J = 5.5 Hz, 3 H), 1.28 (d, J = 6.5 Hz, 6 H), 1.32 (broad s, 8 H), 2.2 (m, 2 H, allylic methylenes), 4.97 (quintet, J = 6.5 Hz, 1 H), 5.66 (doublet of triplets, J = 15 Hz, J = 1.5 Hz, 1 H, C(2) H), and 6.83 (doublet of triplets, J = 15 Hz, J = 6.5 Hz, 1 H, C(3) H); ir 1725 (s), 1660, 1115, and 985 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.91; H, 11.32.

Ethyl 3-Oxo-2-methylpentanoate (5). This β-keto ester was prepared by the Claisen condensation from ethyl propionate and sodium ethoxide, according to the general procedure given by Hauser and Hudson.[9] The final product was distilled (78–79° (13 Torr); lit.[21] 88–90° (12 Torr)): nmr δ 1.05 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.28 (d, J = 6.5 Hz, 3 H), 2.5 (quartet, J = 7 Hz, 2 H), 3.4 (quartet, J = 7 Hz, 1 H), and 4.13 (quartet, J = 7 Hz, 2 H).

Ethyl 3-Hydroxy-2-methylpentanoate (6). Ethyl 3-oxo-2-methylpentanoate (3.16 g, 20 mmol) in 10 ml of absolute ethanol was added to 227 mg (6 mmol) of sodium borohydride in 20 ml of ethanol at 0°. The mixture was stirred for 30 min and then quenched with dilute HCl. Distillation of the crude product gave 1.71 g (53%) of the pure hydroxy ester: bp 63° (1.2 Torr); nmr δ 0.96 (t, J = 7 Hz, 3 H), 1.15 (d, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 2.45 (m, 1 H), 2.72 (s, 1 H, OH), 3.55 (m, 1 H), and 4.13 (quartet, J = 7 Hz, 2 H).

Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.07; H, 10.04.

Ethyl (*E*)-2-Methyl-2-pentenoate (7). Diethoxyaluminum chloride was prepared by adding 667 mg (5 mmol) of aluminum chloride to 1.62 g (10 mmol) of aluminum ethoxide in 20 ml of THF. Two millimoles of this solution was added to 160 mg (1 mmol) of ethyl 3-hydroxy-2-methylpentanoate in 3 ml of THF, and the solution was stirred for 0.5 hr at room temperature. Lithium diisopropylamide (321.4 mg, 3 mmol in 6 ml of THF) was added, and the mixture was warmed to 70° for 1 hr. An additional portion (2 mmol) of lithium diisopropylamide was added, and heating was continued for 1 hr. After the reaction mixture was quenched in dilute HCl, glpc analysis of the isolated product (column A, 100–260°) indicated a 40–50% yield. The material was shown to be identical (glpc analysis, nmr) with the unsaturated ester prepared by the TsCl–pyridine dehydration procedure below: nmr δ 1.06 (t, J = 7 Hz, 3 H), 1.27 (t, J = 7 Hz, 3 H), 1.8 (d, J = 1.2 Hz. 3 H), 2.2 (m, 2 H), 4.13 (quartet J = 7 Hz, 2 H), and 6.7 (t, J = 7 Hz, 1 H).

Ethyl 3,7-Dimethyl-3-hydroxy-6-octenoate (8). A solution of lithium bis(trimethylsilyl)amide (22 mmol, prepared from butyllithium and hexamethyldisilazine) was added to a flask cooled in a Dry Ice bath.[10] Ethyl acetate (1.94 g, 22 mmol) was added dropwise, and the solution was stirred an additional 15 min at −78°. 6-Methyl-5-hepten-2-one (3.05 ml, 20 mmol) was added slowly, and, after 5 min, the reaction was hydrolyzed by the addition of 10 ml of 10% aqueous HCl. Product isolation (pentane extraction) gave 4.7 g (quantitative) of the crude hydroxy ester which was distilled (65–67° (0.2 Torr)) to give 3.75 g (88%) of a colorless liquid: nmr δ 1.16 (s, 3 H), 1.26 (t, J = 7 Hz, 3 H), 1.42 (m, 2 H), 1.60 (s, 3 H), 1.65 (s, 3 H), 2.0 (quartet, J = 7 Hz, 2 H), 2.35 (d, J = 2 Hz, 2 H), 3.24 (s, 1 H, OH), 4.1 (quartet, J = 7 Hz, 2 H), and 5.02 (t, J = 7 Hz, 1 H); ir 3600–3300 (broad), 1730 (broad), 1035, and 925 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.33; H, 10.38.

Ethyl 3,7-Dimethyl-2,6-octadienoate (Ethyl Geranate) (9). The hydroxyl ester **8** (428 mg, 2 mmol) was added to a mixture of 440 mg (2.7 mmol) of aluminum ethoxide and 124 mg (1.3 mmol) of aluminum chloride in 10 ml of THF. The heterogeneous mixture was stirred at room temperature for 1.5 hr, and then 8 mmol of lithium diisopropylamide in 5 ml of THF was added. The reaction was warmed to 65° for 1.5 hr, cooled to room temperature, and quenched with 10% aqueous HCl. Product isolation gave a dark yellow oil (400 mg) which was chromatographed on 20 g of silica gel (5% ether in hexane) to give 220 mg (56%) of the desired unsaturated esters. Traces of solvent were removed by bulb-to-bulb distillation. Glpc analysis (column A, 120°) showed the presence of two components with retention times of 6.0 and 7.6 min, in a ratio of 1.5 to 1.0. These were shown to be, respectively, *Z* and *E* ethyl geranate by comparison with authentic samples (prepared by the condensation 6-methyl-5-hepten-2-one with lithium triethylphosphonoacetate): nmr[22] (mixture) δ 1.22 (t, J = 7 Hz, 3 H), 1.60 (s, 3 H), 1.66 (s, 6 H), 1.85 (d, J = 1.4 Hz, *Z* isomer) and 2.10 (d, J = 1.4 Hz, *E* isomer; 3 H), 2.10 (m, 2 H), 2.56 (m, 2 H), 4.05 (quartet, J = 7 Hz, 2 H), 5.1 (t, J = 7 Hz, 1 H), and 5.55 (s, 1 H); ir 1720 (s), 1655 (m), and 1160 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{20}O_2$ (mixture): C, 73.48; H, 10.27. Found: C, 73.41; H, 10.27.

Ethyl 2,4-Dimethyl-3-oxohexanoate. The procedure of Weiler was used. Ethyl 2-methyl-3-oxopentanoate (**5**) (7.9 g, 50 mmol) in 25 ml of THF was added dropwise to a slurry of 2.53 g (60 mmol) of sodium hydride in 100 ml of THF at 0°. Ten minutes after the addition was complete, 30 ml (57 mmol) of a 1.9 *M* hexane solution of butyllithium was added, and the mixture was stirred for 10 min at 0°. Ethyl bromide (6.45 g, 60 mmol) in 10 ml of THF was added to the orange reaction mixture (color discharged), and stirring was continued for 0.5 hr at room temperature. The reaction mixture was quenched with 10% HCl, and the isolated product was distilled to give 5.6 g (60%) of a fraction boiling at 52–54° (0.3 Torr): nmr δ 0.85 (t, J = 7 Hz, 3 H), 1.06 (d, J = 7 Hz, C(2) CH_3), 1.1–1.4 (m, C(5) H_2, 2 H), 1.24 (d, J = 7 Hz, C(4) CH_3), 1.26 (t, J = 7 Hz, 3 H), 2.63 (quartet, J = 7 Hz, 1 H), and 3.52 (quartets of doublets, J = 7 Hz, J = 2 Hz, 1 H); ir 1745 (s), 1717 (s), and 1198 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.13; H, 9.55.

Ethyl 2,4-Dimethyl-3-hydroxyhexanoate (10). Ethyl 2,4-dimethyl-3-oxohexanoate (5.52 g, 30 mmol) in 10 ml of absolute ethanol was added to 567 mg (15 mmol) of sodium borohydride in 90 ml of ethanol at 0°. The mixture was stirred at 0° for 0.5 hr, and the excess hydride was then destroyed by the addition of 10% aqueous HCl. After evaporation of some of the ethanol, the product was isolated by ether extraction, drying, and evaporation of solvent. The hydroxy ester was separated from small amounts of starting material and diol by column chromatography on silica gel (ethyl acetate–hexane) and alumina (ethyl acetate–hexane) to give 3.2 g (57%) of purified product: nmr δ 1.26 (t, J = 7 Hz, 3 H), 0.8–1.4 (m, 11 H), 2.54 (m, 1 H), 2.6 (s, 1 H, OH), 3.58 (m, 1 H). Mass spectrum (70 eV) m/e 189 (M + 1), 85 (base peak).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.45; H, 10.66.

Ethyl (*E*)-2,4-Dimethyl-2-hexenoate (11). Ethyl 2,4-dimethyl-3-hydroxyhexanoate (**10**) (376 mg, 2 mmol) was added to a mixture of 324 mg (2 mmol) of aluminum ethoxide and 133.4 mg (1 mmol) of aluminum chloride in 10 ml of THF. The heterogeneous mixture was stirred at room temperature for 0.5 hr, and then 6 ml (6 mmol) of 1 *M* lithium diisopropylamide in THF was added. The temperature was raised to 65° for 1 hr, and the resulting clear, yellow solution was quenched with 10% aqueous HCl and diluted with ether. The organic phase was dried and concentrated, and the resulting residue was chromatographed on 20 g of silica gel (hexane–ether) to give 150 mg (44%) of the desired unsaturated ester: nmr δ 0.85 (t, J = 7 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 1.27 (t, J = 7 Hz, 3 H), 1.38 (quintet, J = 7 Hz, 2 H), 1.8 (d, J = 1.4 Hz, 2 H), 2.35 (m, 1 H), 4.1 (q, J = 7 Hz, 2 H), and 6.4 (doublet of quartets, J = 10 Hz, J = 1.4 Hz, 1 H); ir 2970, 2930, 2875, 1710 (s), 1645 (w), 1230, 1150, 1090, and 740 cm^{-1}; mass spectrum (70 eV) m/e 170 (M^+) and 55 (base peak).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.72; H, 10.73.

Dehydration of Ethyl 2,4-Dimethyl-3-hydroxyhexenoate (10) with Toluenesulfonyl Chloride–Pyridine. The hydroxy ester **10** (188 mg, 1 mmol) and 380 mg (2 mmol) of toluenesulfonyl chloride in 2 ml of pyridine was refluxed for 10 hr. Product isolation gave a material which exhibited three components by glpc (column A, 110–250°). Two of these were separated by preparative glpc (10 ft × 0.375 in. 10% SE-30 on 60–80 Chromosorb W, 160°, helium 120 cm^3 min^{-1}) and identified as the desired ester **11** and the corresponding β,γ-unsaturated ester, ethyl 2,4-dimethyl-3-hexenoate (ratio 2:3):[14] nmr δ 0.98 (t, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), 1.2 (t, J = 7 Hz, 3 H), 1.65 (doublet of doublets, J = 5 Hz, J = 1.5 Hz, 3 H), 2.0 (quintet, J = 7 Hz, 2 H), 3.19 (quintet, J = 7 Hz, 1 H),

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4.05 (quartet, J = 7 Hz, 2 H), and 5.06 (d of multiplets, J = 10 Hz, 1 H).

Methyl (*E*)-2,4-Dimethyl-2-hexenoate. The ethyl ester **11** (51 mg, 0.3 mmol) was stirred with 54 mg (1 mmol) of sodium methoxide in 1.5 ml of methanol at room temperature for 8 hr. Acidification with 10% aqueous HCl and product isolation gave 20 mg (42.7%) of desired methyl ester as a colorless oil. This material was chromatographically identical with a synthetic sample prepared by MacConnell.[12,15] Glpc: column B, 130°, 3.5 min; column C, 90°, 3.25 min. Tlc: pentane–ether 4:1, R_f 0.735; ethyl acetate–cyclohexane 3:2, R_f 0.63.

(*E*)-2,4-Dimethyl-2-hexenoic Acid (12). The corresponding ethyl ester **11** (100 mg, 0.59 mmol) was added to a solution of 300 mg (7.5 mmol) of sodium hydroxide in 3 ml of methanol. The solution was refluxed gently for 5 hr, cooled, and acidified with 10% aqueous HCl. Product isolation gave 80 mg (96%) of a malodorous oil. The material was identical with a synthetic sample prepared by MacConnell and previously shown to be identical with the natural acid **12**. Glpc: column A, 120°, 1.9 min; column D, 140°, 1.7 min. Tlc: methanol, R_f 0.53; cyclohexane–ethyl acetate 2:3, R_f 0.56. Bulb-to-bulb distillation gave a purified sample of the acid: nmr (100 MHz) 0.86 (t, J = 7 Hz, 3 H), 1.04 (d, J = 7 Hz, 3 H), 1.4 (quintet, J = 7 Hz, 2 H), 1.8 (d, J = 1.4 Hz, 2 H), 2.4 (m, 1 H), and 6.62 (doublet of quartets, J = 10 Hz, J = 2 Hz, 1 H); ir 3080–2540 (broad), 1685 (s), 1640, and 1285 cm^{-1}; mass spectrum (70 eV) m/e 142 (M^+) and 42 (base peak).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.30; H, 9.93.

(*E*)-2,4-Dimethyl-2-hexenoyl Chloride. The procedure of Engel and Just was used.[23] Oxalyl chloride (0.5 ml) in 1 ml of dry benzene was added to a solution of 50 mg (0.35 mmol) of 2,4-dimethyl-2-hexenoic acid in 2 ml of benzene at 0°. The reaction mixture was stirred for 2 hr at room temperature. The solvent and excess reagent were removed under reduced pressure, and the acid chloride was used without further purification.

(*E*)-4,6-Dimethyl-4-octen-3-one (Manicone, 13).[18] Cuprous iodide (95 mg, 0.5 mmol) was slurried in 1.5 ml of ether under nitrogen and cooled to −10°. Ethyllithium (1 mmol, 1.25 ml of a 0.8 *M* solution in benzene) was added slowly. After 5 min at −10°, the vessel was further cooled to −78°, and a precooled solution of the acid chloride prepared above in 0.3 ml of ether was added *via* syringe. After 15 min at −78°, the reaction was quenched by addition of 0.075 ml (60 mmol) of methanol; the flask was warmed to room temperature, and the reaction mixture was mixed with saturated aqueous NH_4Cl. Product isolation gave 50 mg (92%) of a yellow oil, which was further purified by bulb-to-bulb distillation to give colorless material whose spectroscopic properties were consistent with those reported for the natural material[17]: nmr δ 0.9 (t, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.4 (m, broad, 2 H), 1.73 (d, J = 1.4 Hz, 3 H), 2.4 (m, 1 H), 2.59 (quartet, J = 7 Hz, 2 H), and 6.24 (d, J = 10 Hz, 1 H); ir 1750 (w), 1670 (s), and 1650 cm^{-1}.

The 2,4-dinitrophenylhydrazone derivative was prepared by the addition of 15 mg of the ketone **13** to 1 ml of the derivatizing reagent (prepared by the cautious addition of 0.5 ml of concentrated H_2SO_4 to 0.25 g of 2,4-dinitrophenylhydrazine suspended in 5 ml of methanol). The precipitate which formed immediately was filtered and twice recrystallized from ethanol to give red leaf-like crystals, mp 130–131° (lit.[18] 129–131°).

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Acylal Hydrolysis. The Hydrolysis of 3-(*p*-Nitrophenoxy)phthalide, α-Acetoxybenzyl *p*-Nitrophenyl Ether, and 3-(Para-Substituted Thiophenyl)phthalides

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Abstract: The rates of hydrolysis of the acylals 3-(*p*-nitrophenoxy)phthalide, α-acetoxybenzyl *p*-nitrophenyl ether, and 3-(para-substituted thiophenyl)phthalides have been measured at 30° in H_2O. In hydrolysis of these compounds hydronium ion and hydroxide ion catalysis takes place. There is also a pH-independent spontaneous reaction. The pH-independent hydrolysis of 3-(*p*-nitrophenoxy)phthalide is characterized by a ΔS^* of −47.1 eu, indicating solvent involvement in the reaction. In the hydronium ion catalyzed hydrolysis of α-acetoxybenzyl *p*-nitrophenyl ether ΔS^* is −17.6 eu. There is pronounced catalysis of the hydrolysis of these compounds by the base component of the buffer. In the case of the *p*-nitrophenoxy acylals there is both a first-order and a second-order dependence on base concentration, suggesting base catalysis of nucleophilic attack by a second molecule of base or a kinetic equivalent. With the 3-(para-substituted thiophenyl)phthalides there is strict first-order dependence on the concentration of the catalyzing base. From the D_2O solvent isotope effect for ethanolamine catalysis of the hydrolysis of 3-(*p*-nitrothiophenyl)phthalide (k_B^H/k_B^D = 1.8) it can be inferred that catalysis is by a general base mechanism involving proton transfer in the rate-determining step. The Hammett ρ value for ethanolamine catalysis is 0.55 and that for hydroxide ion is 0.42. It is apparent that these acylals are hydrolyzing as esters not acetals.

X-Ray crystallographic studies[2] of the glycosidic enzyme lysozyme at 2-Å resolution have indicated that carboxyl groups from glutamic acid-35 and aspartic acid-52 are located at the active site. Several mechanisms have been postulated employing these carboxyl groups.[3] A mechanism recently receiving support involves general acid catalysis by glutamic acid-35 and

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