Polyene Synthesis. Ready Construction of Retinol–Carotene Fragments, (±)-6(*E*)-LTB$_3$ Leukotrienes, and Corticrocin†

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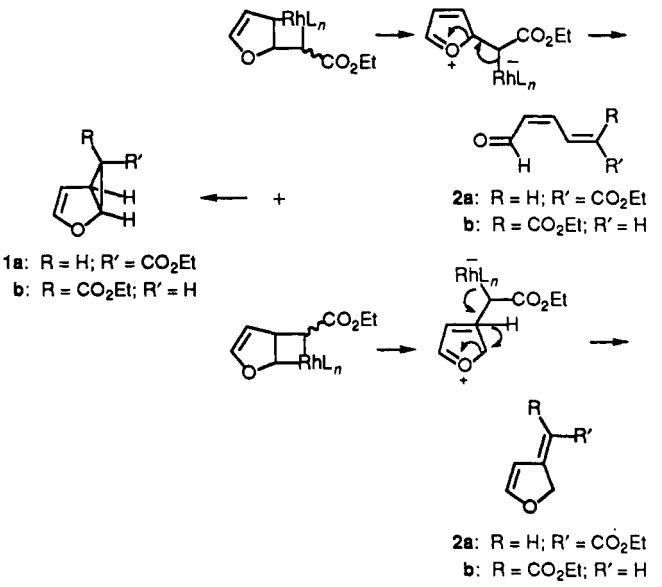
Received March 19, 1990

All products of the dirhodium tetraacetate catalyzed reactions of ethyl diazoacetate with furan, 2-methylfuran, 2,5-dimethylfuran, 2-*n*-octylfuran, methyl furoate and methyl β-(α-furyl)acrylate were isolated and characterized. They consist mostly of *exo*-cyclopropanecarboxylates and 1,4-diacyl-1,3-butadienes and some 3-(acylmethyl)furans. Treatment of the crude reaction mixtures with iodine or boron trifluoride furnishes 1,4-diacyl-1(*E*),3(*E*)-butadienes. Horner–Emmons condensation with the latter dicarbonyl compounds leads to 1,6-diacyl-1,3,5-hexatrienes. Proper combinations of methyl α-diazopropionate, furans, and α-phosphono esters afford segments of retinol and β-carotene, while combinations of α-diazo ketones, furans, and α-phosphono ketones yield LTB$_3$-like leukotrienes. Finally, dirhodium tetraacetate promoted decomposition of ethyl diazoacetate in 1,2-bis(2-furyl)ethane and iodine treatment gives a diketo diester, whose reduction, dehydration, and hydrolysis leads to the naturally occurring dodecahexaenic dicarboxylic acid, corticrocin.

As part of a broad study of metal-catalyzed reactions of enol ethers (or their equivalents) with α-diazo carbonyl compounds and their application in natural product synthesis[2] it became of interest to investigate these reactions in the field of furans (i.e. aromatic equivalents of enol ethers), benzofuran having been the subject of an earlier study.[3] The literature offered only a limited number of examples of copper-induced reactions of diazoacetic ester and diazomethyl ketones with simple furans,[4,5] but left mixed signals in so far as the products were concerned. Most reports pointed to the formation of furan-unravelled 1,4-diacyl-1,3-butadienes,[4] but one set of observations also showed the production of β-(acylmethyl)furans.[5] The product yields of most of these reactions as well as those of photochemically initiated furan–diazoacetic ester reactions[6] were below the level of applicability in general organochemical synthesis. The confluence of this realization, of the abandonment of copper catalysis for the decomposition of α-diazo keto systems in the face of the arrival of the highly efficient dirhodium tetraacetate catalyst[7] and of an early, excellent result with the latter in an interaction of furan with an α-diazo β-lactam[8] suggested the need for an exhaustive study of some model systems—rhodium-promoted decomposition of ethyl diazoacetate in unencumbered fruans—and subsequent application of the observations to organochemical synthesis, in general. The quasi-mechanistic analysis of the alteration of the furan nucleus by an (ethoxycarbonyl)-methine–rhodium complex, depicted in Scheme I, was to serve as general back drop as well as product predictor of the study.

Models.[9,10] Decomposition of a furan solution of ethyl diazoacetate over dirhodium tetraacetate led to a ca. 17:10:5:1 mixture of esters **1a**,[6a] **2a**,[6a,11a] **2b** and **3** in 66% yield. Several features of this result were noteworthy. The cyclopropane product of the present reaction (**1a**) as well as of all subsequent furan additions was exclusively the exo isomer. The stereochemistry of the butadienes (**2a** and **2b**) maintained a reproducible pattern through all furan unravelling processes. Whereas the newly formed double bond between the furan and diazoacetic ester α-carbons could assume a cis or trans configuration, the double bond created between the former furan β-carbons maintained a cis orientation, reflecting the original furan framework. Finally, ester **3** was a single stereoisomer of undetermined configuration (i.e. either **3a** or **3b**), which proved to be the only isolable product of the 3-alkylidene-2,3-dihydrofuran type. The related products of all subsequent furan reac-

Scheme I



† Dedicated to the memory of Professor Holger Erdtman.

(1) Ministerio de Educación y Ciencia (Spain) postdoctoral fellowship holder, 1988–1990.

(2) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

(3) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pelliciari, R.; Cogoli, P. *J. Org. Chem.* **1977**, *42*, 3945.

(4) (a) Novak, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1958**, *23*, 1126. (b) Nefedov, O. M.; Shostakovskii, V. M.; Samoilova, M. Ya.; Kravchenko, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, (7) 1590; **1972**, (10) 2342. (c) Nwaji, M. N.; Onyiriuka, O. S. *Tetrahedron Lett.* **1974**, 2255. (d) Nefedov, O. M.; Shostakovsky, V. M.; Vasilvizky, E. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 646. (e) Nefedov, O. M.; Shostakovskii, V. M.; Vasil'vitskii, A. E. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, (3) 607.

(5) Wenkert, E.; Bakuzis, M. L. F.; Buckwalter, B. L.; Woodgate, P. D. *Synth. Commun.* **1981**, *11*, 533.

(6) (a) Schenk, G. O.; Steinmetz, R. *Liebigs Ann. Chem.* **1963**, *668*, 19. (b) For use of the product of acid-induced isomerization of the furan-diazoacetic ester photoadduct **11a**[6a] in a leukotriene synthesis, see: Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, 1485.

(7) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssié, P. *Synthesis* **1976**, 600.

(8) Matlin, S. A.; Chan, L. *J. Chem. Soc., Chem. Commun.* **1981**, 10; *Tetrahedron Lett.* **1981**, *22*, 1627.

(9) For a preliminary account, see: Wenkert, E. Polyene Synthesis. In *New Trends in Natural Products Chemistry 1986. Studies in Organic Chemistry*; Atta-ur-Rahman, LeQuesne, P. W., Eds.; Elsevier Science Publishers B.V.: Amsterdam, Netherlands, 1986; Vol. 26, p 557.

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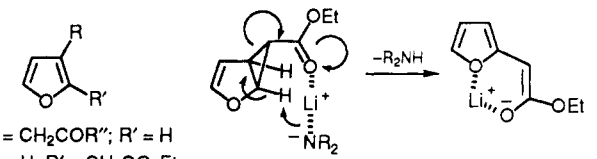
tions appeared in the form of β-(acylmethyl)furans (**4a**), i.e. products of double-bond isomerization.

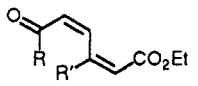


4a: R = CH_2COR''; R′ = H
b: R = H; R′ = CH_2CO_2Et
c: R = CH_2CO_2Et; R′ = H
d: R = CH_2CO_2Et; R′ = Me

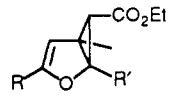
5

The lack of formation of *endo*-cyclopropanecarboxylate **1b** in the face of the usual production of both exo and endo isomers on cyclopropanation of cyclic enol ethers[12] was unusual and suggested its possible rhodium-fostered isomerization into butadienes **2a** and **2b**. The exo isomer (**1a**) proved to be stable under the conditions of the original cyclopropanation process. In order to test the lability of ester **1b**, its synthesis was attempted by means other than furan cyclopropanation, i.e. by isomerization of ester **1a**. Whereas this structure alteration failed, exposure of ester **1a** to lithium diisopropylamide gave an interesting result—isomerization into esters **4b**[13] and **4c**[14] (3:1 mixture). This transformation is explained best by assumption of bond reorganization of an ester–base complex, as illustrated in eq **5** for the **1a** → **4b** conversion. Heating of cyclopropyl ester **1a** or dienic ester **2b** at 160 °C isomerized them into butadiene **2a**, the second reaction taking place more rapidly than the first.

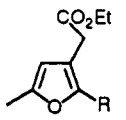
The second model study of a furan/diazoacetic ester reaction catalyzed by dirhodium tetraacetate involved the use of 2,5-dimethylfuran and led (after crude product separation by alumina chromatography) to a ca. 9:6:1 mixture of esters **6a**,[5] **7a**,[5] and **8a**[5] in 78% yield. Silica gel separation of the crude reaction product led, instead, to a ca. 16:1 mixture of esters **9a**[5] and **8a** in 50% yield, thus implicating an acid-induced isomerization of esters **6a** and **7a** into butadiene **9a**.



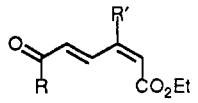
6a: R = R′ = Me
b: R = Me; R′ = H
c: R = $(CH_2)_7Me$; R′ = H



7a: R = R′ = Me
b: R = Me; R′ = H
c: R = H; R′ = Me
d: R = CO_2Me; R′ = H

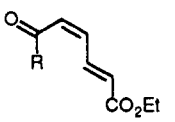


8a: R = Me
b: R = H

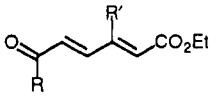


9a: R = R′ = Me
b: R = H; R′ = Me

Finally, the third model experiments, pertaining to the chemistry of the unsymmetrical heterocycle 2-methylfuran, revealed a ca. 19:1 site selectivity in the rhodium-catalyzed diazoacetic ester decomposition in favor of the less substituted side of the heterocycle. This permitted full characterization of only the major components of the complex reaction mixtures. After chromatographic separation of the crude products over alumina there was obtained a ca. 31:12:10:1 mixture of esters **10a**,[11b] **6b**,[11b] **7b**, and **8b** in 54% yield along with a ca. 2:1 mixture of esters **7c** and **4d** in ca. 3% yield. Silica gel chromatography of the crude products furnished, instead, a ca. 38:12:1 mixture of esters **10a**, **6b** and **8b** in 51% yield as well as a ca. 2:1:1 mixture of esters **7c**, **4d**, and **9b** in ca. 4% yield, showing the acid lability of cyclopropane **7b** and its isomerization mostly into butadiene **10a**.



10a: R = Me
b: R = $(CH_2)_7Me$



11a: R = R′ = H
b: R = R′ = Me
c: R = Me; R′ = H
d: R = $(CH_2)_7Me$; R′ = H
e: R = CO_2Me; R′ = H

The high regioselectivity experienced in the reaction of the unsymmetrically substituted furan became even more pronounced in the presence of a bulkier substituent on the furan nucleus. Thus rhodium-promoted decomposition of diazoacetic ester in 2-*n*-octylfuran, prepared by treatment of furan firstly with *n*-butyllithium and thereafter with *n*-octyl bromide, yielded a ca. 1.5:1 mixture of ester **10b** and highly metastable ester **6c** (based on ^1H NMR analysis of the crude mixture), whose silica chromatography afforded one sole product—ester **10b** in 60% yield.

In light of the formation of polycomponent mixtures from the furan/diazoacetic ester reactions described thus far the rhodium-catalyzed processes still left something to be desired from the organochemical synthesis point of view, even though the reactions had yielded products of exceedingly interesting and, by other means, difficultly attainable structure. However, wedding the reaction to a subsequent, mild, acid-induced isomerization of the crude products (and destruction of the minor furan products) made available a high-yielding reaction scheme for the preparation of a single product per reaction sequence. Thus exposure of the crude product mixtures of the reactions of furan, 2,5-dimethylfuran, 2-methylfuran and 2-*n*-octylfuran to iodine in methylene chloride solution led to oxoester **11a**,[11a,15] a 1.5:1 **11b–9a** oxoester mixture,[16] and oxoester **11c**[11b,d] and **11d**, respectively, in 68, 70, 85, and 66% yields, respectively. *This constituted a highly efficient two-step, "one-pot" synthesis of 1,4-diacyl-1(E),3-(E)-butadienes from furans.*

Electron-withdrawing substituents on the furan ring do not interfere with the furan addition reaction, but yield no ring-cleaved products and reduce the unravelling tendency of the cyclopropane adduct. Thus, for example, treatment of methyl furoate or methyl β-(α-furyl)acrylate with ethyl diazoacetate and dirhodium tetraacetate in

(10) Based on B. Porter, Ph.D. Dissertation, University of California—San Diego, 1984.

(11) For the methyl ester equivalent of this ester, see: (a) Tulshian, D. B.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474. (b) Feliu, A. L.; Selzer, S. *J. Org. Chem.* **1985**, *50*, 447. (c) Oren, J.; Schleifer, L.; Weinman, S.; Fuchs, B. *J. Chem. Soc., Chem. Commun.* **1988**, 315. (d) Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhorn, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* **1988**, *71*, 1719.

(12) Wenkert, E.; Buckwalter, B. L.; Sathe, S. S. *Synth. Commun.* **1973**, *3*, 261.

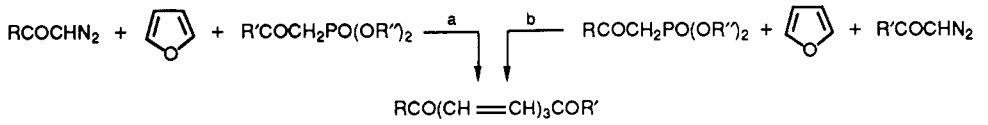
(13) Rayn, J. F.; Plucker, J. III; Armstrutz, E. D. *J. Am. Chem. Soc.* **1940**, *62*, 2037.

(14) (a)Pelletier, S. W.; Djarmati, Z.; Lazsic, S. D.; Micouc, I. V.; Yang, D. T. C. *Tetrahedron* **1975**, *31*, 1659. (b) Srikrishna, A.; Sunderbabu, G. *Chem. Lett.* **1988**, 371.

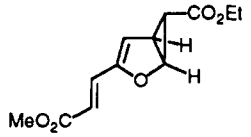
(15) (a) Funke, A.; Karrer, P. *Helv. Chim. Acta* **1949**, *32*, 1016. (b) Saito, I.; Takami, M.; Matsuura, T. *Chem. Lett.* **1972**, 1195. (c) de Koning, H.; Subramanian-Erhart, K. E. C.; Huisman, H. O. *Synth. Commun.* **1973**, *3*, 25. (d) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1982**, *23*, 1285. (e) Le Baut, G.; Sparfel, L.; Clairc, C.; Floc'h, R.; Ducrey, P.; Benazet, F.; Lacroix, L.; Leroy, J. P. *Eur. J. Med. Chem., Chim. Ther.* **1983**, *18*, 447. (f) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533, footnote 20.

(16) This was an equilibrium mixture, as attested by attainment of the same product ratio on submission of each isomer individually to the isomerization conditions.

Scheme II



methylene chloride solution produced cyclopropanes **7d** (55%) and **12** (51%), respectively.[17] Whereas the latter cyclopropanecarboxylate could be unravelled with iodine (affording diester **13** in 77% yield), the former was inert to iodine and needed treatment with boron trifluoride, whereupon it was converted into diester **11e** (80%).[17,18]



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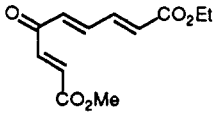
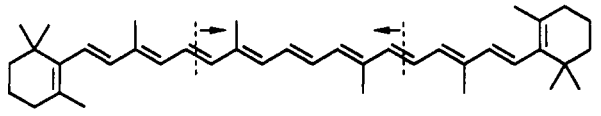


13

Retinol–Carotene Fragments.[9,17] The reaction scheme, developed in the model studies, now was ready to be applied to structurally more complex polyene systems, e.g. the skeleta of β-carotene (**14**) and retinol (**15**). Whereas the construction of the terpenes themselves by way of furan chemistry still lies in the future, the synthesis of dienic and trienic segments of the natural products is the subject of the up-coming discussion. The diene → triene conversion was planned to be executed by condensation of 1,4-diacyl-1(*E*),3(*E*)-butadienes with α-acylalkyl phosphonates, expected to yield 1,6-diacyl-1(*E*),3(*E*),5-(*E*)-hexatrienes, while the methyl branches of the terpenic, polyolefinic chains were intended to be introduced via the diazocarbonyl and/or phosphonate reagents.



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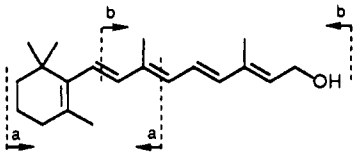
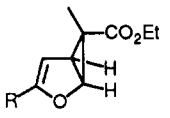


15

Decomposition of ethyl α-diazopropionate[19] over dirhodium tetraacetate in furan solution furnished a ca. 8:1 mixture of esters **16a**[20] and **17a** in 60% yield.[21] When without workup the reaction mixture was treated with iodine, aldehydo ester **18a** (63%) was obtained. Horner–Emmons condensation of the latter with the sodio salt of triethyl α-phosphonopropionate resulted in the formation of trienic diester **19**,[11c,22,23] a substance representative of the central segment of β-carotene (**14**, see dotted lines) with end groups useable for further structure elaboration.



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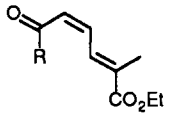

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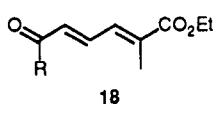

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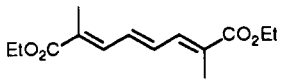
a, R = H; **b**, R = Me



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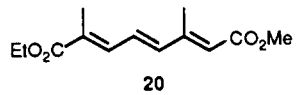

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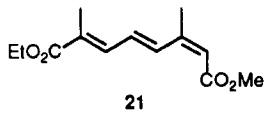
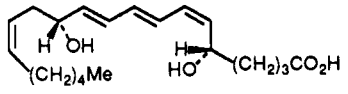


21

On rhodium-catalyzed decomposition of α-diazopropionic ester in 2-methylfuran and alumina chromatography of the products a ca. 3:1 mixture of esters **16b**[20] and **17b** was obtained in 69% yield. Silica chromatography yielded solely the dienic ester **17b** (75%) and iodine treatment of the initial crude product mixture gave isomerized ester **18b**[24] (72%). Condensation of the latter with the sodio salt of trimethyl phosphonoacetate afforded a 2:1 mixture (74%) of diesters **20**[25] and **21**.[25b] Triene **20** constitutes the O-terminal half of the retinol skeleton (**15**, see dotted lines b). It is noteworthy that the nuclear portion of retinol (**15**, see dotted lines a), in the form of 4-oxo-β-ionone, was synthesized recently by an intramolecular version of furan–diazo ketone chemistry.[26]

LTB_3 Leukotrienes.[9,10] In view of the ease of construction of 1,6-diacylhexatrienes illustrated above in the terpene field the synthesis route appeared to be suited ideally to the fabrication of leukotrienes, especially of the LTB variety (e.g. LTB_4–**22**). In order to establish the



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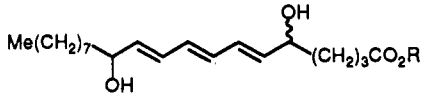


23a: R = H
b: R = Me

ground rules for such fatty acid construction, the all-trans LTB_3 system (**23**) was chosen as the research goal and optimum flexibility in the reaction sequences made a high premium. The latter requirement was felt significant in

(17) Based on J.-H. Sheu, Ph.D. Dissertation, University of California-San Diego, 1985.

(18) Since completion of these model studies[9,10,17] there have appeared reports of related investigations: (a) Nefedov, O. M.; Saltykova, L. E.; Vasil'vitskii, A. E.; Shostakovskii, V. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, (11) 2625. (b) Saltykova, L. E.; Vasil'vitskii, A. E.; Shostakovskii, V. M.; Nefedov, O. M. *Ibid.* **1988**, (12) 2833.

(19) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

(20) Whereas the stereochemistry of the α-methylcyclopropanecarboxylate remained undetermined, the compound is portrayed as an exo ester by analogy with structures **1a**, **7**, and **12**.

(21) It is worthy of note that α-diazopropionic ester behaved as diazoacetic ester under rhodium catalysis instead of undergoing intramolecular carbon-hydrogen insertion leading to ethyl acrylate.

(22) (a) Fischetti, W.; Mak, K. T.; Stakem, F. G.; Kim, J.-I.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948. (b) Kasahara, A.; Izumi, T.; Kudou, N. *Synthesis* **1988**, 704.

(23) For the diacid equivalent of this ester, see: Mildner, P.; Weedon, B. C. L. *J. Chem. Soc.* **1953**, 3294.

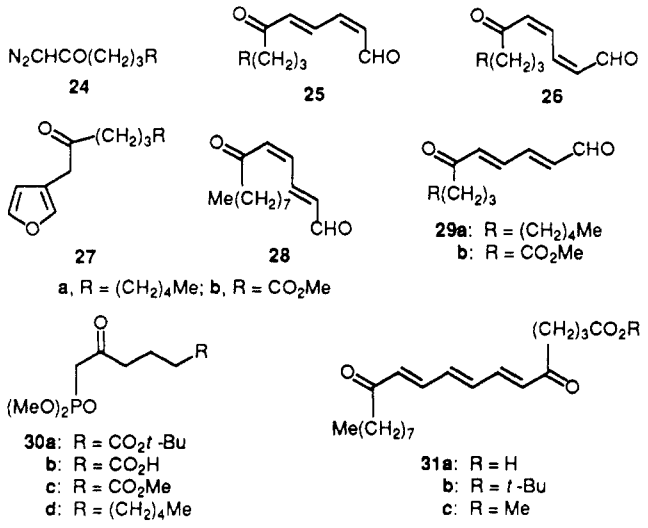
(24) Lucien, T.; Guenther, V. Ger. Offen. 2,652,356, 18 May 1978; *Chem. Abstr.* **1978**, *89*, 110052p.

(25) For an acid ester variant of the diester, see: (a) Schwieter, U.; Arnold, W.; Oberhänsli, W. E.; Rigassi, N.; Vetter, W. *Helv. Chim. Acta* **1971**, *54*, 2447. For diacid and methyl ethyl ester variants: (b) Heck, R. F. *Pure Appl. Chem.* **1981**, *53*, 2323.

(26) Wenkert, E.; Decorzant, R.; Näf, F. *Helv. Chim. Acta* **1989**, *72*, 756.

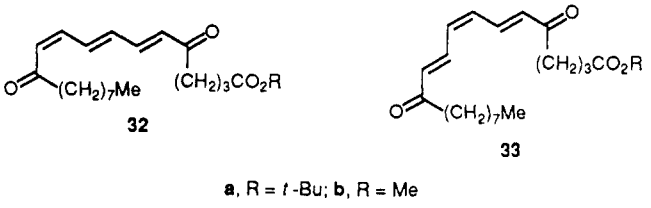
recognition of the fact of the three-component reaction scheme for the requisite 1,6-diacylhexatriene synthesis having available two or more paths for attaining the goal (see Scheme II).

In pursuit of Scheme II (path a) 1-diazo-2-decanone (**24a**), prepared by standard means from pelargonic acid, was exposed to dirhodium tetraacetate in furan. This reaction led to a 7:1:1 mixture (79%) of ketones **25a**, **26a**, and **27a**, whose silica chromatography converted the all-cis diene (**26a**) quantitatively into ketone **28**. Treatment of the crude reaction mixture with iodine resulted in the isolation of the all-trans diene **29a** (72%).[27] The Horner–Emmons reagents needed for condensation with the latter ketone were prepared in the following manner. Interaction of *tert*-butyl methyl glutarate, formed (70%) by the reaction of methyl glutaryl chloride[5] with *tert*-butyl alcohol in pyridine, with dimethyl lithiomethanephosphonate afforded phosphono ester **30a** (75%). Treatment of the latter with glacial trifluoroacetic acid gave phosphono acid **30b** (95%) and with methanolic trifluoroacetic acid phosphono ester **30c** (95%). Exposure of the disodio salt of phosphono acid **30b** to keto aldehyde **29a** furnished keto acid **31a** (60%), also a product of condensation of the sodio salt of phosphono ester **30a** with the same keto aldehyde and acid-induced solvolysis (92% yield) of the resultant keto ester **31b**[28] (75%). As a third alternative, the sodio salt of phosphono ester **30c** was caused to undergo reaction with the keto aldehyde producing keto ester **31c** (70%).



In pursuit of Scheme II (path b) methyl 6-diazo-5-oxohexanoate (**24b**)[5] was induced to decompose in furan over dirhodium tetraacetate. The reaction furnished a 7:1:1 mixture of esters **25b**, **26b**, and **27b** (by ^{1}H NMR spectral integration), whose fragility necessitated its iodine isomerization prior to full characterization of the individual components. Condensation of the product (**29b**) of the two-step reaction sequence (68%) with the sodio salt of ketophosphonate **30d**, prepared by the interaction of dimethyl lithiomethanephosphonate with methyl pelargonate, produced diketo ester **31c** (81%).[29]

Thus the 1,6-diacyl 1,3,5-triene system (**31**), a logical precursor of LTB_3 isomers **23** was accessible by various pathways. In order to illustrate the absence of constraints of the method of synthesis to the all-trans system (**31**), stereoisomers of the diketo ester **31b** were prepared. Condensations of keto aldehyde **28** with the sodio salts of phosphono esters **30a** and **30c** afforded diketo esters **32a** (50%) and **32b** (70%), respectively, while the same reactions of keto aldehyde **25a** gave diketo esters **33a** (50%) and **33b** (65%), respectively. Finally, completion of the synthesis of (±)-6(*E*)-LTB_3 (**23a**) proceeded by the following two paths. Borohydride reduction of diketo acid **31a** yielded quantitatively two diastereomeric dihydroxy acids **23a**.[30] Alternatively, similar reduction of diketo ester **31c** produced dihydroxy ester **23b** diastereomers[30] (90%), each of whose mild alkaline hydrolyses led to a dihydroxy acid (**23a**) diastereomer.



As the above LTB_3 synthesis discussion portrays, the rhodium-induced furan–diazo ketone unravelling process presents a facile, short, high-yielding polyene synthesis route. Advantage thereof was taken recently by a Merck Frosst Canada research team in a broad sweep of leukotriene syntheses.[31]

Corticrocin. In order to extend the polyene construction path yet further, the build-up of a terminally acylated polyene with more conjugated double bonds than the heretofore described 1,6-diacylhexatrienes was undertaken. Corticrocin, a fungal pigment of 1,12-diacyldodeca-1,3,5,7,9,11-hexaene structure **34a**,[32,33] seemed to be an excellent goal for this purpose. The synthesis of the natural product from 1,2-bis(α-furyl)ethane (**35c**),[34] prepared readily from furoin (**35a**)[35] by trimethylsilyl iodide[36] reduction[37] (90%) and Wolff–Kishner reduction (62%) of the resultant deoxyfuroin (**35b**),[38] is the topic of the following discussion.

Treatment of the difurylethane **35c** with dirhodium tetraacetate and ethyl diazoacetate in dichloromethane and thereafter with iodine resulted in the formation of keto ester **36** (52%), while an excess of diazoacetic ester and subsequent boron trifluoride treatment furnished diketo diester **37a** (60%). In an attempt of bis-thioketone for-

(27) Ketone **29a** was also the product of aluminum hydride reduction of keto ester **11d** and pyridinium dichromate oxidation of the resultant diol [IR (Nujol) OH 3305 (br, w), CH=CH 990 (w) cm^{-1}; ^{1}H NMR δ 0.88 (t, 3, *J* = 7 Hz, Me), 1.1–1.4 (m, 12, methylenes), 1.4–1.6 (m, 2, C-7 H's), 4.1–4.2 (m, 3, OCH_2, OCH), 5.70, 5.84 (dd, 1 each, *J* = 16, 6 Hz, H-3, H-4), 6.2–6.3 (m, 2, H-2, H-5); ^{13}C NMR δ 13.9 (Me), 22.5 (C-13), 25.3 (C-8), 29.1, 29.4, 29.6 (C-9 or C-10 or C-11), 31.7 (C-12), 37.1 (C-7), 62.7 (C-1), 72.3 (C-6), 129.3 (C-3 or C-4), 130.3 (C-4 or C-3), 132.0 (C-2), 136.3 (C-5); exact mass, *m/e* ($M^+ - H_2O$) 208.1828 (calcd for $C_{14}H_{24}O$ *m/e* 208.1827)].

(28) This diketo ester could be prepared also be condensation of the furan–diazoketone reaction product mixture **25a–26a–27a** with the sodio salt of phosphono ester **30a** followed by product isomerization with iodine (51%).

(29) Alternatively, condensation of the **25b–26b–27b** mixture with the sodio salt of ketophosphonate **30d**, followed by iodine-promoted product isomerization, led also to diketo ester **31b** (70%).

(30) No attempt was made to establish the relative C(5)–C(12) configurations.

(31) For the first rhodium-based chemistry publication, see: (a) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185. For a review, see: (b) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87.

(32) Erdtman, H. *Acta Chem. Scand.* **1948**, *2*, 209.

(33) Previous syntheses were based on acetylene chemistry: (a) Shaw, B. L.; Whiting, M. *J. Chem. Soc.* **1954**, 3217. (b) Weedon, B. C. L. *J. Chem. Soc.* **1954**, 4168. (c) Kovalev, B. G.; Yanofskaya, L. A.; Kucherov, V. F.; Kogan, G. H. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1963**, 145.

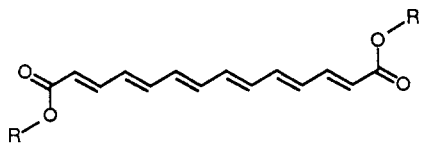
(34) Reichstein, T. *Helv. Chim. Acta* **1930**, *13*, 345.

(35) Hartman, W. W.; Dickey, J. B. *J. Am. Chem. Soc.* **1933**, *55*, 1228.

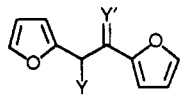
(36) Lissel, M.; Drechsler, K. *Synthesis* **1983**, 459.

(37) Ho, T.-S. *Synth. Commun.* **1979**, *9*, 665.

(38) Scheithauer, M.; Mayer, R. *J. Prakt. Chem.* **1967**, *4*, 35.

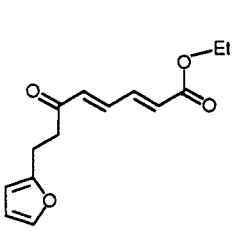


34a: R = H
b: R = Et



35a: Y = OH; Y' = O
b: Y = H; Y' = O
c: Y = H; Y' = H_2

mation (for subsequent transformation of the thione units into a diene) by exposure of the diketone **37a** to Lawesson's reagent[39] the carbonyl compound was converted quantitatively into a thiophene derivative[40] (**38**). Unfortunately the latter could not be desulfurized without serious damage to the multiple bonds.



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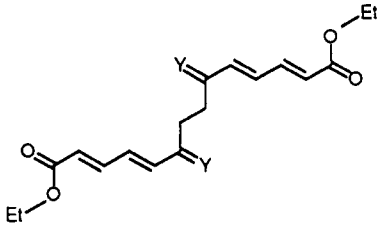
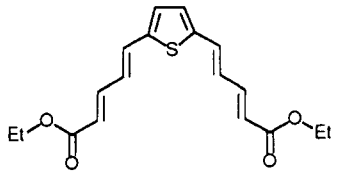


37a: Y = O
b: Y = H, OH

Reduction of diketone **37a** with sodium borohydride in the presence of cerium trichloride produced a ca. 5:1 mixture (95%) of dihydroxy diester diastereomers **37b**.[41] Dehydration of the diols, the next step of the synthesis, had to be executed under mild conditions, in order not to malaffect the sensitive functional groups of the olefinic diester chain. Hence the Martin reaction,[42] i.e. the dehydration of secondary or tertiary alcohols on treatment with bis[[bis(trifluoromethyl)benzyl]oxy]diphenylsulfurane,[43] became the elimination process of choice. Interaction of the diols **37b** with a Martin reagent variant[44] under stoichiometric control at room temperature yielded nearly quantitatively monodehydration products, a ca. 5:1 mixture of tetrahydrofurans **39**.[45] However, this precedented reaction[46] could be overcome by the use of low temperature (−100 °C) and an excess of reagent. Under these conditions diester **34b** (70%) was obtained.[47] Alkaline hydrolysis of the latter gave corticrocin (**34a**) (86%).



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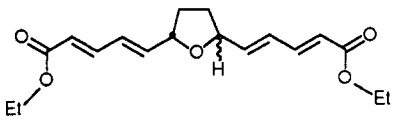

39

Conclusion. The furan–diazo ketone reaction scheme lends itself to the rapid acquisition of substances highly functionalized within a compact space and, when added to its cycle-producing, intramolecular version,[26,48] constitutes a powerful method of organic synthesis.

Experimental Section

Melting points were determined on a Reichert micro hotstage apparatus and are uncorrected. Ultraviolet spectra of methanol solutions were taken on a Perkin-Elmer 550 spectrophotometer and infrared spectra of neat liquids on Pye Unicam 3-200 and Perkin-Elmer 1330 spectrophotometers. ^{1}H NMR spectra of deuteriochloroform solutions were recorded on a Varian EM-390 spectrometer and a 360-MHz instrument (highly modified Varian HR-220 console, Oxford magnet and Nicolet 1180-E computer system) and ^{13}C NMR spectra of deuteriochloroform solutions on a wide-bore, broad-band Nicolet NT-200 spectrometer with an Oxford magnet operating at 50.3 MHz in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 79.6$ ppm.

All reactions were performed under nitrogen, and all extracts were dried over anhydrous sodium sulfate. All solvents were of analytical reagent grade. Column chromatography was executed on 70–230-mesh Merck or Davisil 62 silica gel and medium-pressure liquid chromatography (MPLC) on Merck Lobar (A, B, or C) silica gel columns, equipped with a Fluid Metering, Inc. pump.

Reactions of Ethyl Diazoacetate with Furans. General Procedure. A solution of 20 mmol of ethyl diazoacetate in 2 mL of the required furan was added dropwise over a 18-h period to a stirring suspension of 0.01 mmol of dirhodium tetraacetate in 8 mL of the furan. The mixture was filtered through a Florisil pad, and the filtrate was evaporated under vacuum.

Reactions of Furan. MPLC of the crude product mixture and elution with 20:1 hexane–ethyl acetate afforded colorless, liquid ethyl 2,3-dihydro-3-furylideneacetate (**3**) [2%; ^{1}H NMR δ 1.29 (t, 3, J = 7 Hz, Me), 4.17 (q, 2, J = 7 Hz, OCH_2), 5.03 (d, 2, J = 3 Hz, C-2 H's), 5.3–5.4 (m, 1, α-keto H), 6.78 (d, 1, J = 2 Hz, H-4), 7.1–7.3 (m, 1, H-5)] and thereafter colorless, liquid ethyl *exo*-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**1a**):[6a] 34%; IR C=O 1720 (s), C=C 1620 (m), 1590 (s), 1560 (m) cm^{-1}; ^{1}H NMR δ 0.84 (d, 1, J = 3 Hz, H-6), 1.25 (t, 3, J = 7 Hz, Me), 2.68 (ddd, 1, J = 6, 3, 3 Hz, H-5), 4.06 (q, 2, J = 7 Hz, OCH_2), 4.74 (d, 1, J = 6 Hz, H-1), 5.41 (t, 1, J = 3 Hz, H-4), 6.31 (d, 1, J = 3 Hz, H-3); ^{13}C NMR δ 13.9 (Me), 21.8 (C-6), 31.3 (C-5), 60.2 (OCH_2), 66.7 (C-1), 106.0 (C-4), 146.9 (C-3), 172.4 (C=O).

Further elution gave pale yellow, liquid ethyl 6-oxo-2(*Z*),4-(*Z*)-hexadienoate (**2b**): 10% UV λ_{max} 262 nm (ϵ 6400); IR C=O

(39) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chem. Belg.* **1978**, *87*, 223.

(40) Cf. Pouwer, K. L.; Vries, T. R.; Havinga, E. E.; Meijer, E. W.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1988**, 1432.

(41) If it be assumed that the cerium-promoted hydride reduction of a divinyl 1,4-diketone (**37a**) follows the stereochemical path of titanium-promoted hydride reduction of diaryl 1,3-diketones (Maier, G.; Schmitt, R. K.; Seipp, U. *Chem. Ber.* **1985**, *118*, 722. Meier, G.; Seipp, U.; Boese, R. *Tetrahedron Lett.* **1987**, *28*, 4515. Cf. also: Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704), the major isomer is the meso compound.

(42) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(43) Martin, J. C.; Arhart, R. J.; Franz, J. A.; Perozzi, E. F.; Kaplan, L. J. *Org. Synth.* **1977**, *57*, 22.

(44) Bis[[bis(trifluoromethyl)-*p*-methylbenzyl]oxy]diphenylsulfurane. The authors are indebted to Dr. Andrew D. Batcho (Hoffmann-La Roche, Inc.) for a recipe of the preparation of this reagent.

(45) Were it assumed that (a) the major component of the starting diols (**37b**) is the meso compound,[41] (b) the Martin reagent interacts at only one hydroxy group site, and (c) the second hydroxy function displaces the newly formed functional group under S_N2-like stereochemical control (cf. Armego, W. L. F. *Stereochemistry of Heterocyclic Compounds, Part II*; John Wiley and Sons, Inc.: New York, 1977; p 49 and references therein), the major component of the ether (**39**) mixture must have the trans configuration. This is in accord with NMR spectral observations. Symmetrical, trans-2,5-disubstituted tetrahydrofurans reveal deshielded α-hydrogens and shielded α-carbons in comparison with their cis isomers (Gagnaine, D.; Monzeglio, P. *Bull. Soc. Chim. Fr.* **1965**, 474. Batterham, T. J. *NMR of Simple Heterocycles*, John Wiley and Sons, Inc.: New York, 1973; p 379 and references therein. Anteunis, M.; Daneels, D. *Org. Magn. Reson.* **1975**, *7*, 345. Eliel, E. L.; Rao, V. S.; Pietrusiewicz, K. M. *Ibid.* **1979**, 12, 461). The major **39** isomer exhibits the same NMR spectral characteristics (vs the minor isomer) as the trans compounds.

(46) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

(47) This ester was also the product (25%) of iodine-induced dehydration (see the Experimental Section).

(48) (a) Wenkert, E.; Guo, M.; Pizzo, F.; Ramachandran, K. *Helv. Chim. Acta* **1987**, *70*, 1429. (b) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299. (c) Babu, S. D.; Hrytsak, M. D.; Durst, T. *Can. J. Chem.* **1989**, *67*, 1071.

1715 (s), 1675 (s), C=C 1620 (s), 1580 (m) cm^{-1}; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, Me), 4.20 (q, 2, J = 7 Hz, OCH_2), 6.01 (d, 1, J = 11 Hz, H-2), 6.09 (dd, 1, J = 11, 7 Hz, H-5), 7.58 (dd, 1, J = 12, 11 Hz, H-3), 8.17 (dd, 1, J = 12, 11 Hz, H-4), 10.20 (d, 1, J = 7 Hz, H-6); ^{13}C NMR δ 13.9 (Me), 60.5 (OCH_2), 125.6 (C-2), 131.9 (C-5), 135.2 (C-3), 139.5 (C-4), 164.8 (C-1), 189.8 (C-6); exact mass m/e 154.0622 (calcd for $C_8H_{10}O_3$ 154.0630).

More elution furnished pale yellow, liquid ethyl 6-oxo-2-(*E*),4(*Z*)-hexadienoate (**2a**):[6a] 20%; UV λ_{max} 260 nm (ϵ 18 000); IR C=O 1710 (s), 1675 (s), C=C 1630 (m), 1590 (m) cm^{-1}; ^1H NMR δ 1.26 (t, 3, J = 7 Hz, Me), 4.14 (q, 2, J = 7 Hz, OCH_2), 6.06 (dd, 1, J = 11, 8 Hz, H-5), 6.12 (d, 1, J = 15 Hz, H-2), 6.91 (dd, 1, J = 12, 11 Hz, H-4), 8.10 (dd, 1, J = 15, 12 Hz, H-3), 10.24 (d, 1, J = 8 Hz, H-6); ^{13}C NMR δ 13.8 (Me), 60.7 (OCH_2), 129.5 (C-2), 132.5 (C-5), 135.6 (C-3), 142.5 (C-4), 165.3 (C-1), 189.6 (C-6).

A solution of 200 mg (1.3 mmol) of ester **1a** and 278 mg (2.6 mmol) of lithium diisopropylamide in 5 mL of tetrahydrofuran was stirred at −78 °C for 1 h. Hydrochloric acid (1 M) was added, and the mixture was extracted with ether. The extract was washed with brine, dried and evaporated, leaving 140 mg (70%) of a 3:1 liquid mixture of ethyl 2-furylacetate (**4b**):[13] ^1H NMR δ 1.26 (t, 3, J = 7 Hz, Me), 3.60 (s, 2, CH_2), 4.20 (q, 2, J = 7 Hz, OCH_2), 6.1–6.2 (m, 1, H-3), 6.2–6.3 (m, 1, H-4), 7.3–7.4 (m, 1, H-5), and ethyl 3-furylacetate (**4c**):[14] ^1H NMR δ 1.26 (t, 3, J = 7 Hz, Me), 3.45 (s, 2, CH_2), 4.20 (q, 2, J = 7 Hz, OCH_2), 6.25 (br s, 1, H-4), 7.35 (br s, 2, H-5, H-2).

Washing an ether solution of ester **3** with 5% hydrochloric acid solution converted the compound quantitatively into ester **4c**.

Reaction of 2,5-Dimethylfuran. Chromatography of the crude product mixture on neutral alumina (activity IV) and elution with 20:1 hexane–ethyl acetate led to colorless, liquid ethyl *exo*-1,3-dimethyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**7a**) [30%; IR and ^1H NMR spectrally identical with an authentic sample;[5] ^{13}C NMR 13.1 (1-Me or 3-Me), 13.5 (3-Me or 1-Me), 14.2 (ester Me), 29.6 (C-6), 35.8 (C-5), 60.1 (OCH_2), 74.1 (C-1), 101.5 (C-4), 156.0 (C-3), 172.5 (C=O)], and thereafter colorless, liquid ethyl 2,5-dimethyl-3-furylacetate (**8a** [5%; IR and ^1H NMR spectrally identical with an authentic sample],[5] and, finally, pale yellow, waxy solid ethyl 3-methyl-6-oxo-2(*Z*),4(*Z*)-heptadienoate (**6a**): 43%; IR C=O 1710 (s), 1640 (m), C=C 1590 (m) cm^{-1}; ^1H NMR 1.24 (t, 3, J = 7 Hz, ester Me), 1.99 (s, 3, Me), 2.17 (s, 3, α-keto Me), 4.05 (q, 2, J = 7 Hz, OCH_2), 5.66 (s, 1, H-2), 6.11 (d, 1, J = 12 Hz, H-5), 6.89 (d, 1, J = 12 Hz, H-4); ^{13}C NMR δ 13.6 (ester Me), 22.5 (Me), 30.0 (C-7), 59.2 (OCH_2), 117.6 (C-2), 126.5 (C-5), 141.5 (C-4), 153.0 (C-3), 165.0 (C-1), 197.3 (C-6).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.64; H, 7.74. Found: C, 65.55; H, 7.71.

Chromatography of the crude product mixture on silica gel and elution with 20:1 hexane–ethyl acetate gave ester **8a** (3%) and ethyl 3-methyl-6-oxo-2(*Z*),4(*E*)-heptadienoate (**9a**): 47%; IR and ^1H NMR spectrally identical with an authentic sample;[5] ^{13}C NMR δ 13.9 (ester Me), 20.2 (Me), 26.2 (C-7), 60.0 (OCH_2), 123.5 (C-2), 132.6 (C-5), 139.2 (C-4), 147.9 (C-3), 165.1 (C-1), 199.3 (C-6).

Reaction of 2-Methylfuran. Chromatography of the crude product mixture on neutral alumina (activity IV) and elution with 20:1 hexane–ethyl acetate yielded a ca. 1:2 mixture (2%) of colorless, liquid ethyl 2-methyl-3-furylacetate (**4a**) [^1H NMR δ 1.25 (t, 3, J = 7 Hz, ester Me), 2.23 (s, 3, Me), 3.22 (s, 2, CH_2), 4.09 (q, 2, J = 7 Hz, OCH_2), 6.76 (br s, 1, H-4), 7.14 (br s, 1, H-5)] and of colorless, liquid ethyl 2-methyl-4-furylacetate (**8b**): ^1H NMR δ 1.31 (t, 3, J = 7 Hz, ester Me), 2.25 (s, 3, Me), 3.26 (s, 2, CH_2), 4.20 (q, 2, J = 7 Hz, OCH_2), 5.88 (br s, 1, H-3), 6.20 (br s, 1, H-5); exact mass m/e 168.0780 (calcd for $C_9H_{12}O_3$ 168.0786).

Further elution gave colorless, sweetly odorous, liquid ethyl *exo*-1-methyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**7c**) [2%; ^1H NMR δ 0.90 (d, 1, J = 4 Hz, H-6), 1.26 (t, 3, J = 7 Hz, ester Me), 1.71 (s, 3, Me), 2.56 (dd, 1, J = 4, 4 Hz, H-5), 4.08 (q, 2, J = 7 Hz, OCH_2), 5.37 (dd, 1, J = 4, 3 Hz, H-4), 6.27 (d, 1, J = 3 Hz, H-3); ^{13}C NMR δ 13.3 (Me), 14.2 (ester Me), 28.1 (C-6), 34.6 (C-5), 60.3 (OCH_2), 74.1 (C-1), 106.8 (C-4), 146.1 (C-3), 172.4 (C=O); exact mass m/e 168.0776 (calcd for $C_9H_{12}O_3$ 168.0786)] and colorless, sweet-smelling, liquid ethyl *exo*-3-methyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**7b**): 10%; ^1H NMR δ 0.90 (dd, 1, J = 3, 1 Hz, H-6), 1.24 (t, 3, J = 7 Hz, ester Me), 1.79 (s, 3, Me), 2.61 (dd, 1, J = 6, 3 Hz, H-5), 4.04 (q, 2, J = 7 Hz, OCH_2), 4.67 (dd, 1, J = 6, 1 Hz, H-1), 5.00 (br s, 1, H-4); ^{13}C NMR δ 13.0 (Me), 13.3 (ester Me), 22.9 (C-6), 32.4 (C-5), 60.2 (OCH_2), 67.0 (C-1), 100.6 (C-4), 157.1 (C-3), 172.6 (C=O); exact mass m/e 168.0790 (calcd for $C_9H_{12}O_3$ 168.0786).

Yet more elution yielded pale yellow, liquid ethyl 6-oxo-2-(*Z*),4(*Z*)-heptadienoate (**6b**) [12%; ^1H NMR δ 1.28 (t, 3, J = 7 Hz, ester Me), 2.22 (s, 3, Me), 4.16 (q, 2, J = 7 Hz, OCH_2), 5.90 (d, 1, J = 10 Hz, H-2), 6.26 (d, 1, J = 10 Hz, H-5), 7.68 (dd, 1, J = 11, 10 Hz, H-3), 7.70 (dd, 1, J = 11, 10 Hz, H-4); ^{13}C NMR δ 13.9 (ester Me), 31.4 (C-7), 60.0 (OCH_2), 124.5 (C-2), 130.1 (C-5), 134.9 (C-3), 138.2 (C-4), 165.2 (C-1), 198.5 (C-6); exact mass m/e 168.0795 (calcd for $C_9H_{12}O_3$ 168.0786)] and, finally, yellow, waxy, solid ethyl 6-oxo-2(*E*),4(*Z*)-heptadienoate (**10a**): 31%; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, ester Me), 2.24 (s, 3, Me), 4.18 (q, 2, J = 7 Hz, OCH_2), 6.00 (d, 1, J = 16 Hz, H-5), 6.24 (d, 1, J = 11 Hz, H-2), 6.42 (dd, 1, J = 12, 11 Hz, H-3), 8.18 (dd, 1, J = 16, 12 Hz, H-4); ^{13}C NMR δ 13.5 (ester Me), 30.8 (C-7), 59.9 (OCH_2), 128.9 (C-2), 130.4 (C-5), 137.1 (C-3), 138.3 (C-4), 165.2 (C-1), 197.5 (C-6).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.07.

MPLC of the crude product mixture and elution with 20:1 hexane–ethyl acetate led (in order of elution) to a ca. 1:1 mixture (2%) of esters **4d** and **8b**, and ester**7c** (2%), **6b** (12%), ethyl 3-methyl-6-oxo-2(*Z*),4(*E*)-hexadienoate (**9b**) [ca. 1%; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, ester Me), 2.09 (s, 3, Me), 4.14 (q, 2, J = 7 Hz, OCH_2), 5.92 (br s, 1, H-2), 6.30 (dd, 1, J = 16, 8 Hz, H-5), 8.58 (d, 1, J = 16 Hz, H-4), 9.69 (d, 1, J = 8 Hz, H-6); ^{13}C NMR δ 14.0 (ester Me), 20.3 (Me), 60.4 (OCH_2), 124.4 (C-2), 133.2 (C-5), 147.2 (C-3), 147.3 (C-4), 165.3 (C-1), 194.3 (C-6)], and **10a** (38%).

Reaction of 2-(*n*-Octyl)furan. A hexane solution (1.6 M, 200 mL) of *n*-butyllithium was added over a 0.5-h period to a stirring solution of 19.0 g (0.28 mol) of furan in 100 mL of tetrahydrofuran at −40 °C, and the stirring was continued for 4 h. A solution of 48.2 g (0.25 mol) of *n*-octyl bromide in 100 mL of tetrahydrofuran was added, and the solution was permitted to warm to room temperature. After 12 h water was added, and the mixture was extracted with ether. The extract was dried and evaporated, leaving liquid 2-*n*-octylfuran [^1H NMR δ 0.87 (t, 3, J = 7 Hz, Me), 1.1–1.4 (m, 12, methylenes), 2.58 (t, 2, J = 7 Hz, benzyl H's), 5.90 (d, 1, J = 3 Hz, H-3), 6.22 (dd, 1, J = 3, 2 Hz, H-4), 7.23 (d, 1, J = 2 Hz, H-5)], which was used in the reaction with diazoacetic ester and dirhodium tetraacetate.

The yellow, solid, crude product mixture consisted of a ca. 1.5:1 two-component system, whose minor substance was chromatographically too unstable to be isolated in pure state. However the ^1H NMR spectrum of the mixture revealed it to be ethyl 6-oxo-2(*Z*),4(*Z*)-tetradecadienoate (**6c**) [δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.4 (m, 10, methylenes), 1.31 (t, 3, J = 7 Hz, ester Me), 1.62 (quint, 2, J = 7 Hz, H-8), 2.50 (t, 2, J = 7 Hz, H-7), 4.23 (q, 2, J = 7 Hz, OCH_2), 6.2–6.3 (m, 2, H-2, H-5), 7.6–7.8 (m, 2, H-3, H-4). MPLC of the crude mixture and elution with 20:1 hexane–ethyl acetate gave yellow needles of ethyl 6-oxo-2(*E*),4(*Z*)-tetradecadienoate (**10b**): 60%; mp 60–61 °C; IR (Nujol) C=O 1700 (s), 1685 (s), C=C 1625 (s), 1570 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.4 (m, 10, methylenes), 1.31 (t, 3, J = 7 Hz, ester Me), 1.62 (quint, 2, J = 7 Hz, H-8), 2.52 (t, 3, J = 7 Hz, H-7), 4.23 (q, 2, J = 7 Hz, OCH_2), 6.10 (d, 1, J = 15 Hz, H-2), 6.28 (d, 1, J = 11 Hz, H-5), 6.46 (dd, 1, J = 11, 11 Hz, H-4), 8.29 (dd, 1, J = 15, 11 Hz, H-3); ^{13}C NMR δ 14.0 (Me), 14.1 (Me), 22.5 (C-13), 23.8 (C-8), 29.0 and 29.0 and 29.3 (C-9, C-10, C-11), 31.7 (C-12), 44.3 (C-7), 60.6 (OCH_2), 129.6 (C-2), 130.5 (C-5), 137.9 (C-4), 138.7 (C-3), 165.9 (C-1), 200.9 (C-6).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.20; H, 9.80.

Ethyl *exo*-3-(Methoxycarbonyl)-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (7d). A solution of 1.90 g (16.7 mmol) of ethyl diazoacetate in 8 mL of methylene chloride (distilled from calcium hydride) was added dropwise over a 12-h period to a stirring mixture of 2.10 g (16.7 mmol) of methyl furoate and 25 mg of dirhodium tetraacetate in 10 mL of dry methylene chloride at room temperature. Stirring was continued for 3 h, and the mixture was then filtered through an alumina pad. The filtrate was evaporated, and the residue was chromatographed on neutral alumina (activity III). Elution with 10:1 hexane–ethyl acetate led to the recovery of 708 mg of methyl furoate and then to 1.28 g (55%) of colorless, liquid ester **7d**: IR C=O 1730 (s), 1719 (s), C=C 1608 (m) cm^{-1}; ^1H NMR δ (CCl_4) 1.02 (d, 1, J = 3 Hz, H-6),

1.25 (t, 3, J = 7 Hz, Me), 2.74 (ddd, 1, J = 5, 3, 3 Hz, H-5), 3.75 (s, 3, OMe), 4.08 (q, 2, J = 7 Hz, OCH_2), 4.88 (d, 1, J = 5 Hz, H-1), 6.26 (d, 1, J = 3 Hz, H-4); ^{13}C NMR δ 14.1 (Me), 21.4 (C-6), 31.9 (C-5), 52.1 (OMe), 61.0 (OCH_2), 67.4 (C-1), 116.0 (C-4), 149.0 (C-3), 159.4 (C=O on C-3), 171.6 (C=O); m/e 212 (M^+, 8), 153 (27), 139 (base), 29 (32); exact mass m/e 212.0687 (calcd for $C_{10}H_{12}O_5$ 212.0685).

Ethyl *exo*-3-[(*E*)-2-Carbomethoxyvinyl]-2-oxabicyclo-[3.1.0]hex-3-ene-6-carboxylate (12). The same reaction was carried out with 1.32 g (10.8 mmol) of ethyl diazoacetate, 4.20 g (27.6 mmol) of methyl β-(2-furyl)acrylate, and 20 mg of dirhodium tetraacetate. Elution of the alumina chromatogram of the crude product mixture with 15:1 hexane–ethyl acetate yielded 2.94 g of recovered furan derivative and 1.01 g (51%) of colorless, crystalline diester **12**: mp 77–79 °C; UV λ_{max} 218 nm (ϵ 8200), 295 (12 100); IR (CCl_4) C=O 1724 (s), C=C 1647 (m), 1586 (w) cm^{-1}; ^1H NMR δ 1.12 (d, 1, J = 3 Hz, H-6), 1.24 (t, 3, J = 7 Hz, Me), 2.81 (ddd, 1, J = 6, 3, 3 Hz, H-5), 3.74 (s, 3, OMe), 4.17 (q, 2, J = 7 Hz, OCH_2), 4.88 (d, 1, J = 6 Hz, H-1), 5.73 (d, 1, J = 3 Hz, H-4), 6.08 (d, 1, J = 16 Hz, acroyl α-H), 7.02 (d, 1, J = 16 Hz, acroyl β-H); ^{13}C NMR δ 14.1 (Me), 23.1 (C-6), 32.5 (C-5), 51.6 (OMe), 60.7 (OCH_2), 67.0 (C-1), 112.8 (C-4), 119.1 (α-C), 130.9 (β-C), 155.0 (C-3), 166.7 (C=O on C-3), 171.6 (C=O); m/e 238 (M^+, 6), 165 (base), 97 (53), 29 (42).

Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.55; H, 5.82.

1,4-Diacyl-1(*E*),3(*E*)-butadienes. A solution of the crude product mixture of the furan–diazoester reaction and two iodine crystals in 15 mL of dry methylene chloride was kept at room temperature for 6 h and then evaporated. An ether solution of the residue was washed with 10% sodium thiosulfate solution and with brine, dried, and evaporated.

MPLC of the residue derived from furan and elution with 20:1 hexane–ethyl acetate afforded pale yellow, liquid ethyl 6-oxo-2-(*E*),4(*E*)-hexadienoate (**11a**): 68% IR C=O 1715 (s), 1685 (s), C=C 1635 (w), 1600 (m) cm^{-1}; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, Me), 4.19 (q, 2, J = 7 Hz, OCH_2), 6.23 (d, 1, J = 15 Hz, H-2), 6.38 (dd, 1, J = 15, 8 Hz, H-5), 7.14 (dd, 1, J = 15, 12 Hz, H-3), 7.40 (dd, 1, J = 15, 12 Hz, H-4), 9.62 (d, 1, J = 8 Hz, H-6); ^{13}C NMR δ 14.0 (Me), 60.9 (OCH_2), 129.8 (C-2), 136.8 (C-5), 140.1 (C-3), 147.1 (C-4), 165.3 (C-1), 192.8 (C-6); exact mass m/e 154.0619 (calcd for $C_8H_{10}O_3$ 154.0630).

MPLC of the residue derived from 2,5-dimethylfuran and elution with 10:1 hexane–ethyl acetate led to a mixture of ester **9a**[5] (23%; identical with the sample reported above) and crystalline ethyl 3-methyl-6-oxo-2(*E*),4(*E*)-heptadienoate (**11b**): 47%; mp 49–51 °C; IR (Nujol) C=O 1715 (s), 1665 (s), C=C 1660 (m), 1609 (m) cm^{-1}; ^1H NMR spectrally identical with previous data;[5] ^{13}C NMR δ 13.0 (Me), 13.7 (ester Me), 27.3 (C-7), 59.7 (OCH_2), 125.6 (C-2), 130.8 (C-5), 144.8 (C-4), 148.6 (C-3), 165.3 (C-1), 197.2 (C-6).

Anal. Calcd for $C_{10}H_{14}O_3$: C. 65.64; H, 7.74. Found: C, 65.70; H, 7.82.

Treatment of each isomer with iodine separately gave the same isomer mixture.

MPLC of the residue derived from 2-methylfuran and elution with 10:1 hexane–ethyl acetate furnished a yellow, waxy solid of ethyl 6-oxo-2(*E*),4(*E*)-heptadienoate (**11c**): 85%; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, ester Me), 2.25 (s, 3, Me), 4.17 (q, 2, J = 7 Hz, OCH_2), 6.16 (d, 1, J = 15 Hz, H-2), 6.37 (d, 1, J = 15 Hz, H-5), 7.07 (dd, 1, J = 15, 11 Hz, H-3), 7.25 (dd, 1, J = 15, 11 Hz, H-4); ^{13}C NMR δ 13.5 (Me), 27.0 (C-7), 60.0 (OCH_2), 128.3 (C-2), 135.6 (C-5), 138.5 (C-4), 140.7 (C-3), 164.9 (C-1), 196.9 (C-6).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.20.

MPLC of the residue derived from 2-*n*-octylfuran and elution with 20:1 hexane–ethyl acetate gave colorless, crystalline ethyl 6-oxo-2(*E*),4(*E*)-tetradecadienoate (**11d**): 66%; mp 79–80 °C; UV λ_{max} 273 nm (ϵ 18 000); IR (Nujol) C=O 1710 (s), 1685 (s), C=C 1590 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.6 (br s, 12, methylenes), 1.30 (t, 3, J = 7 Hz, ester Me), 2.60 (t, 2, J = 7 Hz, C-7 H's), 4.24 (q, 2, J = 7 Hz, OCH_2), 6.23 (d, 1, J = 15 Hz, H-2), 6.45 (d, 1, J = 15 Hz, H-5), 7.18 (dd, 1, J = 15, 12 Hz, H-3), 7.32 (dd, 1, J = 15, 11 Hz, H-4); ^{13}C NMR δ 14.0 (Me), 14.1 (Me), 22.5 (C-13), 23.9 (C-8), 29.0 and 29.1 and 29.2 (C-9, C-10, C-11), 31.6 (C-12), 41.2 (C-7), 60.9 (OCH_2), 128.7 (C-2), 135.2 (C-5), 138.0 (C-4), 141.2 (C-3), 165.6 (C-1), 200.0 (C-6).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.29; H, 9.80.

Chromatography of the residue derived from methyl β-(2-furyl)acrylate on Florisil and elution with methylene chloride yielded yellow, crystalline methyl 9-ethoxy-4,9-dioxo-2(*E*),5(*E*),7(*E*)-nonatrienoate (**13**): 77%; mp 107–108 °C; UV λ_{max} 288 nm (ϵ 15 800); IR (CCl_4) C=O 1728 (s), 1681 (m), 1670 (s), C=C 1625 (m), 1595 (s) cm^{-1}; ^1H NMR δ 1.33 (t, 3, J = 7 Hz, Me), 3.84 (s, 3, OMe), 4.26 (q, 2, J = 7 Hz, OCH_2), 6.31 (d, 1, J = 16 Hz, H-8), 6.69 (d, 1, J = 16 Hz, H-5), 6.83 (dd, 1, J = 16, 16 Hz, H-7), 7.35 (d, 1, J = 14 Hz, H-2), 7.36 (d, 1, J = 14 Hz, H-3), 7.38 (dd, 1, J = 16, 16 Hz, H-6); ^{13}C NMR δ 14.1 (Me), 52.3 (OMe), 60.9 (OCH_2), 130.2 (C-8), 131.4 (C-5), 133.7 (C-2), 137.9 (C-3), 140.6 (C-6 or C-7), 141.0 (C-7 or C-6), 165.4 (C-1 or C-9), 165.6 (C-9 or C-1); m/e 238 (M^+, 6), 165 (base), 97 (90), 29 (73).

Anal. Calcd for $C_{12}H_{14}O$: C, 60.50; H, 5.92. Found: C. 60.25; H, 5.99.

Ethyl 7-Methoxy-6,7-dioxo-2(*E*),4(*E*)-heptadienoate (11e). An ethereal solution (5 mL) of boron trifluoride etherate and 700 mg (3.3 mmol) of diester **7d** was kept at 0 °C for 12 h and then evaporated. The residue was chromatographed through a short Florisil column and eluted with methylene chloride. The eluates were evaporated and the residue crystallized from hexane–ether, yielding 559 mg (80%) of yellow, crystalline diester **11e**: mp 105–106 °C; UV λ_{max} 282 nm (ϵ 14 600); IR ($CHCl_3$) C=O 1740 (s), 1714 (s), 1700 (s), C=C 1598 (s) cm^{-1}; ^1H NMR δ 1.31 (t, 3, J = 7 Hz, Me), 3.92 (s, 3, OMe), 4.24 (q, 2, J = 7 Hz, OCH_2), 6.34 (d, 1, J = 15 Hz, H-2), 7.08 (d, 1, J = 15 Hz, H-5), 7.37 (dd, 1, J = 15, 12 Hz, H-3), 7.52 (dd, 1, J = 15, 12 Hz, H-4); ^{13}C NMR δ 14.1 (Me), 53.1 (OMe), 61.0 (OCH_2), 129.6 (C-2), 131.4 (C-5), 140.3 (C-3), 143.8 (C-4), 161.5 (C-7), 165.3 (C-1), 181.9 (C-6).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.50; H, 5.80.

Reactions of Ethyl α-Diazopropionate with Furans. General Procedure. The above conditions for diazoacetic ester reactions were adopted for those of ethyl α-diazopropionate.

Reaction of Furan. Chromatography of the crude product mixture on neutral alumina (activity III) and elution with 20:1 hexane–ethyl acetate furnished colorless, pleasantly odoriferous, liquid ethyl *exo*-6-methyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**16a**): 53%; IR (CCl_4) C=O 1712 (s), C=C 1592 (m) cm^{-1}; ^1H NMR δ 0.94 (s, 3, Me), 1.25 (t, 3, J = 7 Hz, ester Me), 2.84 (dd, 1, J = 6, 3 Hz, H-5), 4.12 (q, 2, J = 7 Hz, OCH_2), 4.73 (d, 1, J = 6 Hz, H-1), 5.23 (t, 1, J = 3 Hz, H-4), 6.42 (d, 1, J = 3 Hz, H-3); m/e 168 (M^+, 25), 95 (base); exact mass m/e 168.0793 (calcd for $C_9H_{12}O_3$ 168.0786).

Further elution afforded pale yellow, liquid ethyl 2-methyl-6-oxo-2(*E*),4(*Z*)-hexadienoate (**17a**): 7%; IR (CCl_4) C=O 1712 (s), 1682 (s), C=C 1629 (m), 1592 (w) cm^{-1}; ^1H NMR δ 1.32 (t, 3, J = 7 Hz, ester Me), 2.06 (s, 3, Me), 4.25 (q, 2, J = 7 Hz, OCH_2), 6.06 (dd, 1, J = 11, 8 Hz, H-5), 7.22 (dd, 1, J = 12, 11 Hz, H-4), 8.03 (d, 1, J = 12 Hz, H-3), 10.33 (d, 1, J = 8 Hz, H-6); m/e 168 (M^+, 25), 123 (30), 111 (29), 95 (base), 73 (30); exact mass m/e 168.0786 (calcd for $C_9H_{12}O_3$ 168.0786).

Reaction of 2-Methylfuran. Chromatography of the crude produce mixture on neutral alumina (activity III) and elution with 20:1 hexane–ethyl acetate yielded colorless, sweet-smelling, liquid ethyl *exo*-3,6-dimethyl-2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (**16b**): 51%; IR (CCl_4) C=O 1710 (s), C=C 1652 (m) cm^{-1} ^1H NMR δ 0.91 (s, 3, Me), 1.24 (t, 3, J = 7 Hz, ester Me), 1.83 (s, 3, 3-Me), 2.78 (dd, 1, J = 6, 3 Hz, H-5), 4.08 (q, 2, J = 7 Hz, OCH_2), 4.66 (d, 1, J = 6 Hz, H-1), 4.87 (d, 1, J = 3 Hz, H-4); ^{13}C NMR δ 5.6 (6-Me), 12.7 (3-Me), 14.2 (ester Me), 18.6 (C-6), 37.9 (C-5), 60.5 (OCH_2), 70.5 (C-1), 97.5 (C-4), 158.4 (C-3), 174.6 (C=O); m/e 182 (M^+, 16), 153 (25), 109 (base), 43 (82); exact mass m/e 182.0929 (calcd for $C_{10}H_{14}O_3$ 182.0943).

Further elution gave pale yellow, liquid ethyl 2-methyl-6-oxo-2(*E*),4(*Z*)-heptadienoate (**17b**): 18%, IR (CCl_4) C=O 1714 (s), 1695 (s), C=C 1620 (w), 1574 (w) cm^{-1}; ^1H NMR δ 1.30 (t, 3, J = 7 Hz, ester Me), 2.01 (s, 3, 2-Me), 2.27 (s, 3, α-keto Me), 4.20 (q, 2, J = 7 Hz, OCH_2), 6.21 (d, 1, J = 12 Hz, H-5), 6.65 (dd, 1, J = 12, 12 Hz, H-4), 8.18 (d, 1, J = 12 Hz, H-3); ^{13}C NMR δ 12.6 (Me), 14.1 (ester Me), 31.6 (C-7), 61.0 (OCH_2), 129.4 (C-5), 132.2 (C-3), 135.1 (C-4), 135.9 (C-2), 167.8 (C-1), 198.7 (C-6); m/e 182 (M^+, 9), 153 (24), 109 (86), 43 (base), 29 (38); exact mass m/e

182.0942 (calcd for $C_{10}H_{14}O_3$: 182.0943).

Chromatography of the initial crude product mixture on silica gel and elution with 15:1 hexane–ethyl acetate produced keto ester **17b** (75%).

Ethyl 2-Methyl-6-oxo-2(*E*),4(*E*)-hexadienoate (18a). Treatment of the crude product mixture of the furan–diazopropionic ester reaction with iodine under the conditions described above, chromatography of the resultant crude product on neutral alumina (activity III) and elution with 15:1 hexane–ethyl acetate led to colorless, crystalline aldehydo ester **18a**: 63%; mp 34–35 °C; UV λ_{max} 277 nm (ϵ 29 300); IR (CCl_4) C=O 1715 (s), 1692 (s), C=C 1633 (m), 1594 (w) cm^{-1}; ^1H NMR δ 1.34 (t, 3, J = 7 Hz, ester Me), 2.12 (d, 3, J = 1 Hz, Me), 6.40 (dd, 1, J = 15, 8 Hz, H-5), 7.33 (dd, 1, J = 12, 1 Hz, H-3), 7.45 (dd, 1, J = 15, 12 Hz, H-4), 9.70 (d, 1, J = 8 Hz, H-6); ^{13}C NMR δ 13.4 (Me), 14.1 (ester Me), 61.2 (OCH_2), 133.9 (C-3), 135.8 (C-5), 137.0 (C-2), 144.9 (C-4), 166.9 (C-1), 193.1 (C-6).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.35; H, 7.10.

Ethyl 2-Methyl-6-oxo-2(*E*),4(*E*)-heptadienoate (18b). Treatment of the crude product mixture of the 2-methylfuran-/α-diazopropionic ester reaction with iodine under the conditions described above, MPLC of the resultant crude product and elution with 20:1 hexane–ethyl acetate afforded pale yellow, liquid keto ester **18b**: 72%: UV λ_{max} 279 nm (ϵ 28 000); IR (CCl_4) C=O 1714 (s), 1696 (s), 1675 (s), C=C 1624 (w), 1596 (m) cm^{-1}; ^1H NMR δ 1.33 (t, 3, J = 7 Hz, ester Me), 2.09 (d, 3, J = 1 Hz, Me), 2.34 (s, 3, α-keto Me), 4.25 (q, 2, J = 7 Hz, OCH_2), 6.41 (d, 1, J = 15 Hz, H-5), 7.24 (dd, 1, J = 12, 1 Hz, H-3), 7.44 (dd, 1, J = 15, 12 Hz, H-4); ^{13}C NMR δ 13.3 (2-Me), 14.1 (ester Me), 28.0 (C-7), 61.0 (OCH_2), 134.7 (C-3), 134.7 (C-4), 136.0 (C-2), 136.5 (C-5), 167.2 (C-1), 197.8 (C-6); m/e 182 (M^+, 4), 153 (12), 43 (base), 29 (27); exact mass m/e 182.0943 (calcd for $C_{10}H_{14}O_3$ 182.0943).

Diethyl 2,7-Dimethyl-2(*E*),4(*E*),6(*E*)-octatriene-1,8-dioate (19). A suspension of 54 mg (1.8 mmol) of 80% sodium hydride (washed with hexane) in 5 mL of dry tetrahydrofuran was added dropwise over a 5-min period to a stirring solution of 352 mg (1.5 mmol) of triethyl α-phosphonopropionate in 5 mL of dry tetrahydrofuran at room temperature, and stirring was continued for 10 min. A solution of 150 mg (0.9 mmol) of aldehydo ester **18a** in 5 mL of tetrahydrofuran was added dropwise over a 5-min period, and the stirring was continued for 12 h. Water (10 mL) was added, and the mixture was extracted with ether. The extract was washed with brine, dried, and evaporated. Crystallization of the residual solid from hexane–ether gave 141 mg (63%) of pale yellow, crystalline diester **19**: mp 87–89 °C; UV λ_{max} 313 nm (ϵ 56 400), $\lambda_{shoulder}$ 324 (50 300); IR (CCl_4) C=O 1730 (s), C=C 1655 (m) cm^{-1}; ^1H NMR δ 1.34 (t, 6, J = 7 Hz, ester methyls), 2.02 (d, 6, J = 1 Hz, methyls), 4.23 (q, 4, J = 7 Hz, 2 OCH_2), 6.80 (dm, 2, J = 8 Hz, H-4, H-5), 7.30 (dd, 2, J = 8, 1 Hz, H-3, H-6); ^{13}C NMR δ 12.9 (Me), 14.2 (ester Me), 60.7 (OCH_2), 130.1 (C-2), 133.4 (C-4), 137.0 (C-3), 167.9 (C=O); m/e 252 (M^+, 30), 223 (49), 177 (82), 107 (base), 93 (67), 43 (52), 29 (32).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.75; H, 7.81.

Ethyl 2,6-Dimethyl-8-methoxy-8-oxo-2(*E*),4(*E*),6(*E*)-octatrienoate (20) and Its 6(*Z*) Isomer (21). The reaction conditions and workup of the **18a** → **19** transformation were applied to the reactions of 740 mg (4.1 mmol) of trimethyl phosphonoacetate, 123 mg (4.1 mmol) of 80% sodium hydride, and 372 mg (2.2 mmol) of keto ester **18b**. MPLC of the solid, crude product mixture and elution with 10:1 hexane–ethyl acetate led to a ca. 2:1 **20–21** product mixture (by ^1H NMR analysis), whose crystallization from hexane–ether yielded 117 mg (24%) of colorless, crystalline diester **20**: mp 64–66 °C; UV λ_{max} 307 nm (ϵ 42 100); IR (CCl_4) C=O 1711 (s), C=C 1623 (m), 1609 (m), 1590 (w) cm^{-1}; ^1H NMR δ 1.32 (t, 3, J = 7 Hz, ester Me), 2.02 (d, 3, J = 1 Hz, 2-Me), 2.35 (d, 3, J = 1 Hz, 6-Me), 3.73 (s, 3, OMe), 4.23 (q, 2, J = 7 Hz, OCH_2), 5.89 (d, 1, J = 1 Hz, H-7), 6.55 (d, 1, J = 15 Hz, H-5), 6.87 (dd, 1, J = 15, 12 Hz, H-4), 7.25 (dd, 1, J = 12, 1 Hz, H-3); ^{13}C NMR δ 13.0 (2-Me), 13.7 (6-Me), 14.2 (ester Me), 51.1 (OMe), 60.7 (OCH_2), 121.2 (C-7), 128.9 (C-4), 130.2 (C-2), 136.8 (C-3), 141.4 (C-5), 151.3 (C-6), 166.9 (C-8), 167.8 (C=O); m/e 238 (M^+, 1), 109 (20), 43 (base), 29 (19).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.70; H, 7.55.

Evaporation of the mother liquor gave 243 mg (50%) of a ca. 1:1 mixture of diesters **20** and **21** [^1H NMR δ 1.32 (t, 3, J = 7 Hz, ester Me), 2.02 (s, 3, 2-Me), 2.09 (s, 3, 6-Me), 3.73 (s, 3, OMe), 4.23 (q, 2, J = 7 Hz, OCH_2), 5.79 (s, 1, H-7), 6.8–7.4 (m, 2, H-3, H-4), 8.02 (d, 1, J = 16 Hz, H-5); ^{13}C NMR δ 12.9 (2-Me), 14.2 (ester Me), 20.6 (6-Me), 51.0 (OMe), 60.6 (OCH_2), 119.1 (C-7), 130.0 (C-4), 130.2 (C-2), 135.2 (C-5), 137.6 (C-3), 149.7 (C-6), 166.2 (C-8), 167.8 (C=O)].

Reaction of 1-Diazo-2-decanone (24a) with Furan. A solution of 30 mg (0.17 mmol) of pelargonyl chloride in 20 mL of ether was added dropwise into a stirring solution of 0.36 mmol of diazomethane in 30 mL of ether at −78 °C. Evaporation of the solvent under vacuum led to 26 mg (85%) of liquid, yellow 1-diazo-2-decanone (**24a**): IR N_2 2100 (s), C=O 1635 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.7 (m, 12, methylenes), 2.3–2.4 (m, 2, α-keto H's), 5.26 (s, 1, H-1). Rhodium-catalyzed decomposition of the latter in furan followed the conditions of the furan–diazoacetic ester reaction described above and led to a ca. 7:1:1 mixture of ketones **25a**, **26a**, and **27a** in which chromatographically labile 6-oxo-2(*Z*),4(*Z*)-tetradecadienal (**26a**) could be discerned [^1H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.2–1.7 (m, 12, methylenes), 2.48 (t, 2, J = 7 Hz, C-7 H's), 6.04 (dd, 1, J = 11, 7 Hz, H-2), 6.43 (d, 1, J = 11 Hz, H-5), 7.38 (dd, 1, J = 11, 11 Hz, H-3), 8.05 (dd, 1, J = 11, 11 Hz, H-4), 10.17 (d, 1, J = 7 Hz, H-1)].

MPLC of the crude mixture and elution with 20:1 hexane–ethyl acetate produced colorless, liquid 1-(3-furyl)-2-decanone (**27a**) [9%; IR C=O 1718 (s), C=C 1595 (w) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.6 (m, 12, methylenes), 2.36 (t, 2, J = 7 Hz, C-3 H's), 3.39 (s, 2, C-1 Hs), 6.22 (br s, 1, furyl H-4), 7.30 (br s, 2, furyl H-2, H-5); ^{13}C NMR δ 14.0 (Me), 22.5 (C-9), 23.7 (C-4), 29.0 and 29.0 and 29.2 (C-5, C-6, C-7), 31.7 (C-8), 39.0 (C-3), 41.9 (C-1), 111.3 (furyl C-4), 117.4 (furyl C-3), 140.3 (furyl C-5), 142.9 (furyl C-2), 208.0 (C-2); exact mass m/e 222.1610 (calcd for $C_{14}H_{22}O_2$ 222.1620)]; and then pale yellow, liquid 6-oxo-2(*E*),4-(*Z*)-tetradecadienal (**28**) [10%; UV λ_{max} 275 nm (ϵ 21 700); IR ald CH 2720 (w), C=O 1683 (s), C=C 1620 (m), 1575 (s) cm^{-1}; ^1H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.2–1.7 (m, 12, methylenes), 2.49 (t, 2, J = 7 Hz, C-7 H's), 6.22 (dd, 1, J = 16, 8 Hz, H-2), 6.26 (d, 1, J = 11 Hz, H-5), 6.54 (dd, 1, J = 11 11 Hz, H-4), 8.25 (dd, 1, J = 16, 11 Hz, H-3), 9.69 (d, 1, J = 8 Hz, H-1); ^{13}C NMR δ 13.9 (Me), 22.5 (C-13), 23.7 (C-8), 29.0 and 29.0 and 29.2 (C-9, C-10, C-11), 31.6 (C-12), 44.4 (C-7), 131.5 (C-5), 137.4 (C-4), 137.9 (C-2), 137.9 (C-3), 145.9 (C-3), 193.9 (C-1), 201.2 (C-6); exact mass m/e 222.1609 (calcd for $C_{14}H_{22}O_2$ 222.1620)]; and finally pale yellow, waxy, solid 6-oxo-2(*Z*),4(*E*)-tetradecadienal (**25a**): 60%; UV λ_{max} 279 nm (ϵ 45 000); IR ald CH 2720 (w), C=O 1665 (s), C=C 1614 (m), 1574 (m) cm^{-1}; ^1H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.2–1.6 (m, 12, methylenes), 2.57 (t, 2, J = 7 Hz, C-7 H's), 6.08 (dd, 1, J = 12, 7 Hz, H-2), 6.36 (d, 1, J = 16 Hz, H-5), 6.94 (dd, 1, J = 12, 12 Hz, H-3), 7.98 (dd, 1, J = 16, 12 Hz, H-4), 10.20 (d, 1, J = 7 Hz, H-1); ^{13}C NMR δ 13.9 (Me), 22.5 (C-13), 23.8 (C-8), 28.9 and 29.0 and 29.2 (C-9, C-10, C-11), 31.6 (C-12), 41.4 (C-7), 133.0 (C-2), 133.0 (C-5), 136.3 (C-4), 143.2 (C-3), 189.6 (C-1), 199.8 (C-6).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.70; H, 10.02.

6-Oxo-2(*E*),4(*E*)-tetradecadienal (29a). The crude product mixture of the furan/1-diazo-2-decanone reaction was treated with iodine under the conditions of the above 1,4-diacyl-1(*E*),3(*E*)-butadiene preparations. MPLC of the crude product and elution with 20:1 hexane–ethyl acetate afforded pale yellow, liquid keto aldehyde **29a**: 72%; UV λ_{max} 276 nm (ϵ 28 700); IR ald CH 2720 (w), C=O 1675 (s), C=C 1622 (m), 1590 (s) cm^{-1}; ^1H NMR δ 0.89 (t, 3, J = 7 Hz, Me), 1.2–1.7 (m, 12, methylenes), 2.53 (t, 2, J = Hz, C-7 Hs), 6.38 (dd, 1, J = 16, 7 Hz, H-2), 6.43 (d, 1, J = 16 Hz, H-5), 7.07 (dd, 1, J = 16, 11 Hz, H-4), 7.21 (dd, 1, J = 16, 11 Hz, H-3), 9.62 (d, 1, J = 7 Hz, H-1); ^{13}C NMR δ 13.7 (Me), 22.3 (C-13), 23.6 (C-8), 28.8 and 28.8 and 29.0 (C-9, C-10, C-11), 31.5 (C-12), 40.9 (C-7), 136.4 and 137.0 and 137.3 (C-2, C-4, C-5), 147.6 (C-3), 192.4 (C-1), 199.4 (C-6); exact mass m/e 222.1612 (calcd for $C_{14}H_{22}O_2$ 222.1620).

Reaction of Methyl 6-Diazo-5-oxohexanoate (24b) with Furan. Rhodium-promoted decomposition of diazo ketone **24b** in furan followed the conditions of the furan–diazoacetic ester reaction described above and led to a ca. 7:1:1 mixture of methyl 5,10-dioxo-6(*E*),8(*Z*)-decadienoate (**25b**) [^1H NMR δ 1.7–2.0 (m,

2, C-3 H's), 2.40 (t, 2, J = 7 Hz, C-2 H's), 2.75 (t, 2, J = 7 Hz, C-4 H's), 3.61 (s, 3, OMe), 6.20 (dd, 1, J = 11, 7 Hz, H-9), 6.45 (d, 1, J = 15 Hz, H-6), 7.15 (dd, 1, J = 11, 11 Hz, H-8), 8.05 (dd, 1, J = 15, 11 Hz, H-7), 10.30 (d, 1, J = 7 Hz, H-10)], methyl 5,10-dioxo-6(*Z*),8(*Z*)-decadienoate (**26b**) [^{1}H NMR δ 1.7–2.0 (m, 2, C-3 H's), 2.36 (t, 2, J = 7 Hz, C-2 H's), 2.70 (t, 2, J = 7 Hz, C-4 H's), 3.61 (s, 3, OMe), 6.15 (dd, 1, J = 11, 7 Hz, H-9), 6.42 (d, 1, J = 11 Hz, H-6), 7.40 (dd, 1, J = 11, 11 Hz, H-8), 8.06 (dd, 1, J = 11, 11 Hz, H-7), 10.26 (d, 1, J = 7 Hz, H-10)], and methyl 6-(3-furyl)-5-oxohexanoate (**27b**) [^{1}H NMR δ 1.6–1.9 (m, 2, C-3 H's), 2.20 (t, 2, J = 7 Hz, C-2 H's), 2.40 (t, 2, J = 7 Hz, C-4 H's), 3.40 (s, 2, C-6 H's), 3.52 (s, 3, OMe), 6.20 (br s, 1, furyl H-4), 7.26 (br s, 2, furyl H-2, H-5)] whose fragility in the laboratory air and on chromatography prevented its separation and full characterization of its constituents. Hence the mixture was treated immediately with iodine under the conditions of the above 1,4-diacyl-1(*E*),3(*E*)-butadiene preparations. MPLC of the crude products and elution with 4:1 hexane–ethyl acetate resulted in the isolation of pale yellow, crystalline methyl 5,10-dioxo-6(*E*),8(*E*)-decadienoate (**29b**): 68%; mp 67–68 °C; UV λ_{max} 279 nm (ϵ 32000); IR (Nujol) C=O 1728 (s), 1690 (s), 1676 (s), C=C 1618 (w), 1585 (m) cm^{-1}; ^{1}H NMR δ 1.89 (quint, 2, J = 7 Hz, C-3 H's), 2.30 (t, 2, J = 7 Hz, C-2 H's), 2.63 (t, 2, J = 7 Hz, C-4 H's), 3.61 (s, 3, OMe), 6.40 (dd, 1, J = 16, 8 Hz, H-9), 6.42 (d, 1, J = 16 Hz, H-6), 7.06 (dd, 1, J = 16, 11 Hz, H-8), 7.23 (dd, 1, J = 16, 11 Hz, H-7), 9.60 (d, 1, J = 8 Hz, H-10; ^{13}C NMR δ 18.4 (C-3), 32.3 (C-2), 39.3 (C-4), 51.0 (OMe), 136.0 (C-6), 137.0 (C-7 or C-9), 137.6 (C-9 or C-6), 147.5 (C-8), 172.9 (C-1), 192.5 (C-10), 198.3 (C-5).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.70; H, 6.68.

Ketophosphonates 30. A solution of 7.9 g (0.1 mol) of pyridine and 10.4 g (0.14 mol) of *tert*-butyl alcohol in 10 mL of dry tetrahydrofuran was added to a solution of 11.5 g (70 mmol) of methyl glutaryl chloride in 20 mL of dry tetrahydrofuran at −78 °C, and the mixture was permitted to warm to room temperature. After refluxing for 10 h the mixture was poured into water and extracted with ether. The extract was dried and evaporated, leaving 9.90 g (70%) of *tert*-butyl methyl glutarate [^{1}H NMR δ 1.45 (s, 9, methyls), 1.90 (q, 2, J = 7 Hz, β-C H's), 2.30 and 2.38 (t each, 2 each, J = 7 Hz, α-keto H's), 3.68 (s, 3, OMe)].

A 1.6 M hexane solution (3.75 mL) of *n*-butyllithium was added dropwise over a 0.5-h period to a stirring solution of 744 mg (6 mmol) of dimethyl methanephosphonate in 10 mL of tetrahydrofuran at −78 °C. A solution of 505 mg (2.5 mmol) of the diester in 10 mL of tetrahydrofuran was added, stirring was continued for 2 h, and the mixture was permitted to warm to room temperature. Ammonium chloride solution (5%) was added, and the mixture was extracted exhaustively with ether. Drying the extract and evaporation gave 550 mg (75%) of colorless, viscous, liquid *tert*-butyl 6-(dimethoxyphosphonyl)-5-oxohexanoate (**30a**): IR C=O 1720 (s), PO 1250 (s), 1150 (s) cm^{-1}; ^{1}H NMR δ 1.44 (s, 9, methyls), 1.86 (q, 2, J = 7 Hz, C-3 H's), 2.25 (t, 2, J = 7 Hz, C-2 H's), 2.68 (t, 2, J = 7 Hz, C-4 H's), 3.09 (d, 2, J = 23 Hz, H-6), 3.79 (d, 6, J = 11 Hz, methoxyls); ^{13}C NMR δ 18.5 (C-3), 27.8 (methyls), 34.0 (C-2), 41.3 (d, J = 128 Hz, C-6), 42.8 (C-4), 52.8 (d, J = 7 Hz, methoxyls), 80.1 (OC), 172.1 (C-1), 200.8 (d, J = 6 Hz, C-5); exact mass: m/e 234.1210 (calcd for $C_{12}H_{23}O_6P$ 234.1215).

A solution of 588 mg (2.0 mmol) of ketophosphonate **30a** in 10 mL of neat trifluoroacetic acid was kept at room temperature for 0.5 h. Removal of the solvent by vacuum distillation left 452 mg (95%) of colorless, viscous, liquid 6-(dimethoxyphosphonyl)-5-oxohexanoic acid (**30b**): IR OH 3400 (br m), C=O 1715 (s), PO 1210 (s), 1160 (s) cm^{-1}; ^{1}H NMR δ 1.90 (quint, 2, J = 7 Hz, C-3 H's), 2.40 (t, 2, J = 7 Hz, C-2 H's), 2.71 (t, 2, J = 7 Hz, C-4 H's), 3.19 (d, 2, J = 23 Hz, H-6), 3.79 (d, 6, J = 6 Hz, methyls); ^{13}C NMR δ 18.0 (C-3), 32.3 (C-2), 40.2 (d, J = 130 Hz, C-6), 42.7 (C-4), 53.5 (d, J = 7 Hz, methyls), 178.1 (C-1), 201.0 (d, J = 7 Hz, C-5); exact mass m/e (M^+ − OH) 221.0570 (calcd for $C_8H_{14}O_5P$ 221.0579).

A solution of 588 mg (2.0 mmol) of ketophosphonate **30a** and 5 mL of trifluoroacetic acid in 25 mL of dry methanol was refluxed for 10 h, and thereafter both acid and alcohol were removed by vacuum distillation. MPLC of the residue and elution with ethyl acetate afforded 479 mg (95%) of liquid, viscous, colorless methyl 6-(dimethoxyphosphonyl)-5-oxohexanoate (**30c**): IR C=O 1715 (s), 1725 (s), PO 1250 (s), 1172 (s) cm^{-1}; ^{1}H NMR δ 1.90 (quint, 2, J = 7 Hz, C-3 H's), 2.35 (t, 2, J = 7 Hz, C-2 H's), 2.70 (t, 2, J = 7 Hz, C-4 H's), 3.15 (d, 2, J = 23 Hz, H-6), 3.67 (s, 3, OMe), 3.80 (d, 6, J = 11 Hz, phosphonate methoxyls); ^{13}C NMR δ 18.0 (C-3), 32.1 (C-2), 40.3 (d, J = 128 Hz, C-6), 42.3 (C-4), 51.0 (OMe), 52.8 (d, J = 6 Hz, phosphonate methoxyls), 172.9 (C-1), 200.5 (d, J = 6 Hz, C-5); exact mass m/e 252.0762 (calcd for $C_9H_{17}O_6P$ 252.0763).

The reaction conditions and workup for the above preparation of ketophosphonate **30a** were duplicated for the interaction of *n*-butyllithium with dimethyl methanephosphonate and thereafter with methyl pelargonate. This procedure yielded colorless, liquid, viscous dimethyl 2-oxodecane-1-phosphonate (**30d**): IR C=O 1715 (s), PO 1250 (s), 1180 (m) cm^{-1}; ^{1}H NMR δ 0.88 (t, 3, J = 7 Hz, Me), 1.2–1.6 (m, 12, methylenes), 2.61 (t, 2, J = 7 Hz, C-3 H's), 3.09 (d, 2, J = 23 Hz, C-1 H's), 3.79 (d, 6, J = 11 Hz, methoxyls); ^{13}C NMR δ 13.9 (C-10), 22.0 (C-4 or C-9), 22.8 (C-9 or C-4), 28.3 and 28.5 and 28.7 (C-5, C-6, C-7), 31.2 (C-8), 40.5 (d, J = 129 Hz, C-1), 43.5 (C-3), 52.2 (d, J = 6 Hz, methoxyls), 201.6 (d, 2, J = 6 Hz, C-2 H's); exact mass m/e 264.1491 (calcd for $C_{12}H_{25}O_4P$ 264.1490).

Horner–Emmons Reactions. General Procedure. A mixture of 5.2 mmol of ketophosphonate and 125 mg (5.2 mmol) of sodium hydride in 30 mL of anhydrous 1,2-dimethoxyethane was stirred at room temperature for 2 h and a solution of 4.7 mmol of keto aldehyde was then added dropwise. Stirring was continued for 0.5 h, 5% ammonium chloride solution was added, and the mixture was extracted with ether. The extract was dried and evaporated.

The **29a–30a** reaction produced colorless, amorphous *tert*-butyl 5,12-dioxo-6(*E*),8(*E*),10(*E*)-eicosatrienoate (**31b**): 75%; mp 110–111 °C; UV λ_{max} 316 nm (ϵ 35000); IR (Nujol) C=O 1720 (s), 1670 (s), C=C 1595 (s) cm^{-1}; ^{1}H NMR δ 0.89 (t, 3, J = 7 Hz, C-20 H's), 1.2–1.9 (m, 14, methylenes), 1.42 (s, 9, methyls), 2.20 (t, 2, J = 7 Hz, C-2 H's), 2.47 (t, 2, J = 7 Hz, C-4 H's), 2.56 (t, 2, J = 7 Hz, C-13 H's), 6.20 (d, 1, J = 15 Hz, H-6 or H-11), 6.21 (d, 1, J = 15 Hz, H-11 or H-6), 6.6–6.7 (m, 2, H-8, H-9), 7.1–7.2 (m, 2, H-7, H-10); ^{13}C NMR δ 13.9 (C-20), 19.3 (C-3), 22.5 (C-19), 24.0 (C-14), 27.9 (methyls), 29.0 and 29.1 and 29.2 (C-15, C-16, C-17), 31.6 (C-18), 34.4 (C-2), 39.8 (C-4), 41.0 (C-13), 80.1 (OC), 131.8 (C-6 or C-11), 132.1 (C-11 or C-6), 137.9 (C-8 or C-9), 138.2 (C-9 or C-8), 139.9 (C-7 or C-10), 140.3 (C-10 or C-7), 172.2 (C-1), 199.1 (C-5), 200.1 (C-12).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.95; H, 9.90.

The **29a–30c** reaction gave colorless, crystalline methyl 5,12-dioxo-6(*E*),8(*E*),10(*E*)-eicosatrienoate (**31c**): 70%; mp 125–125.5 °C; UV λ_{max} 316 nm (ϵ 40000); IR (Nujol) 1725 (s), 1680 (s), C=C 1590 (s) cm^{-1}; ^{1}H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–2.0 (m, 14, methylenes), 2.39 (t, 2, J = 7 Hz, C-2 H's), 2.58 (t, 2, J = 7 Hz, C-13 H's), 2.67 (t, 2, J = 7 Hz, C-4 H's), 3.68 (s, 3, OMe), 6.29 (d, 1, J = 15 Hz, H-6 or H-11), 6.32 (d, 1, J = 15 Hz, H-11 or H-6), 6.6–6.8 (m, 2, H-8, H-9), 7.1–7.3 (m, 2, H-7, H-10); ^{13}C NMR δ 14.0 (C-20), 19.1 (C-3), 22.5 (C-19), 24.1 (C-14), 29.0 and 29.2 and 29.3 (C-15, C-16, C-17), 31.7 (C-18), 32.9 (C-2), 39.7 (C-4), 41.1 (C-13), 51.5 (OMe), 131.8 (C-6 or C-11), 132.2 (C-11 or C-6), 137.9 (C-8 or C-9), 138.3 (C-9 or C-8), 140.0 (C-7 or C-10), 140.4 (C-10 or C-7), 173.4 (C-1), 199.0 (C-5), 200.3 (C-12).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.20; H, 9.21.

The **29a–30b** reaction (an extra equivalent of base being used to neutralize acid **30b**) and workup (the crude product being acidified with 1 M hydrochloric acid) led to colorless, amorphous 5,12-dioxo-6(*E*),8(*E*),10(*E*)-eicosatrienoic acid (**31a**): 60%; mp 150–152 °C; UV λ_{max} 316 nm (ϵ 38000); IR (Nujol) OH 3400 (br w), C=O 1700 (s), 1670 (s), C=C 1595 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–2.1 (m, 14, methylenes), 2.44 (t, 2, J = 7 Hz, C-2 H's), 2.57 (t, 2, J = 7 Hz, C-13 H's), 2.70 (t, 2, J = 7 Hz, C-4 H's), 6.30 (d, 1, J = 15 Hz, H-6 or H-11), 6.32 (d, 1, J = 15 Hz, H-11 or H-6), 6.6–6.8 (m, 2, H-8, H-9), 7.1–7.3 (m, 2, H-7, H-10); ^{13}C NMR δ 13.9 (C-20), 19.0 (C-3), 22.5 (C-19), 24.1 (C-14), 29.0 and 29.1 and 29.2 (C-15, C-16, C-17), 31.6 (C-18), 32.8 (C-2), 39.6 (C-4), 41.0 (C-13), 131.7 (C-6 or C-11), 132.1 (C-11 or C-6), 138.0 (C-8 or C-9), 138.3 (C-9 or C-8), 140.2 (C-7 or C-10), 140.7 (C-10 or C-7), 175.5 (C-1), 199.7 (C-5), 200.9 (C-12).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.90; H, 8.95.

A solution of 30 mg (0.077 mmol) of diketo ester **31b** in 5 mL of glacial trifluoroacetic acid was kept at 0 °C for 5 min. Solvent removal by vacuum distillation yielded 24 mg (92%) of diketo acid **31a**, identical in all respects with the above sample.

The **29b–30d** reaction furnished diketo ester **31c** (81%), identical in all respects with the above sample.

The **28–30a** reaction yielded pale yellow, waxy *tert*-butyl 5,12-dioxo-6(*E*),8(*E*),10(*Z*)-eicosatrienoate (**32a**): 50% IR (Nujol) C=O 1720 (s), 1675 (s), C=C 1590 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–2.0 (m, 14, methylenes), 1.45 (s, 9, methyls), 2.27 (t, 2, J = 7 Hz, C-2 H's), 2.50 (t, 2, J = 7 Hz, C-13 H's), 2.65 (t, 2, J = 7 Hz, C-4 H's), 6.15 (d, 1, J = 11 Hz, H-11), 6.24 (d, 1, J = 16 Hz, H-6), 6.47 (dd, 1, J = 11, 11 Hz, H-10), 6.56 (dd, 1, J = 16, 11 Hz, H-8), 7.25 (dd, 1, J = 16, 11 Hz, H-7), 7.88 (dd, 1, J = 16, 11 Hz, H-9); ^{13}C NMR δ 14.0 (C-20), 19.4 (C-3), 22.6 (C-19), 24.0 (C-14), 28.0 (methyls), 29.0 and 29.1 and 29.3 (C-15, C-16, C-17), 31.7 (C-18), 34.5 (C-2), 39.1 (C-4), 44.4 (C-13), 80.3 (OC), 127.1 (C-11), 132.3 (C-6), 136.8 (C-9), 138.9 (C-8), 140.0 (C-7), 141.3 (C-10), 172.4 (C-1), 199.5 (C-5), 201.3 (C-12).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 72.20; H, 10.46.

The **28–30c** reaction gave pale yellow, solid methyl 5,12-dioxo-6(*E*),8(*E*),10(*Z*)-eicosatrienoate (**32b**): 70%; mp 80–82 °C; IR (Nujol) C=O 1740 (s), 1675 (s), C=C 1590 (m) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–2.0 (m, 14, methylenes), 2.38 (t, 2, J = 7 Hz, C-2 H's), 2.50 (t, 2, J = 7 Hz, C-13 H's), 2.67 (t, 2, J = 7 Hz, C-4 H's), 3.68 (s, 3, OMe), 6.17 (d, 1, J = 11 Hz, H-11), 6.25 (d, 1, J = 15 Hz, H-6), 6.47 (dd, 1, J = 11, 11 Hz, H-10), 6.56 (dd, 1, J = 15, 11 Hz, H-8), 7.21 (dd, 1, J = 15, 11 Hz, H-7), 7.89 (dd, 1, J = 15, 11 Hz, H-9); ^{13}C NMR δ 14.0 (C-20), 19.1 (C-3), 22.5 (C-19), 24.0 (C-14), 29.0 and 29.1 and 29.3 (C-15, C-16, C-17), 31.7 (C-18), 32.9 (C-2), 38.9 (C-4), 44.1 (C-13), 51.5 (OMe), 127.1 (C-11), 132.2 (C-6), 136.8 (C-8), 139.8 (C-7), 141.3 (C-10), 173.4 (C-1), 199.2 (C-5), 201.2 (C-12).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.24; H, 9.30.

The **25a–30a** reaction provided pale yellow, semisolid *tert*-butyl 5,12-dioxo-6(*E*),8(*Z*),10(*E*)-eicosatrienoate (**33a**): 50%; ^1H NMR δ 0.86 (t, 3, J = 7 Hz, C-20 H's), 1.2–2.0 (m, 14, methylenes), 1.45 (s, 9, methyls), 2.20 (t, 2, J = 7 Hz, C-2 H's), 2.60 (t, 2, J = 7 Hz, C-13 H's), 2.70 (t, 3, J = 7 Hz, C-4 H's), 6.30 (d, 2, J = 15 Hz, H-6, H-11), 6.4–6.6 (m, 2, H-8, H-9), 7.70 (dd, 2, J = 15, 11 Hz, H-7, H-10); ^{13}C NMR δ 13.9 (C-20), 19.3 (C-3), 22.5 (C-19), 24.0 (C-14), 27.9 (methyls), 28.9 and 29.0 and 29.2 (C-15, C-16, C-17), 31.6 (C-18), 34.3 (C-2), 40.0 (C-4), 41.0 (C-13), 80.1 (OC), 132.1 (C-6 or C-11), 132.6 (C-11 or C-6), 134.4 and 134.6 and 134.8 and 135.0 (C-7, C-8, C-9, C-10), 172.2 (C-1), 199.3 (C-5), 200.2 (C-12).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 73.75; H, 9.95.

The **25a–30c** reaction resulted in a pale, yellow, solid methyl 5,12-dioxo-6(*E*),8(*Z*),10(*E*)-eicosatrienoate (**33b**): 65%, mp 76–78 °C; IR (Nujol) C=O 1730 (s), 1680 (s), C=C 1592 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.1–2.1 (m, 14, methylenes), 2.40 (t, 2, J = 7 Hz, C-2 H's), 2.62 (t, 2, J = 7 Hz, C-13 H's), 2.70 (t, 2, J = 7 Hz, C-4 H's), 3.69 (s, 3, OMe), 6.28 (d, 1, J = 15 Hz, H-6 or H-11), 6.31 (d, 1, J = 15 Hz, H-11 or H-6), 6.3–6.5 (m, 2, H-8, H-9), 7.6–7.8 (m, 2, H-7, H-10); ^{13}C NMR δ 13.9 (C-20), 19.1 (C-3), 22.4 (C-19), 24.0 (C-14), 28.9 and 29.0 and 29.2 (C-15, C-16, C-17), 31.6 (C-18), 32.8 (C-2), 39.5 (C-4), 41.1 (C-13), 51.4 (OMe), 132.1 (C-6 and C-11), 132.6 (C-11 or C-6), 134.4 and 134.6 and 134.8 and 135.1 (C-7, C-8, C-9, C-10), 173.3 (C-1), 199.1 (C-5), 200.3 (C-12).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.30; H, 9.34.

(±)-6(*E*)-LTB$_3$ (23a). A mixture of 100 mg (0.29 mmol) of diketo ester **31c** and 11 mg (0.29 mmol) of sodium borohydride in 5 mL of water and 20 mL of methanol was stirred at room temperature for 2 h. Acetic acid (3 mL) was added, and the mixture was extracted with ether. The extract was washed with 5% sodium bicarbonate and brine, dried, and evaporated. MPLC of the waxy residue and elution with 1.5:1 hexane–ethyl acetate yielded 46 mg (45%) of colorless, crystalline methyl 5ζ,12ζ-dihydroxy-6(*E*),8(*E*),10(*E*)-eicosatrienoate (**23b**): mp 92–94 °C; UV λ_{max} 258 nm (ϵ 35 000), 268 (45 000), 279 (36 500); IR (Nujol) OH 3340 (br m), 3260 (br m), C=O 1745 (s), C=C 1640 (w) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–1.3 (m, 12, methylenes), 1.5–1.7 (m, 6, C-3, C-4, C-13 H's), 2.36 (t, 2, J = 7 Hz, C-2 H's), 3.68 (s, 3, OMe), 4.09 (q, 1, J = 7 Hz, H-5 or H-12), 4.10 (q, 1, J = 7 Hz, H-12 or H-5), 5.6–5.7 (m, 2, H-8, H-9), 6.1–6.2 (m, 4, H-6, H-7, H-10, H-11); ^{13}C NMR δ 14.0 (C-20), 20.6 (C-3), 22.6 (C-19), 25.3 (C-14), 29.2 and 29.5 and 29.5 (C-15, C-16, C-17), 31.8 (C-18), 33.7 (C-2), 36.4 (C-4 or C-13), 37.2 (C-13 or C-4), 51.5 (OMe), 72.0 (C-12), 72.6 (C-5), 130.0 and 130.4 and 131.9 and 132.3 (C-6, C-7, C-10, C-11), 135.8 (C-8 or C-9), 136.7 (C-9 or C-8).

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.90; H, 10.50.

Further elution gave 46 mg (45%) of colorless, liquid **23b** diastereoisomer, spectrally nearly the same as the crystalline isomer.

A mixture of 50 mg (0.14 mmol) of crystalline **23b** diastereomer and 1.4 mL of 1 M lithium hydroxide solution (1.4 mmol) in 5 mL of 1,2-dimethoxyethane was stirred at room temperature for 1 h. It then was neutralized with 1 M hydrochloric acid solution and extracted with ether. The extract was washed with sodium bicarbonate solution and brine and dried. Evaporation of the extract yielded 36 mg (75%) of colorless, amorphous, powdery 5ζ,12ζ-dihydroxy-6(*E*),8(*E*),10(*E*)-eicosatrienoic acid (**23a**, (±)-6(*E*)-LTB$_3$ diastereomer): mp 112–114 °C; UV λ_{max} 258 nm (ϵ 36 000), 268 (47 000), 279 (39 000); IR (Nujol) OH 3250 (br m), C=O 1705 (s), 1680 (s), C=C 1640 (w) cm^{-1}; ^1H NMR δ 0.88 (t, 3, J = 7 Hz, C-20 H's), 1.2–1.3 (m, 12, methylenes), 1.5–1.7 (m, 6, C-3, C-4, C-13 H's), 2.30 (t, 2, J = 7 Hz, C-2 H's), 4.10 (q, 1, J = 7 Hz, H-5 or H-12), 4.12 (q, 1, J = 7 Hz, H-12 or H-5), 5.6–5.7 (m, 2, H-8, H-9), 6.1–6.2 (m, 4, H-6, H-7, H-10, H-11).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.65.

The same reaction on the liquid diastereomeric ester **23b** led to a colorless, liquid isomer of (±)-6(*E*)-LTB$_3$ (55%), spectrally nearly the same as the crystalline acid.

Sodium borohydride reduction of diketo acid **31a** under the conditions of the **31c** → **23b** transformation yielded quantitatively a mixture of the two (±)-6(*E*)-LTB$_3$ isomers, which could be separated by RP-HPLC and were identical in all respects with the above samples.

1,2-Bis(2-furyl)ethane (35c). Freshly distilled trimethylsilyl chloride (3.3 mL, 25 mmol) was added dropwise over a 10-min period to a stirring mixture of 1.92 g (10 mmol) of furoin (**35a**)[35] and 3.90 g (26 mmol) of sodium iodide in 20 mL of dry acetonitrile, and stirring was continued for 1 h. The mixture was concentrated under vacuum, and an ether solution (20 mL) of the residue was washed with 10% sodium thiosulfate solution, water, and brine, dried, and evaporated. Silica chromatography of the residue and elution with 4:1 hexane–ethyl acetate gave 1.59 g (90%) of deoxyfuroin (**35b**):[38] UV λ_{max} 268 nm (ϵ 4000); IR ($CHCl_3$) C=O 1670 (s), C=C 1600 (w), 1567 (s) cm^{-1}; ^1H NMR δ 4.14 (s, 2, CH_2), 6.2–6.3 (m, 1, furyl H-4), 6.3–6.4 (m, 1, furoyl H-4), 6.5–6.6 (m, 1, furyl H-3), 7.22 (d, 1, J = 4 Hz, furoyl H-3), 7.34 (s, 1, furyl H-5), 7.58 (s, 1, furoyl H-5); ^{13}C NMR δ 37.8 (CH_2), 108.0 (furyl C-4), 110.3 (furoyl C-4), 112.1 (furyl C-3), 118.0 (furoyl C-3), 141.8 (furyl C-5), 146.6 (furoyl C-5), 147.5 (furyl C-2), 151.6 (furoyl C-2), 183.4 (C=O).

A mixture of 4.81 g (27 mmol) of deoxyfuroin (**35b**) and 3.6 mL of 80% hydrazine hydrate was added to a solution of 4.90 g (88 mmol) of potassium hydroxide in 190 mL of diethylene glycol being heated at 120 °C. The temperature was kept at 120 °C for 0.5 h and then at 185 °C for 1.5 h. The cooled solution was extracted exhaustively with ether, and the extract was washed with water and brine, dried, and evaporated. Chromatography of the residual oil on neutral alumina (activity III) and elution with hexane afforded 2.73 g (62%) of colorless, liquid 1,2-bis(2-furyl)ethane (**35c**):[34] UV λ_{max} 216 nm (ϵ 1000); IR ($CHCl_3$) C=C 1601 (m) cm^{-1}; ^1H NMR δ 2.97 (s, 4, methylenes), 5.9–6.0 (m, 2, C-3 H's), 6.2–6.3 (m, 2, C-4 H's), 7.3–7.4 (m, 2, C-5 H's); ^{13}C NMR δ 26.6 (CH_2), 105.0 (C-3), 110.0 (C-4), 140.9 (C-5), 154.7 (C-2).

Ethyl 8-(2-Furyl)-6-oxo-2(*E*),4(*E*)-octadienoate (36). A solution of 456 mg (4.0 mmol) of ethyl diazoacetate in 20 mL of dry methylene chloride was added dropwise over a 24-h period to a stirring mixture of 10 mg of dirhodium tetraacetate and 324 mg (2.0 mmol) of 1,2-bis(2-furyl)ethane (**35c**) in 5 mL of dry methylene chloride, and stirring was continued for 2 h. The

mixture was filtered through a Celite pad, and the filtrate was treated with two crystals of iodine and kept at room temperature for 1 h. The solution was evaporated, and the residue was dissolved in 20 mL of ether. The latter solution was washed with 10% sodium thiosulfate, water, and brine, dried, and evaporated. Silica chromatography of the residue and elution with 4:1 hexane–ethyl acetate provided 365 mg (52%) of colorless, crystalline keto ester **36**: mp 62–63 °C; UV λ_{max} 271 nm (ϵ 28100); IR ($CHCl_3$) C=O 1705 (s), 1670 (s), C=C 1600 (s) cm^{-1}; ^1H NMR δ 1.32 (t, 3, J = 7 Hz, Me), 2.79, 2.80 (s, 2 each, methylenes), 4.15 (q, 2, J = 7 Hz, OCH_2), 5.95 (d, 1, J = 3 Hz, furan H-3), 6.17 (d, 1, J = 15 Hz, H-2), 6.1–6.2 (m, 1, furan H-4), 6.37 (d, 1, J = 15 Hz, H-5), 7.0–7.3 (m, 3, H-3, H-4, furan H-5); ^{13}C NMR δ 14.0 (Me), 22.1 (C-8), 39.0 (C-7), 60.7 (OCH_2), 105.2 (furan C-3), 110.0 (furan C-4), 129.0 (C-2), 134.8 (C-5), 138.4 (C-3), 140.9 (C-4), 141.0 (furan C-5), 154.0 (furan C-2), 165.5 (C-1), 198.0 (C-6); exact mass m/e 248.1048 (calcd for $C_{14}H_{16}O_4$ 248.1044).

Diethyl 6,9-Dioxo-2(*E*),4(*E*),13(*E*)-tetradecatetraenedioate (37a). A solution of 912 mg (8.0 mmol) of ethyl diazoacetate in 40 mL of dry methylene chloride was added dropwise over a 25-h period to a stirring mixture of 324 mg (2.0 mmol) of 1,2-bis(2-furyl)ethane and 20 mg of dirhodium tetraacetate in 5 mL of dry methylene chloride, and stirring was continued for 2 h. The mixture was filtered through a Celite pad, and the filtrate was treated with 0.1 mL of boron trifluoride etherate and kept at room temperature for 1 h. The solution was evaporated under reduced pressure. Crystallization of the residue from 4:1 ether–dichloromethane yielded 401 mg (60%) of colorless, crystalline diketo diester **37a**: mp 183–184 °C; UV λ_{max} 274 nm (39600); IR C=O 1708 (s), 1668 (s), C=C 1592 (s) cm^{-1}; ^1H NMR δ 1.32 (t, 6, J = 7 Hz, methyls), 2.98 (s, 4, C-7, C-8 H's), 4.24 (q, 4, J = 7 Hz, 2 OCH_2), 6.24 (d, 2, J = 15 Hz, H-2, H-13), 6.49 (d, 2, J = 15 Hz, H-5, H-10), 7.1–7.4 (m, 4, H-3, H-4, H-11, H-12); ^{13}C NMR δ 14.1 (Me), 34.5 (C-7), 60.8 (OCH_2), 129.2 (C-2), 134.9 (C-5), 138.7 (C-3), 141.1 (C-4), 165.7 (C-1), 197.8 (C-6).

Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.50; H, 6.70.

2,5-Bis[4-(ethoxycarbonyl)-1(*E*),3(*E*)-butadienyl]-thiophene (38). A mixture of 27 mg (0.08 mmol) of diketo diester **37a** and 81 mg (0.20 mmol) of Lawesson reagent[39] in 15 mL of dry toluene was stirred at 80 °C for 10 min. It was cooled and filtered. The filtrate was evaporated, and the residue was chromatographed on silica gel. Elution with ether furnished 27 mg (100%) of yellow, crystalline diester **38**: mp 93–95 °C; UV (EtOH) λ_{max} 242 nm (ϵ 10600), 287 (11400), 400 (19200), $\lambda_{shoulder}$ 424 (ϵ 14500); IR (CCl_4) C=O 1712 (s), C=C 1618 (s) cm^{-1}; ^1H NMR δ 2.31 (t, 6, J = 7 Hz, methyls), 4.22 (q, 4, J = 7 Hz, 2 OCH_2), 5.96 (d, 2, J = 15 Hz, C-4 H's), 6.64 (dd, 2, J = 15, 11 Hz, C-2 H's), 6.94 (d, 2, J = 15 Hz, C-1 H's), 7.00 (s, 2, thiophene β-H's), 7.36 (dd, 2, J = 15, 11 Hz, C-3 H's); ^{13}C NMR δ 14.2 (Me), 60.2 (OCH_2), 121.5 (thiophene β-C), 126.7 (C-4), 129.4 (C-2), 132.1 (C-1), 142.3 (thiophene α-C), 143.5 (C-3), 166.7 (C=O); exact mass m/e 332.1092 (calcd for $C_{18}H_{20}O_4S$ 332.1077).

Diethyl 6,9-Dihydroxy-2(*E*),4(*E*),10(*E*),12(*E*)-tetradecatetraenedioate (37b). Sodium borohydride (12 mg, 0.32 mmol) was added to a stirring solution of 89 mg (0.27 mmol) of diketo diester **37a** and 104 mg (0.28 mmol) of cerium trichloride heptahydrate in 2 mL of methylene chloride and 4 mL of ethanol, and stirring was continued for 10 min. The mixture was poured into 25 mL of water and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated, leading to 85 mg (95%) of a liquid, ca. 5:1 mixture (by ^1H NMR analysis) of dihydroxy diester **37b** diastereomers: UV (EtOH) λ_{max} 259 nm (ϵ 49100); IR ($CHCl_3$) OH 3590 (m), 3400 (br w), C=O 1705 (s), C=C 1645 (m), 1615 (m), cm^{-1}; ^1H NMR δ (major isomer) 1.29 (t, 3, J = 7 Hz, Me), 1.6–1.8 (m, 4, C-7, C-8 H's), 4.20 (q, 4, J = 7 Hz, 2 OCH_2), 4.2–4.3 (m, 2, H-6, H-9), 5.87 (d, 2, J = 15 Hz, H-2, H-13), 6.10 (dd, 2, J = 15, 5 Hz, H-5, H-10), 6.36 (dd, 2, J = 15, 11 Hz, H-4, H-11), 7.26 (dd, 2, J = 15, 11 Hz, H-3, H-12); δ (minor isomer) 1.0–5.0 same resonances, 5.67 (d, 2, J = 15 Hz, H-2, H-13), 6.05 (dd, 2, J = 15, 5 Hz, H-5, H-10), 6.58 (dd, 2, J = 15, 11 Hz, H-4, H-11), 7.48 (dd, 2, J = 15, 11 Hz, H-3, H-12); ^{13}C NMR δ (major isomer) 14.1 (Me), 32.4 (C-7), 60.3 (OCH_2), 71.3 (C-6), 121.5 (C-2), 127.4 (C-4), 143.6 (C-5), 144.4 (C-3), 166.9 (C-1); δ (minor isomer) 14.1 (Me), 32.5 (C-7), 60.0 (OCH_2), 71.4 (C-6), 117.7 (C-2), 126.1 (C-4), 143.8 (C-5), 145.4 (C-3), 166.0 (C-1); exact mass m/e 338.1745 (calcd for $C_{18}H_{26}O_6$ 338.1748).

Diethyl 6,9-Oxy-2(*E*),4(*E*),10(*E*),12(*E*)-tetradecatetraenedioate (39). A solution of 57 mg (0.17 mmol) of diol **37b** in 2 mL of dry methylene chloride was added dropwise to a stirring solution of 245 mg (0.35 mmol) of Martin reagent[43] variant[44] in 5 mL of dry methylene chloride at room tempeature, and stirring was continued for 12 h. The mixture was washed with 10% sodium hydroxide solution and water, dried, and evaporated. Chromatography of the residue on silica gel and elution with 1.5:1 hexane–ether afforded 36 mg (67%) of a pale yellow, liquid ca. 7:1 mixture and 17 mg (32%) of a similar ca. 1:1 mixture of diastereomeric tetrahydrofurans **39**: UV (EtOH) λ_{max} 241 nm (ϵ 10100); IR (CCl_4) C=O 1718 (s), C=C 1649 (m), 1620 (m) cm^{-1}; ^1H NMR δ (major isomer) 1.29 (t, 6, J = 7 Hz, methyls) 1.6–2.3 (m, 4, C-7, C-8 H's), 4.20 (q, 4, J = 7 Hz, 2 OCH_2), 4.63 (m, 2, H-6, H-9), 5.88 (d, 2, J = 15 Hz, H-2, H-13), 6.09 (dd, 2, J = 15, 6 Hz, H-5, H-10), 6.38 (dd, 2, J = 15, 11 Hz, H-4, H-11), 7.27 (dd, 2, J = 15, 11 Hz, H-3, H-12); δ (minor isomer) 1.0–4.4 same resonances, 4.51 (dd, 2, J = 11, 6 Hz, H-6, H-9), 5.87 (d, 2, J = 15 Hz, H-2, H-14), 6.0–6.2 (m, 2, H-2, H-10), 6.3–7.5 same resonances; ^{13}C NMR δ (major isomer) 14.1 (Me), 32.2 (C-7), 60.1 (OCH_2), 78.7 (C-6), 121.4 (C-2), 127.6 (C-4), 142.4 (C-5), 143.4 (C-3), 166.7 (C-1); δ (minor isomer) 14.1 (Me), 31.7 (C-7), 60.1 (OCH_2), 79.2 (C-6), 121.6 (C-2), 128.1 (C-4), 142.4 (C-5), 143.4 (C-3), 166.7 (C-1); exact mass m/e (M^+ – OEt) 275.1275 (calcd for $C_{16}H_{19}O_4$ 275.1278).

Diethyl Corticrocin (34b). A solution of 40 mg (0.12 mmol) of diol **37b** in 2 mL of dry methylene chloride was added dropwise to a stirring solution of 500 mg (0.71 mmol) of para-methylated variant[44] of Martin reagent[43] in 5 mL of dry methylene chloride at −100 °C, and stirring was continued at this temperature for 6 h. The mixture was allowed to warm to room temperature, and then stirring was continued for 12 h. Workup as in the preparation of diester **39**, chromatography on silver nitrate impregnated silica gel and elution with 1:1 hexane–ether furnished firstly 9 mg (25%) of a chromatographically (and otherwise) unstable hexaenic diester [UV λ_{max} 255 nm (ϵ 9400); IR (CH_2Cl_2) 1705 (s), C=C 1645 (m), 1620 (m) cm^{-1}; ^1H NMR δ 1.28 (t, 6, J = 7 Hz, methyls), 4.21 (q, 4, J = 7 Hz, 2 OCH_2), 5.8–6.2 (m, 4), 7.0–7.6 (m, 7), 7.95 (d, 1, J = 7 Hz)] of unknown constitution and secondly 25 mg (70%) of yellow, crystalline diethyl corticrocin (**34b**): mp 202–203 °C (lit.[33c] mp 203–204 °C); UV λ_{max} 352 nm (ϵ 7600), 372 (14300), 388 (21600), 410 (20500); IR (CCl_4) C=O 1702 (s), C=C 1620 (w), 1604 (m) cm^{-1}; ^1H NMR δ 1.22 (t, 3, J = 7 Hz, methyls), 4.15 (q, 4, J = 7 Hz, 2 OCH_2), 5.83 (d, 2, J = 15 Hz, H-2, H-13), 6.31 (dd, 2, J = 15, 12 Hz, H-4, H-11), 6.4–6.5 (m, 4, H-6, H-7, H-8, H-9), 6.54 (dd, 2, J = 15, 11 Hz, H-5, H-10), 7.25 (dd, 2, J = 15, 12 Hz, H-3, H-12); ^{13}C NMR δ 14.1 (Me), 60.3 (OCH_2), 121.3 (C-2), 131.2 (C-4), 134.0 (C-6), 136.3 (C-7), 140.0 (C-5), 143.9 (C-3), 166.8 (C-1).

A solution of 318 mg (0.94 mmol) of diol **37b** and one crystal of iodine in 15 mL of anhydrous methylene chloride was stirred at room temperature for 12 h. It then was evaporated, and an ether solution of the residue was washed with 10% sodium thiosulfate solution, water, and brine. The solution was dried and evaporated. Chromatography of the residue on silica gel and elution with 10:1 hexane–ethyl acetate afforded 71 mg (25%) of crystalline diester **34b**.

Corticrocin (34a). A mixture of 10 mg (0.03 mmol) of diethyl corticrocin (**34b**) and 20 mg (0.36 mmol) of potassium hydroxide in 4 mL of 1:1 methanol–water was stirred at room temperature for 12 h. The precipitated potassium salt of the natural product was shaken with 1:1 H_3PO_4–H_2O (pH 3–4), and the precipitated diacid was filtered. Washing with water produced 7 mg (86%) of yellow, solid corticrocin (mp >350 °C), totally insoluble in all conceivable solvents (in accord with previous experience).[32,33]

Registry No. **1a**, 128300-08-3; **2a**, 75415-24-6; **2b**, 128227-67-8; **3**, 130120-99-9; **4b**, 4915-21-3; **4c**, 57393-62-1; **4d**, 130121-01-6; **6a**, 130121-00-5; **6b**, 110072-12-3; **6c**, 130121-05-0; **7a**, 80105-49-3; **7b**, 130194-10-4; **7c**, 130121-03-8; **7d**, 130121-07-2; **8a**, 80105-48-2; **8b**, 130121-02-7; **9a**, 80105-50-6; **9b**, 130121-04-9; **10a**, 110072-11-2; **10b**, 130121-06-1; **11a**, 6071-66-5; **11b**, 54520-22-8; **11c**, 54520-21-7; **11d**, 130121-09-4; **11e**, 130121-10-7; **12**, 130121-08-3; **13**, 130145-30-1; **16a**, 130121-11-8; **16b**, 130121-13-0; **17a**, 130121-12-9; **17b**, 130121-14-1; **18a**, 130121-15-2; **18b**, 130121-16-3; **19**, 64768-01-0;

20, 130121-17-4; **21**, 130121-18-5; (±)-(*R**,*R**)-**23a**, 130194-11-5; (±)-(*R**,*S**)-**23a**, 130194-12-6; (±)-(*R**,*R**)-**23b**, 130121-31-2; (±)-(*R**,*S**)-**23b**, 130121-32-3; **24a**, 58697-26-0; **24b**, 76700-84-0; **25a**, 130121-22-1; **25b**, 89682-40-6; **26a**, 130121-19-6; **26b**, 89682-39-3; **27a**, 130121-20-9; **27b**, 130121-23-2; **28** (R = Me), 130121-21-0; **29a**, 114730-45-9; **29b**, 104226-89-3; **30a**, 87517-46-2; **30b**, 130121-24-3; **30c**, 104227-38-5; **30d**, 37497-13-5; **31a**, 130121-26-5; **31b**, 130121-25-4; **31c**, 114730-22-2; **32a**, 130121-27-6; **32b**, 130121-28-7; **33a**, 130121-29-8; **33b**, 130121-30-1; **34b**, 5941-45-7; **35a**, 552-86-3; **35b**, 51490-07-4; **35c**, 36707-31-0; **36**, 130121-33-4; **37a**, 130121-34-5; (*R**,*R**)-**37b**, 130121-36-7; (*R**,*S**)-**37b**, 130194-13-7; **38**, 130121-35-6; (*R**,*R**)-**39**, 130121-37-8; (*R**,*S**)-**39**, 130194-14-8; ethyl diazoacetate, 623-73-4; furan, 110-00-9; 2,5-dimethylfuran, 625-86-5; 2-methylfuran, 534-22-5; 2-*n*-octylfuran, 4179-38-8; methyl 2-furoate, 611-13-2; methyl β-(2-furyl)acrylate, 623-18-7; ethyl α-diazopropionate, 6111-99-5; triethyl α-phosphonopropionate, 3699-66-9; trimethyl phosphonoacetate, 5927-18-4; pelargonyl chloride, 764-85-2; methyl glutaryl chloride, 1501-26-4; *tert*-butyl methyl glutarate, 59378-98-2; dimethyl methanephosphonate, 756-79-6.

Notes

New Chemoenzymatic Synthesis of (*R*)- and (*S*)-4-(Phenylsulfonyl)-2-methyl-1-butanol: A Chiral C_5 Isoprenoid Synthon

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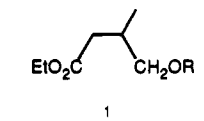
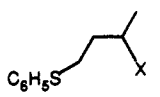
Received March 1, 1990

The chiral C_5 isoprenoid synthon of general formula **1** is a useful intermediate for the synthesis of various natural products and has been prepared by several chemoenzymatic approaches.[1] We had already prepared one of the possible synthetic equivalents of **1**, namely, (*S*)-(−)-1-(ethoxymethoxy)-2-methyl-4-(phenylthio)butane (**2a**), and used it for a new synthesis of (25*S*)-26-hydroxycholesterol.[2]



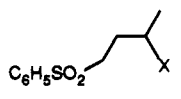
1

a. R= H
b. R= CH_2OEt



2

a. X= $CH_2OCH_2OC_2H_5$
b. X= COOH
c. X= $COOCH_3$
d. X= CH_2OH
e. X= CH_2OCOCH_3
f. X= $CH_2OCOC_3H_7$



3

a. X= $COOCH_3$
b. X= CH_2OH
c. X= CH_2OCOCH_3
d. X= $CH_2OCH_2OC_2H_5$

In that synthesis we used the biohydrogenation of ethyl 4,4-dimethoxy-3-methylbut-2-enoate with fermenting bakers' yeast for the preparation of ethyl (*S*)-(−)-4-hydroxy-3-methylbutanoate (**1a**),[3] which was further transformed into the chiral synthon **2a**. The above biotransformation, however, was not always reproducible, and the chiral intermediates had sometimes variable optical purities.[4] We therefore conceived a different approach for the preparation of enantiomerically pure (*S*)-(−)-**2a** and considered feasible the enzymatic hydrolysis of suitable esters related to the structure of the required intermediate. By this route, the recovery of the unreacted substrate should lead to the preparation of the other stereoisomer, (*R*)-(+)-**2a**. Benzenethiolate opening of commerically available (*R*,*S*)-2-methyl-γ-butyrolactone[5] afforded the racemic thio acid **2b**. Attempted hydrolysis of the methyl ester **2c** to optically active acid **2b**[6] in the presence of pig liver esterase (PLE) proceeded in good chemical yields, but with virtually no enantioselectivity. The ester **2c** was not a substrate for α-chymotrypsin, and the same negative results were obtained from the enzymatic hydrolysis of the methyl ester of phenylsulfonyl acid **3a**, easily obtained by *m*-chloroperbenzoic acid oxidation of the ester **2c**.

We then prepared the phenythio alcohol **2d** and its acetate **2e** and butanoate **2f**, in order to submit these esters to the action of a few hydrolases which have been successfully used for enantioselective hydrolysis of a great variety of substrates.[7] Aqueous hydrolysis was carried out in the presence of a lipase from *Pseudomonas fluorescens* and acetyl cholinesterase from electric eel on the acetate **2e** and with lipase from *Candida cylindracea* and butyryl cholinesterase from horse serum on the butanoate **2f**, prepared by direct esterification of the alcohol **2d** with butyryl chloride in pyridine. In no case did the enantiomeric excess (ee) of the product exceed a mere 20–30%. At this point, the recently published lipase-catalyzed irreversible transesterification using enol esters as acylating reagents[8] was considfered for the resolution of our alcohol.

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(1) Fuganti, C.; Grasselli, P.; Servi, S.; Hogberg, H. E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3061 and references cited therein.
(2) Ferraboschi, P.; Fiecchi, A.; Grisenti, P.; Santaniello, E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1749.
(3) Ferraboschi, P.; Grisenti, P.; Casati, R.; Fiecchi, A.; Santaniello, E. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1743.
(4) The optical rotations of the phenylthio and phenylsulfonyl derivatives **2a** and **3d** reported in ref 2 do not correspond to optically pure material. The values reported in the present paper must, therefore, be considered for reference to optically pure compounds.
(5) The experimental conditions were essentially as descried for ring opening of 3-methyl-γ-butyrolactone: Ferraboschi, P.; Santaniello, E. *Synth. Commun.* **1984**, 1199.
(6) The *R* acid **2b** has already been prepared by enantioselective bakers' yeast hydrogenation: Sato, T.; Hanayama, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**,*29*, 2197.
(7) For a recent review on the use of enzymes in organic synthesis, see: *Enzymes as Catalysts in Organic Synthesis*; Proc. NATO Adv. Res. Workshop; Schneider, M., Ed.; Reidel: Dorchrecht,Holland, 1986.
(8) Wang, Y. F.; Lalonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7200.

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