(IR, UV), Ray Richardson (IR, UV), and Joe Lazar (MS) of the Analytical Division of DuPont Central Research is greatly appreciated. Thanks are also extended to John Roderick, Frank Dobson, and John Berry for technical assistance, to Dr. Renuka Misra for gifts of gilvocarcin V and defucogilvocarcin V, and to Prof. Danishefsky for communication of results prior to publication. The in vitro DNA nicking activity was recorded by Dr. Y. C. Tse-Dinh.

Registry No. **4a**, 80155-95-9; **4e**, 110582-91-7; **5a**, 114862-70-3; **5c**, 114862-69-0; **6a**, 114862-61-2; **6b**, 114862-62-3; **6c**, 114862-63-4; **6d**, 114862-64-5; **7**, 83-56-7; **8**, 114862-60-1; **9c**, 114862-66-7; **10b**, 114862-65-6; **10c**, 114862-67-8; **11c**, 114862-68-9; **13d**, 114862-71-4; **16d**, 114862-72-5; **17d**, 114862-73-6; **18d**, 114862-74-7; **19a**, 114862-76-9; **19d**, 114862-75-8; **19e**, 110582-87-1; **20e**, 110582-90-6.

Stereoselective Generation and Facile Dimerization of (*E*)-2-Methylene-3-alkenoic Acid Esters[1]

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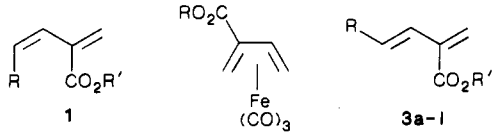
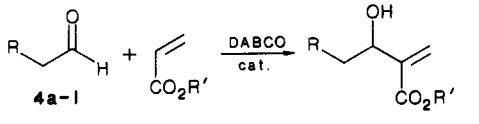
1,4-Diazabicyclo[2.2.2]octane (DABCO)-induced coupling of selected aldehydes and acrylic esters gave some new [2 + 2 + 2] cycloadducts. As a rule, however, aldehydes and acrylic esters coupled to 3-hydroxy-2-methylenealkenoic acid esters **5**. These were dehydrated by a mild and specific procedure (methanesulfonyl chloride, DABCO, catalytic 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, room temperature, 24 h). The novel 2-methylene-3-alkenoic acid esters **3** were generated as *E* isomers and they dimerized spontaneously to give 4-[(*E*)-1-alkenyl]-3-alkyl-1-cyclohexene-1,4-dicarboxylic acid esters **6**. The dimerization was endo-selective (>5:1 to 10:1) with respect to the alkenyl chain and exo with respect to the ester grouping and completely para-selective. Stereoselectivity and separability of the dimers **6** depended on the steric bulk of the alkyl group R. The stereochemical assignments were corroborated by X-ray crystal structures of **6h** (R = $PhCH_2$) (major isomer) and also tricyclic lactone **7a**. Selected (*E*)-2-methylene-3-alkenoic acid esters **3** were intercepted in crossed Diels–Alder reactions with cyclopentadiene and also pyrrolidinoisobutene.

Although a number of (*Z*)-2-methylene-3-alkenoic acid esters[2] **1** and the simple iron tricarbonyl protected **2**[3] have

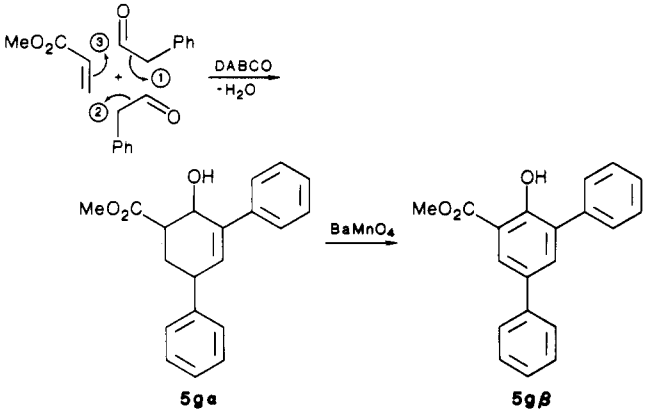


been prepared and isolated, the class of stereoisomeric (*E*)-2-methylene-3-alkenoic acid esters **3** is practically unknown.[4] In principle, synthesis of 3-hydroxy-2-methylenealkanoic acid esters **5** and their dehydration should yield 1,3-diene esters. In practice, a number of experimental hurdles had to be overcome first of all.

We begin by describing the preparation of α-(hydroxyalkyl)acrylic acid esters **5**, which are known to arise by coupling of aldehydes **4** with acrylic acid esters in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane).[1,6–8]



We have now found that suitably functionalized aldehydes enter into interesting tandem processes. For example, 2-phenylethanal (**4g**), which enolizes more readily than a simple aliphatic aldehyde, reacted with methyl acrylate in the presence of DABCO to give not only **5g** (17%) but also **5gα** (40%). The formation of cyclohexenol **5gα** is



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§ Gesellschaft für Biotechnologische Forschung mbH.

(1) (a) DABCO-Catalyzed Coupling of Aldehydes with Activated Double Bonds. 6. (b) For 5, see: Grundke, C.; Hoffmann, H. M. R. *Chem. Ber.* **1987**, *120*, 1461.

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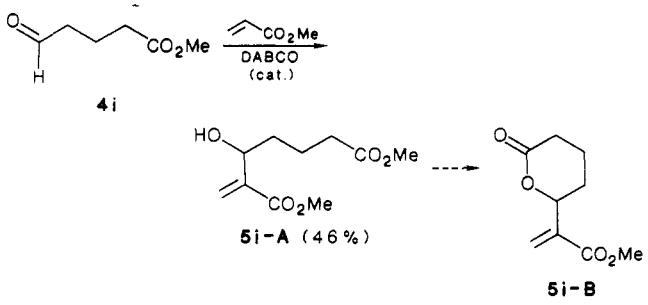
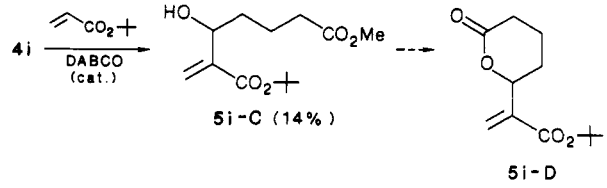
interpreted as [2 + 2 + 2] cycloaddition,[5] which is brought about sequentially by (1) aldol addition, (2) aldol dehydration and intermolecular Michael addition of the d^4-dienolate donor, and, finally, (3) intramolecular aldol addition. The cyclohexenol moiety of **5gα** was aromatized by oxidation with $BaMnO_4$ (**5gα** → **5gβ**).

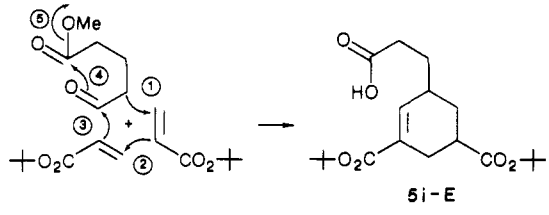
Aldehydes with a second acceptor group placed 1,5 and 1,4 to the formyl carbon were also investigated. Ester aldehyde **4i** and methyl acrylate, in the presence of DABCO, gave **5i-A** (46%), which, under the reaction conditions, partially lactonized to **5i-B**.



After changing the Michael acceptor from methyl acrylate to *tert*-butyl acrylate, we obtained the corresponding coupling product **5i-C** in 14% yield only.

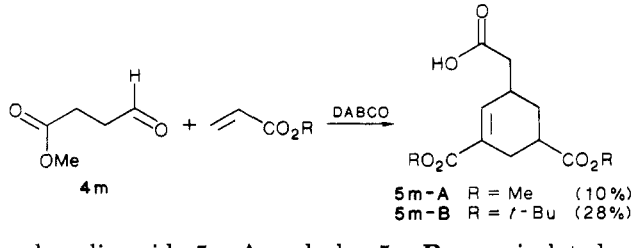


A major product was cyclohexenecarboxylic acid **5i-E** (20%). Its formation can be rationalized by a (1) Michael



addition, (2) Michael addition, (3) intramolecular aldol reaction, (4) *6-Exo-Trig* lactonization and, finally, (5) formation of the cyclohexene double bond with liberation of the carboxylic acid. Steps 4 and 5 terminate the [2 + 2 + 2] cycloaddition[5] in a novel way.

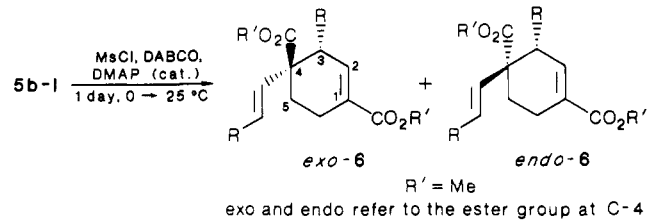
Ester aldehyde **4m**, which has one carbon less than ester aldehyde **4i**, gave the corresponding α-(hydroxyalkyl)-acrylic acid ester in traces only. The cyclohexene-



carboxylic acids **5m-A** and also **5m-B** were isolated as solids. Presumably, the [2 + 2 + 2] cycloaddition is more prominent than for **5i-E**, because the reaction is terminated by a more efficient *5-Exo-Trig* lactonization instead of the *6-Exo-Trig* process.

We now turn to the dehydration of 3-hydroxy-2-methylenealkanoic acid esters **5a–l**, which should yield 1,3-diene esters. On first sight, this is a very simple reaction, although the parent compound **3a** (R = H) was previously obtained with some difficulty, i.e. by flash vapor thermolysis (FVT).[3] As α-vinylated Michael acceptors, the desired esters **3** were expected to be sensitive to nucleophiles and also prone to oligomerization.

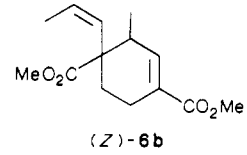
Exploratory experiments showed quickly that we had to dehydrate **5b–l** under mild conditions in order to suppress *E*/*Z* isomerization, 1,5-hydrogen shifts,[9] and also undesirable S_N2' reactions. Eventually, we developed an in situ mesylation/elimination procedure, using DABCO as a base, methanesulfonyl chloride, and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in solvent dichloromethane in the presence of **5**: Under these conditions, neither the monomeric *E*-configurated ester **3** nor the *Z*-configurated ester **1** were discernible after 24 h at room temperature. Instead, the functionalized cyclohexene esters **6** were formed in good to very good yields (Table I).



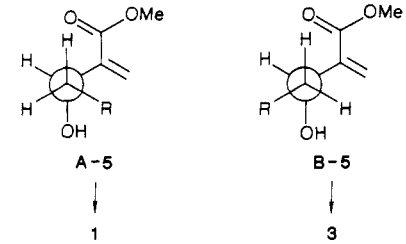
exo and endo refer to the ester group at C-4

Although the mechanism of the DABCO/DMAP/CH_3SO_2Cl-induced elimination cannot be fully defined at present, we report on a number of observations and control experiments.

1. Steric Course and Mechanism of Dehydration of Allylic Alcohols 5. The exocyclic double bond of the cycloadducts **6** was *E*-configurated. Therefore, the elimination is highly *E*-selective and diene esters **3** are reactive intermediates. Had any *Z* esters **1** been formed, they should have either survived as monomers[2] or show up as dimers of type **6** an with external *Z*-configurated double bond. For example, an isomer such as (*Z*)-**6b** would have



been detected by ^{13}C NMR. However, the spectrum showed only signals for two isomers, *exo*-**6b** and *endo*-**6b**. One could argue that the alcohol and mesylate derived from rotamer B (1 gauche interaction) is favored over



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(8) Hoffmann, H. M. R.; Rabe, J. *Helv. Chim. Acta* **1984**, *67*, 413.

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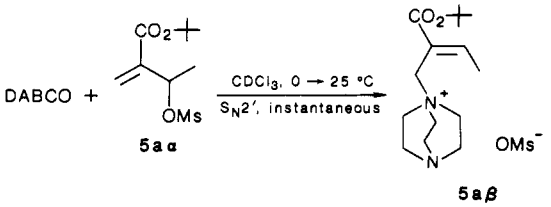
Table I. Representative 4-[(*E*)-1-Alkenyl]-3-alkyl-1-cyclohexene-1,4-dicarboxylic Esters (6b-l) by Dehydration of 3-Hydroxy-2-methylenealkanoic Esters (5b-l). Characteristic ^{13}C NMR Data (δ, ppm, $CDCl_3$) and Yields

6	R	chemical shift difference $\Delta = \delta_{major} - \delta_{minor}$	^{13}C NMR shifts [δ, $CDCl_3$] C-1	C-2	C-3	C-4	C-5	isolated yield [%] (after chromatography) with respect to **5**
b	Me	δ_{major}	128.2	143.6	35.7	50.3	25.3	
		δ_{minor}	128.7	142.0	37.0	49.6	24.3	90
		Δ	−0.5	+1.6	−1.3	+0.7	+1.0	
c	Et[a]		128.8	142.1	42.7	50.6	25.9	
			129.4	140.5	44.1	50.1		83
			−0.6	+1.6	−1.4	+0.5		
d	*i*-Pr[b]		129.7	*c*	45.8	50.2	26.3	
			130.8		48.1	50.0	25.5	77
			−1.1		−2.3	+0.2	+0.8	
e	*t*-Bu[d]		129.3	141.4	50.3	50.7	29.4	
			130.6	140.1 (2)	53.0	48.1	25.1	65
			−1.3	+1.3 (2)	−2.7	+2.6	+4.3	
f	CH_2OMe		129.8	139.5	41.6	49.3	27.4	
			130.2	138.4	43.3	48.4		92
			−0.4	+1.1	−1.7	+0.9		
g	Ph		130.0	139.6	47.8	51.4	24.8	
					48.9		23.6	45
					−1.1		+1.2	
h	CH_2Ph		128.8	141.2	43.1	50.6	26.4	
				140.1	44.4	50.2	25.6	80
				+1.1	−1.3	+0.4	+0.8	
i	$CH_2CH_2CO_2Me$		129.4	140.4	39.7	50.4	27.9	
				138.8	41.2	49.9	27.8	80
				+1.6	−1.5	+0.5	+0.1	
j	CH_2COCH_3		129.2	141.1	35.8	50.2	25.9	
			129.5	140.0	37.3			36
			−0.3	+1.1	−1.5			
k	CH_2OCH_2Ph[e]		129.9	139.2	41.8	49.3	27.5	
			130.2		43.4	48.5	26.9	72
			−0.3		−1.6	+0.8	+0.6	
l	CH_2CH_2OMs[f]		130.0	139.7	37.1	50.5	25.6	
			130.4	138.4	39.5	50.2	25.5	59
			−0.4	+1.3	−2.4	+0.3	+0.1	

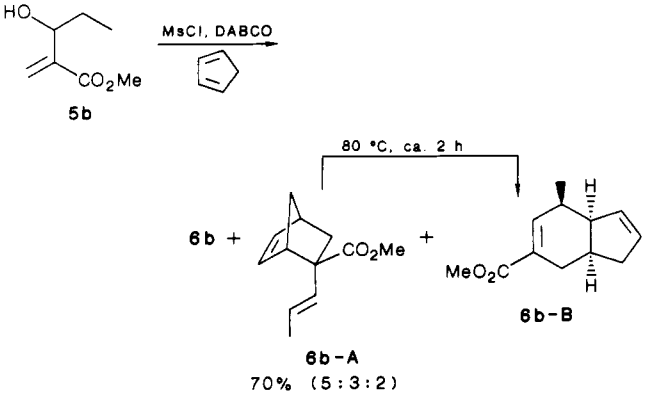
[a] GC (8:1 diastereomeric ratio). [b] GC (6:1). [c] Assignment not possible. [d] Isolation (10:1). [e] Contribution by E. Fett. [f] Diol **5l** is starting material, elimination at −20 °C with 2.4 equiv of $MeSO_2Cl$, 5 equiv of DABCO.

rotamer A (2 gauche interactions): In a concerted bimolecular elimination, the mesylates derived from rotamer A will give *Z* esters **1**, and only the mesylates derived from rotamer B yield stereospecifically the observed *E* esters **3**. However, this is not the whole story. Amine bases such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), and EtN-*i*-Pr_2 (ethyldiisopropylamine) were not successful or inefficient. [Only for the most simple alcohol **5a** (from ethanol and methyl acrylate) dehydrative dimerization with MsCl/EtN-*i*-Pr_2 (70% yield) was more efficient than with MsCl/DABCO (ca. 35% yield). Selected *tert*-butyl esters (from aldehydes and *tert*-butyl acrylate) were also dehydrated with MsCl/DABCO. The yields of dimers were always somewhat lower than for the methyl esters.] In order to cast more light on the generation of α-alkenylacrylic acid esters **3**, we treated alcohol **5a** with methanesulfonyl chloride and EtN-*i*-Pr_2 at −20 °C and after aqueous workup, isolated mesylate **5a**α, free from base and any ammonium salts. Reaction of **5a**α with DABCO (2 equiv) in $CDCl_3$ at room temperature gave a *homogeneous* solution. ^1H NMR showed that the ammonium salt **5a**β was formed in a spontaneous S_N2' reaction. The olefinic double bond was



mainly in the *E* configuration (cf. **5a**β) (*E*:*Z* = 9:1). Traces of diene ester **3A** could be detected, which dimerized slowly. However, salt **5a**β was comparatively stable in $CDCl_3$ solution at room temperature and did not react further.

In contrast to the reaction of the preformed allylic mesylate **5a**α, dehydration of the alcohol **5b** by the in situ procedure gave a precipitate, and the reaction could not be followed by NMR. However, TLC showed the presence of dimer **6b**, already after ca. 30 min. After 1 day at room temperature, dimer **6b** was isolated as detailed in Table I. Therefore, monomeric diene ester **3b** must have been present in solution, and dimer **6b** is *not* formed in the neat liquid state after the solvent is evaporated.



2. Kinetic Stability of the Monomeric *E* Diene Esters 3. The reactivity of the diene esters **3** and their

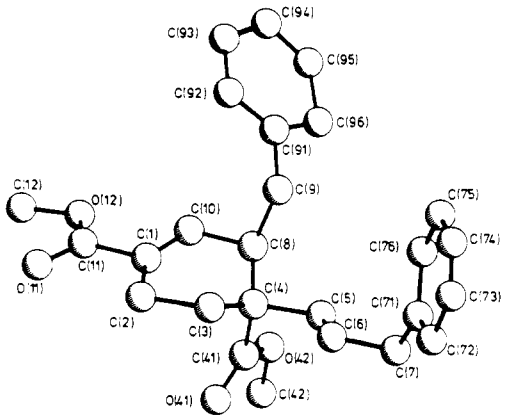
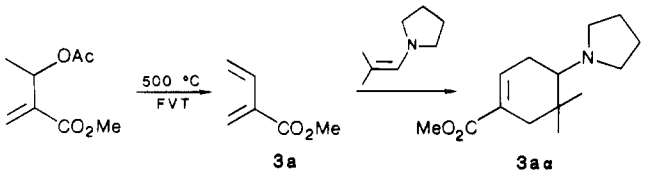


Figure 1. ORTEP plot of the major dimer, i.e., *exo*-**6h**, from the dehydration of **5h** (the ester group at C-4 is exo, i.e., trans to the vicinal benzyl group).

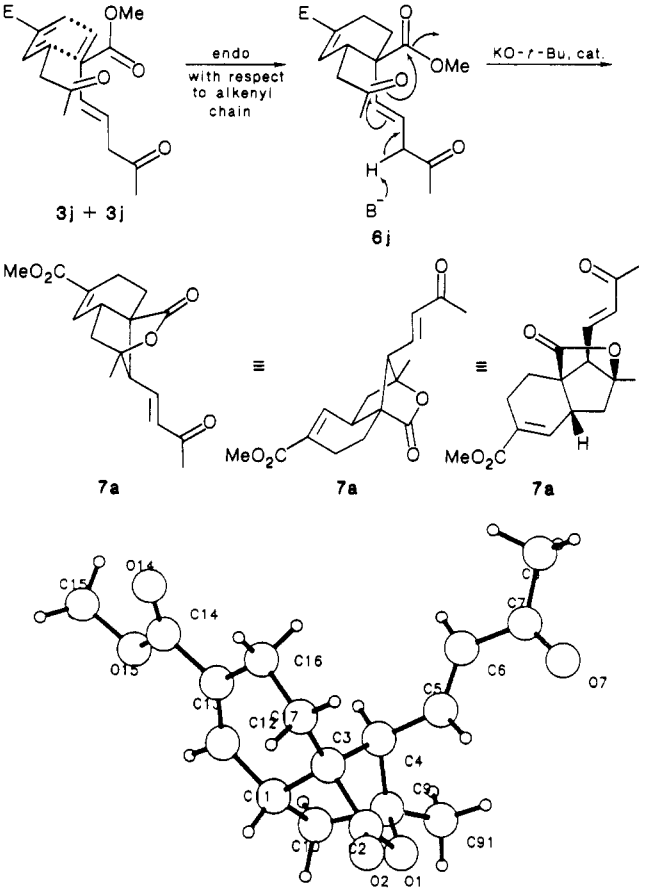
tendency to undergo self-dimerization is remarkable. When cyclopentadiene was added to the reaction mixture producing **3b**, some crossed Diels–Alder adduct and the Cope rearrangement product could be obtained, similar to findings of Franck–Neumann and Brion.[3] The parent diene ester **3a**, generated free from solvent by flash vapor thermolysis of the derived acetate, could also be induced to react with neat pyrrolidinoisobutene in a Diels–Alder addition with inverse electron demand[9] (see also ref 1b).



3. Regiochemistry of Diels–Alder Dimerization. The dimerization of *E* esters **3** is highly para-selective. No meta-oriented dimer was detected. The high reactivity of **3** is of interest, because it contrasts with that of the stereoisomeric *Z* diene ester **1**[2] and with other 1,3-dienes having an alkyl and ester group attached to any of the four diene carbons.

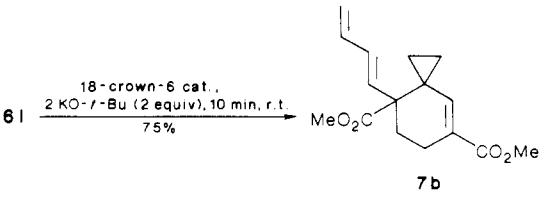
4. Stereochemistry of Formation of 4-[(*E*)-1-Alkenyl]-3-alkyl-1-cyclohexene-1,4-dicarboxylic Acid Esters 6. A priori, the Diels–Alder reaction can yield *exo*-**6**, where the ester group C-4 is exo with respect to a roof-like cyclohexene moiety, or endo isomer *endo*-**6**. One stereoisomer was always formed diastereoselectively (>5:1 to 10:1). The major and the minor isomer of all dimers **6b–l** could be assigned to a sterically uniform series, via the chemical shift differences $\Delta = \delta_{major} - \delta_{minor}$ for carbons C-1 to C-5 (Table I). All five carbon signals should be scrutinized for detecting the minor isomer. While the C-1 and C-4 signals are potentially diagnostic, these signals are not very intense in the minor isomer, C-1 and C-4 being quaternary carbons.

The actual *separation* of the isomeric cyclohexene diesters **6** was not trivial in the case of **6b** and related unbranched isomers such as **6c** and **6f**. For example, **6b** appeared to be homogeneous by capillary GC and TLC and, in fact, Dreiding and his co-workers, without using ^{13}C NMR spectroscopy, reported only one dimer **6b** in their paper.[4] With increasing branching and size of R, the separation of exo and endo isomers was feasible: Thus, the *tert*-butyl derivatives *exo*-**6e** and *endo*-**6e**, where the bulky *tert*-butyl group confronts the neighboring quaternary center, could be separated, as crystals in this case, without mixed fractions. In view of the conformational mobility of the acrylic diene/dienophile precursor **3e**, the observed diastereoselectivity for **6e** (10:1, 82% de) is quite high. An attempt to determine the stereochemistry of the major isomer of **6e** by X-ray crystallography failed, because the compound formed twin crystals. When the major isomer of **6j** was allowed to react with base, the crystalline lactone **7a** [IR ($CHCl_3$) inter al. 1780, 1710 cm^{-1}] was obtained, the structure of which was secured by X-ray crystallography. Tricycle **7a** arises by an intramolecular vinylogous aldol addition, which is terminated by a spontaneous spirolactonization. Since the cyclohexenoid and the cyclopentanoid moiety in **7a** are fused cis, the major isomer in the series of dimers **6b–l** is the exo isomer (endo with respect to alkenyl chain).

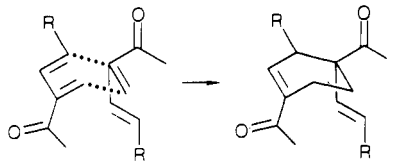


X-ray crystal structure of **7a**

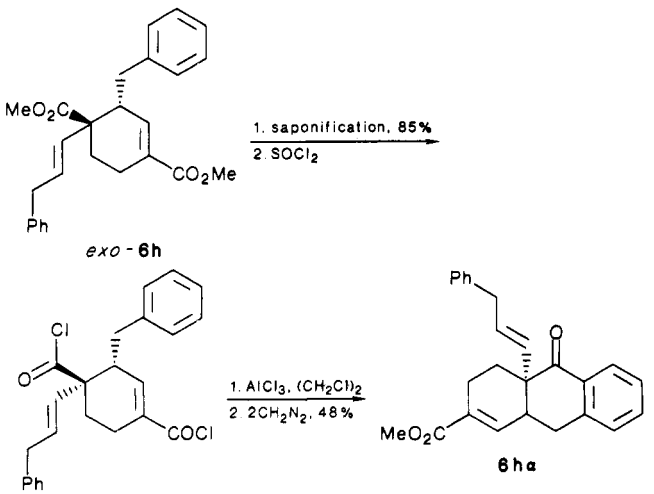
A referee suggested that the transformation of **6j** into **7a** could have entailed epimerization at carbon C-3 in **6j** (numbering as in Table I), e.g. by retro-Michael isomerizations. In this case our assignment could be wrong. Since the stereoisomers of **6l** did *not* epimerize under identical experimental conditions (KO-*t*-Bu, cat., CH_2Cl_2, −20 °C, 20 min), we did not consider an epimerization very likely. More forcing conditions, i.e. higher temperature, more base, and the presence of crown ether were required to convert dimesylate **6l** into functionalized spiro[2.5]octene **7b**. The stereochemical problem was finally settled by a further X-ray crystal structure determination, namely



Scheme I. Dimerization of (E)-3-Methylene-4-alken-2-ones is Moderately Exo-selective (ca. 4:1 to 2:1) with Respect to the Acetyl Group at C-4[11]



that of the major isomer of **6h** which was obtained by chromatography of the diastereomeric product mixture. In the major isomer, the ester group attached to the quaternary carbon and the neighboring benzyl group were trans (Figure 1). Adduct *exo*-**6h** could be transformed in a simple manner into anthrone derivative **6hα**. Thus, the



stereochemistry and preferred mode of dimerization of **3b–l** are secure: the ester group is exo and the alkenyl chain is endo with respect to the roof-like cyclohexene moiety. Moreover, this finding shows the preferred mode of dimerization of (*E*)-3-methylene-4-alken-2-ones, reported previously. Here again, the alkenyl chain is endo and the acetyl group is exo in the major dimer, although the reaction is less diastereoselective[11] (Scheme I). The rapid construction of the cis-fused *cis*-hydrindane system of **7a**[12] from the major isomer of **6j** and the preparation of **6hα** illustrate the molecular complexity that can be attained in few simple stages. Note also that the two base/nucleophile-sensitive CH_2OMs groups which appear in **6l** stayed intact after generation of the acyclic precursor **3l** from diol **5l** (Table I, footnote f).

In summary, the DABCO/DMAP/CH_3SO_2Cl-induced mesylation–dehydration of α-(hydroxyalkyl)acrylic acid esters **5** works well for the generation of α-alkenylacrylic acid esters in situ. The new diene esters, which are *E*-configurated as in **3**, undergo self-dimerization with great ease. Functionality in the alkyl chain has been introduced via precursor RCH_2CHO and is useful for tandem cyclizations and other reactions. The formation of cyclohexene 1,4-diesters **6** is para-selective and of interest in terpene synthesis. The neighboring chiral centers in **6** are installed diastereoselectively, and the % diastereomeric excess (% de) appears to increase with increasing steric demand of the group R.

Experimental Section

Preparation of α-Hydroxyalkylated Acrylic Acid Esters 5.[6] General Procedure. The aldehyde (20 mmol) and methyl acrylate (2.58 g, 30 mmol) were mixed and 1,4-diazabicyclo-[2.2.2]octane (0.336 g, 3.0 mmol) and glacial acetic acid (36 mg, 0.6 mmol) were added. After the given reaction time at room temperature, the mixture was diluted with ether and washed with water (3×). The organic phase was dried ($MgSO_4$), the solvent and the excess of the methyl acrylate were distilled off, and the residue was purified as detailed.

Methyl 3-Hydroxy-5-methoxy-2-methylenepentanoate (5f). 3-Methoxypropanal (**4f**) (4.0 g, 45.5 mmol) (prepared by oxidation of 3-methoxypropanol with pyridinium chlorochromate in absolute CH_2Cl_2 followed by distillation at reduced pressure) was allowed to react with methyl acrylate in the absence of glacial acetic acid. The crude product was distilled in a Kugelrohr apparatus (100 °C/oil pump), giving **5f** (2.8 g, 36%): IR (film) 3450 (m), 2960 (m), 2940 (m), 2890 (m), 1725 (vs), 1635 (m), 1440 (s), 1390 (m), 1295 (s), 1270 (s), 1200 (s), 1155 (s), 1120 (s), 1030 (m), 960 (m), cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 6.28 (m, 1 H, $=CH_2$), 5.84 (t, J = 1.5 Hz, 1 H, $=CH_2$), 4.64 (m, 1 H, C*H*OH), 3.76 (s, 3 H, CO_2CH_3), 3.58 (m, 2 H, CH_2OCH_3), 1.61–2.21 (m, 2 H at C-4); 50-MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (s, C=O), 142.7 (s, C-2), 124.8 (t, $=CH_2$), 70.8 (t, C-5), 69.8 (d, C-3), 58.7 (q, OCH_3), 51.7 (q, CO_2CH_3), 35.9 (t, C-4); mass spectrum (70 eV), m/z (relative intensity) 174 (0, M^+), 156 (4), 143 (4), 142 (19), 141 (5), 125 (17), 124 (17), 115 (100), 110 (28), 83 (90), 55 (42); exact mass calcd for $C_8H_{12}O_3$ 156.078674, found 156.078674.

Methyl 3-Hydroxy-2-methylene-4-phenylbutanoate (5g). 2-Phenylethanal (**4g**) (10.27 g, 85 mmol) was allowed to react with methyl acrylate and the mixture was worked up after 33 days. The crude product was a viscous light yellow oil (12 g), which was purified by chromatography on silica gel (500 g) with 1:1 ether/petroleum ether. The first fraction was **5g**, colorless oil, 3.0 g (17%): IR ($CHCl_3$) 3600 (w), 3020 (w), 3010 (w), 2970 (w), 2940 (w), 1720 (s), 1635 (w), 1610 (w), 1500 (m), 1460 (m), 1445 (m), 1345 (m), 1320 (m), 1280 (m), 1155 (m), 1085 (m), 1070 (m), 1040 (m), 970 (w), 705 (s), cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 7.21 (m, 5 H, Ar H), 6.22 (br s, 1 H, $=CH_2$), 5.76 (t, J = 1 Hz, 1 H, $=CH_2$), 4.64 (m, 1 H, C*H*OH), 3.77 (s, 3 H, OCH_3), 2.89 (m, 2 H, CH_2Ph), 2.48 (d, J = 6 Hz, 1 H, OH); 50-MHz ^{13}C NMR ($CDCl_3$) δ 166.8 (s, C-1), 142.0, 139.1 (s, C-2 and Ar), 129.6, 128.3, 126.6 (d, 3 × Ar), 125.3 (t, $=CH_2$), 72.2 (d, C-3), 51.8 (q, OCH_3), 43.3 (t, C-4); mass spectrum (70 eV), m/z (relative intensity) 206 (0, M^+), 188 (3), 157 (6), 129 (18), 128 (9), 116 (6), 115 (100), 92 (46), 91 (65), 83 (86); exact mass calcd for $C_{12}H_{12}O_2$ 188.0837302, found 188.0837783.

Methyl 1,3-Diphenyl-6-hydroxy-1-cyclohexene-5-carboxylate (5gα). The second fraction (5.4 g) was flash chromatographed (silica gel, 400 g; 12:1 CH_2Cl_2/ether). After further chromatography (1:2 ether/light petroleum ether), **5gα** was obtained as a very viscous, colorless oil (3.5 g, 40%, 2:1 diastereomeric mixture, the signals of the minor isomer are in square brackets): IR ($CHCl_3$) 3600 (w), 3080 (w), 3050 (w), 3020 (w), 2960 (m), 2880 (w), 1720 (vs), 1605 (w), 1495 (m), 1450 (m), 1435 (s), 1280 (m), 1200 (s), 1180 (s), 1130 (m), 1105 (m), 1075 (m), 1055 (m), 1010 (m), 985 (m), 945 (w), 910 (w), 890 (w), 700 (s) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 7.18–7.63 (m, 10 H, Ar H), 6.25 (m, 1 H, C=CH), [6.09 (d, J = 4 Hz, 1 H, C=CH)], [5.12 (m, 1 H, C*H*OH)], 5.03 (m, 1 H, C*H*OH), 3.76 (s, 3 H, OCH_3), [3.71 (s, 3 H, OCH_3)], 3.57 (m, 1 H, CHPh), 2.78–2.98 (m, 2 H at C-5 and OH), 1.97–2.40 (m, 2 H at C-4); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.4, [174.3] (s, C=O), 144.5, 139.6, 138.2, [143.89, 140.0, 139.4] (s, 3 $=C_{sp^2}$), 131.7, 129.8, 128.5, 128.1, 127.5, 126.7, 126.0, [128.7, 127.6, 126.5] (d, 7 × =C—), 65.2, [67.0] (d, C-6), 51.9 (q, OCH_3), 46.1, 43.8, [44.8, 40.0] (d, C-3, C-5), 28.1, [30.3] (t, C-4); mass spectrum (70 eV, 80 °C), m/z (relative intensity) 308 (4, M^+), 290 (26), 276 (8), 231 (87), 129 (21), 115 (100), 92 (39), 91 (69), 86 (46), 84 (69), 83 (49),

(10) Assignment of the characteristic ^{13}C NMR signals of C-1 to C-5 in the major isomer of **6e** was secured by Dr. L. Ernst, by applying extensive NMR techniques.

(11) Hoffmann, H. M. R.; Eggert, U.; Poly, W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1015.

(12) The basic skeleton of tricyclic lactone **7a** has previously been found in the cactus triterpene lactone thurberogenone,[13a] in a lanostadienelactone,[13b] and in trinorlupanelactone.[13c]

(13) (a) Marx, M.; Leclerq, J.; Tursch, B.; Djerassi, C. *J. Org. Chem.* **1967**, *32*, 3150. (b) Sharypov, V. F.; Kalinovskii, A. I.; Stonik, V. A.; Avilov, S. A.; Elyakov, G. B. *Khim. Prirod. Soed.* **1985**, 55. (c) Provita, J.; Klinotova, E.; Skorkovska, H.; Vystrcil, A. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1023; cf. *Chem. Abstr.* **1981**, *95*, 150949s.

50 (54); exact mass calcd for $C_{20}H_{18}O_2$ 290.1306805, found 290.1306817.

Methyl 3,5-Diphenyl-2-hydroxybenzoate (5gβ). 5gα (400 mg, 1.3 mmol) in absolute dichloroethane (20 mL) and anhydrous barium manganate ($BaMnO_4$) (3.0 g, 11.7 mmol) were refluxed for 36 h. After the black mixture had been cooled down, it was filtered and washed with CH_2Cl_2. The solvents were evaporated and the residue was chromatographed (silica gel, 1:2 ether/light petroleum), giving unchanged starting material and a yellow oil which crystallized from petroleum ether. The product contained a minor byproduct (dehydration product?) which could not separated (cf. also microanalytical data): yield 235 mg, 58%, mp 108 °C; IR (CHCl) 3450 (w), 3070 (w), 3040 (w), 2950 (w), 1675 (s), 1605 (m), 1580 (w), 1500 (w), 1460 (s), 1440 (s), 1355 (s), 1295 (m), 1240 (s), 1200 (m), 1165 (m), 1090 (w), 975 (w), 905 (m), 765 (m), 745 (m), 700 (s), cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 11.31 (s, 1 H, OH), 8.04 (d, J = 2.2 Hz, 1 H at C-6), 7.73 (d, J = 2.2 Hz, 1 H at C-4), 7.22–7.64 (m, 1 H, Ar H), 3.89 (s, 3 H, OCH_3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 170.9 (s, C=O), [166.9 (s)], 158.4 (s, C-2), 139.8, 137.2, 132.2, 130.9 (s, 4 $=C_{sp^2}$, [142.0, 140.1, 131.3 (s)], 135.3, 129.4, 128.8, 128.2, 126.6 (d, 5 × Ar), 130.2, 128.4, 127.8, 127.5, 127.4, 127.1, 127.0 (d, 4 × Ar and byproduct), 112.8 (s, C-1), 52.4 (q, OCH_3); mass spectrum (70 eV, 90 °C), m/z (relative intensity) 305 (14), 304 (56, M^+), 288 (34), 273 (25), 272 (100), 256 (17), 244 (35),215 (48), 152 (12), 73 (30); exact mass calcd for $C_{20}H_{16}O_3$ 304.1099451, found 304.1099286. Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found C, 79.41; H, 5.25.

Methyl 3-Hydroxy-2-methylene-5-phenylpentanoate (5h). 3-Phenylpropanal (dihydrocinnamaldehyde) (**4h**) (10.1 g, 75 mmol) was allowed to react with methyl acrylate. The mixture was worked up after 18 days, giving 13.8 g of crude product, 8 g of which were chromatographed (silica gel, ether/petroleum ether), giving **5h**, light yellow oil, 6.3 g, 72%: IR ($CHCl_3$) 3610 (w), 3550 (w), 3080 (w), 3020 (m), 2970 (m), 2880 (w), 1720 (s), 1635 (w), 1500 (w), 1460 (m), 1445 (m), 1345 (m), 1305 (m), 1205 (m), 1155 (m), 1075 (m), 1050 (m), 965 (m), 835 (m), 700 (m), cm^{-1}; 90-MHz ^1H NMR ($CDCl_3$) δ 7.24 (m, 5 H, Ar H), 6.20 (d, J = 1.0 Hz, 1 H, $=CH_2$), 5.82 (t, J = 1.0 Hz, 1 H, $=CH_2$), 4.40 (q, J = 6.5 Hz, 1 H, C*H*OH), 3.72 (s, 3 H, OCH_3), 2.73 (m, 3 H, CH_2Ph, O*H*), 1.95 (m, 2 H at C-4); 50-MHz ^{13}C NMR ($CDCl_3$) δ 166.9 (s, C-1), 143.1, 141.8 (s, 2 $=C_{sp^2}$), 128.5, 128.4, 125.8 (d, 3 Ar), 124.7 (t, $=CH_2$), 70.3 (d, C-3), 51.7 (q, OCH_3), 37.9, 32.0 (t, C-4, C-5); mass spectrum (70 eV), m/z (relative intensity) 220 (1, M^+), 202 (40), 171 (11), 144 (13), 143 (100), 142 (36), 141 (20), 115 (38), 110 (36), 92 (55), 84 (49); exact mass calcd for $C_{13}H_{16}O_3$ 220.1099451, found 220.1099173.

Dimethyl 3-Hydroxy-2-methylene-1,7-heptanedioate (5i-A) and 3-(1-(Methoxycarbonyl)ethenyl)-2-oxacyclohexanone (5i-B). Methyl 4-formylbutanoate (**4i**) (prepared by oxidation of 5-hydroxypentanoic acid methyl ester with pyridinium chlorochromate and distillation at 60 °C) (5.4 g, 41 mmol) was allowed to react with methyl acrylate. The crude product (6.9 g) was distilled in a Kugelrohr apparatus (100 °C, oil pump), giving **5i-A**, colorless oil, 3.95 g, 46%; IR ($CHCl_3$) 3590 (w), 3520 (w), 3000 (m), 2950 (m), 1720 (vs), 1625 (w), 1435 (s), 1360 (w), 1325 (m), 1160 (m), 1080 (m), 955 (m) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.26 (d, J = 1 Hz, 1 H, $=CH_2$), 5.85 (t, J = 1 Hz, 1 H, $=CH_2$), 4.42 (br m, 1 H, C*H*OH), 3.79, 3.68 (s, 2 × 3 H, 2 OCH_3), 2.79 (br s, 1 H, OH), 2.36 (m, 2 H at C-6), 1.55–2.00 (m, 4 H, 2 × CH_2 at C-4, C-5); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.1 (s, C-7), 166.9 (s, C-1), 143.3 (s, C-2), 124.6 (t, $=CH_2$), 70.0 (d, C-3), 51.8, 51.5 (q, 2 OCH_3), 35.8, 33.7, 21.2 (t, 3 CH_2); mass spectrum (70 eV), m/z (relative intensity) 216 (0, M^+), 184 (7), 167 (18), 152 (29), 135 (20), 124 (37), 115 (100), 101 (19), 83 (78), 74 (79); exact mass calcd for $C_9H_{12}O_4$ 184.0735597, found 184.0736087. The signals of lactone **5i-B** were determined subtractively form the spectra of crude **5i-A**: 200-MHz ^1H NMR ($CDCl_3$) δ 6.42 (m, 1 H, $=CH_2$), 6.00 (m, 1 H, $=CH_2$), 5.22 (m, 1 H, CHOCO), 3.80 (s, 3 H, OCH_3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 171.4, 165.4 (s, 2 C=O), 139.2 (s, *C*=CH_2), 126.4 (t, $=CH_2$), 77.8 (d, *C*HCO), 52.1 (q, OCH_3), 29.6, 28.3, 18.2 (t, 3 CH_2).

***tert*-Butyl 3-Hydroxy-2-methylene-6-methoxyhexanoate (5i-C), 1-((*tert*-Butoxycarbonyl)ethenyl)-2-oxacyclohexanone (5i-D), and Di-*tert*-butyl 3-(2-(Hydroxycarbonyl)ethyl)-1-cyclohexene-1,5-dicarboxylate (5i-E).** Methyl 4-formylbutanoate (**4i**) (1.02 g, 8 mmol) and *tert*-butyl acrylate were allowed to react for 63 days, and the product was worked up by chromatography (silica gel, 1:1 ether/petroleum ether). The first fraction consisted of acid **5i-E**, colorless solid, 285 mg, 20%, mp 109–110 °C. The second fraction contained coupling product **5i-C** together with lactone **5i-D** as a minor constituent. Yield 280 mg, 14%. Spectroscopic data of **5i-C**: IR ($CHCl_3$) 3530 (bw), 3000 (w), 2980 (m), 2960 (m), 1725 (vs), 1625 (w), 1455 (m), 1435 (m), 1390 (m), 1370 (s), 1340 (m), 1150 (s), 1080 (m), 1010 (w), 960 (w); 200-MHz ^1H NMR ($CDCl_3$) δ 6.13 (m, 1 H, $=CH_2$), 5.72 (t, J = 1.5 Hz, 1 H, $=CH_2$), 4.36 (m, 1 H, C*H*OH), 3.69 (s, 3 H, OCH_3), 1.65–2.60 (m, 7 H, 3 CH_2, OH), 1.51 [s, 9 H, $C(CH_3)_3$]; 50-MHz ^{13}C NMR ($CDCl_3$) δ 175.9 (s, CO_2CH_3), 165.9 [s, $CO_2C(CH_3)_3$], 144.5 (s, C-2), 125.1 (t, $=CH_2$), 81.2 [s, $C(CH_3)_3$], 70.3 (d, C-3), 51.5 (s, OCH_3), 35.9, 33.8, 21.3 (t, 3 CH_2); mass spectrum (70 eV), m/z (relative intensity) 258 (0, M^+), 224 (1), 202 (2), 184 (17), 153 (33), 152 (29), 135 (19), 124 (14), 102 (24), 101 (54), 99 (31), 98 (25), 74 (25), 57 (100); exact mass calcd for $C_9H_{14}O_5$ 202.0841245, found 202.0840128. Lactone **5i-D** (data determined subtractively): 200-MHz H NMR ($CDCl_3$) δ 6.31 (1 H, $=CH_2$), 5.89 (1 H, $=CH_2$), 5.17 (1 H, CHOCO), 1.48 [s, 9 H, $C(CH_3)_3$]. Carboxylic acid **5i-E** (2 diastereomers): IR ($CHCl_3$) 2450–3600 (bw), 2980 (m), 2940 (m), 1710 (vs), 1645 (w), 1475 (w), 1455 (w), 1390 (m), 1370 (s), 1280 (m), 1255 (m), 1155 (vs), 1090 (m), 910 (s) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.85 (m, 1 H, =CH), [6.70 (m, 1 H, =CH)], 1.55–2.70 (m, 10 H, 4 × CH_2, 2 × CH), 1.48, 1.46 (s, 2 × 9 H, 2 $C(CH_3)_3$); 50-MHz ^{13}C NMR ($CDCl_3$) (major isomer) δ 178.7, 174.6, 166.5 (s, 3 C=O), 138.9 (d, C-2), 132.1 (s, C-1), 80.7 80.3 (s, 2 $C(CH_3)_3$), 43.3, 36.0 (d, C-3, C-5), 31.8, 26.6, 23.7, 21.0 (t, 4 CH_2), 28.1, 28.0 (q, 2 $C(CH_3)_3$); minor isomer 174.4, 166.3 (s, 3 C=O), 139.1 (d, C-2), 131.9 (s, C-1), 80.8, 80.4 (s, 2 $C(CH_3)_3$), 45.3, 37.3 (d, C-3, C-5), 33.1, 31.0, 28.4, 25.6 (t, 4 CH_2); mass spectrum (70 eV, 90 °C), m/z (relative intensity) 345 (0, M^+), 298 (1), 280 (5), 242 (28), 224 (10), 206 (33), 196 (66), 179 (50), 178 (78), 57 (91). Anal. Calcd for $C_{19}H_{30}O_4$: C, 64.38; H, 8.53. Found: C, 63.99; H, 8.54.

Methyl 3-Hydroxy-2-methylene-1-oxo-6-heptan-1-oate (5j). 4-Oxopentanal (**4j**) (levulinic aldehyde)[6a] (1.7 g, 17 mmol) was allowed to react with methyl acrylate in CH_2Cl_2 (2 mL) without adding acetic acid. After 5 days the dark reaction mixture was worked up and the crude product (1.0 g) was flash chromatographed (silica gel, 5:1 ether/petroleum ether), giving **5j**, colorless oil, 0.78 g (25%): IR ($CHCl_3$) 3600 (w), 3450 (w), 3010 (m), 2960 (m), 1715 (vs), 1630 (m), 1440 (s), 1405 (m), 1370 (m), 1340 (m), 1300 (m), 1275 (m), 1155 (s), 1080 (m), 960 (m), 820 (w) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.25 (s, 1 H, $=CH_2$), 5.85 (t, J = 1.0 Hz, 1 H, $=CH_2$), 4.45 (m, 1 H, C*H*OH), 3.76 (s, 3 H, OCH_3), 3.11 (d, 1 H, OH), 2.64 (dt, J = 7 Hz, J = 3 Hz, 2 H at C-5), 2.16 (s, 3 H, $COCH_3$), 1.95 (m, 2 H at C-4); 50-MHz ^{13}C NMR ($CDCl_3$) δ 209.4 (s, C-6), 166.8 (s, C-1), 143.3 (s, C-2), 124.6 (t, $=CH_2$), 69.4 (d, C-3), 51.8 (q, OCH_3), 39.7, 29.8 (t, C-4, C-5), 30.3 (q, C-7); mass spectrum (70 eV), m/z (relative intensity) 186 (0, M^+), 168 (11), 154 (17), 137 (20), 128 (22), 126 (24), 115 (100), 83 (79), 55 (33); exact mass calcd for $C_8H_{10}O_3$ 154.0629948, found 154.0629701.

The half-acetal of **5j** was also discernible: 200-MHz ^1H NMR ($CDCl_3$) inter al. δ 5.00, 5.75 (m, 1 H, OCH), 3.75 (s, 3 H, OCH_3), 1.62 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 166.6, 166.4 (s, C=O), 142.0, 141.9 (s, CH_2=*C*), 125.0, 123.3 (t, $=CH_2$), 105.6, 105.5 (s, COH), 78.8, 76.3 (d, OCH), 51.7 (q, OCH_3), 40.0, 37.0, 31.8, 31.5 (t, 2 CH_2), 27.0 (q, CH_3).

Dimethyl 3-((Hydroxycarbonyl)methyl)-1-cyclohexene-1,5-dicarboxylate (5m-A). Methyl 3-formylpropanoate (**4m**) (1.0 g, 8.6 mmol) and methyl acrylate were allowed to react for 40 days. The crude product (700 mg) was chromatographed on silica gel (ether) and was recrystallized from ether/pentane to give a colorless solid, 150 mg, 10%, mp 123–127 °C, mixture of 2 diastereomers. Further recrystallization (ether/pentane) gave the main diastereomer, colorless solid, 90 mg (6%), mp 126–128 °C: IR (KBr) 2400–3600 (w), 2980 (m), 1745 (s), 1715 (s), 1655 (w), 1450 (m), 1440 (m), 1420 (w), 1390 (w), 1375 (w), 1310 (m), 1290 (m), 1255 (s), 1235 (m), 1210 (m), 1195 (m), 1165 (m), 1095 (m), 1085 (m), 1010 (w), 995 (w) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 10.58 (br s, 1 H, OH), 6.95 (m, 1 H, =CH), 3.76, 3.70 (s, 2 × 3 H, 2 OCH_3), 3.17 (br m, 1 H at C-4), 2.81 (m, 1 H at C-6), 1.74–1.62 (m, 6 H, 3 CH_2); 50-MHz ^{13}C NMR ($CDCl_3$) δ 177.1, 173.7, 167.3 (s, 3 C=O), 139.4 (d, C-1), 130.6 (s, C-2), 51.6, 51.5 (q, 2 OCH_3), 41.5, 33.0 (d, C-4, C-6), 35.6, 23.1, 21.5 (t, 3 CH_2); mass spectrum (70 eV, 70 °C), m/z (relative intensity) 256 (1, M^+), 239 (2), 238

(12), 225 (12), 224 (23), 210 (5), 206 (14), 196 (20), 193 (15), 192 (24), 179 (10), 178 (10), 165 (33), 164 (24), 151 (34), 137 (100), 119 (24), 105 (25), 98 (27), 96 (88), 79 (39), 59 (41); exact mass calcd for $C_{12}H_{14}O_5$ 238.0841245, found 238.0840648. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29. Found: C, 56.20; H, 6.19.

Carboxylic acid **5m-A** was also allowed to react with diazomethane, giving the methyl ester, mp 46–50 °C.

Di-*tert*-butyl 3-((Hydroxycarbonyl)methyl)-1-cyclohexene-1,5-dicarboxylate (5m-B). Methyl 3-formylpropanoate (4.67 g, 40 mmol) and *tert*-butyl acrylate were allowed to react for 38 days. The crude product was recrystallized twice from ether/pentane to give a light yellow solid, 2.5 g (28%), 2 diastereomers. Column chromatography (silica gel, ether) gave the pure major diastereomer, colorless solid, 1.70 g (19%), mp 114–115 °C: IR ($CHCl_3$) 2400–3520 (w), 3010 (w), 2980 (m), 2940 (w), 1720 (s), 1655 (w), 1480 (w), 1460 (w), 1440 (w), 1395 (m), 1370 (m), 1280 (m), 1260 (m), 1155 (s), 1095 (m), 1070 (w), 1045 (w), 940 (w); 200-MHz ^{1}H NMR ($CDCl_3$) δ 6.85 (m, 1 H, =CH), 3.10 (m, 1 H at C-5), 2.66 (m, 1 H at C-3), 2.15–2.58, 1.66–2.00 (m, 4 + 2 H, 3 CH_2), 1.48, 1.45 (s, 2 × 9 H, 2 $C(CH_3)_3$); 50-MHz ^{13}C NMR ($CDCl_3$) δ 177.3, 172.8 (s, 2 C=O), 166.4 (s, C=O at C-1), 138.4 (d, C-2), 132.0 (s, C-1), 80.8, 80.4 (s, 2 $C(CH_3)_3$), 42.6, 33.2 (d, C-3, C-5), 35.8, 23.2, 21.8 (t, 3 CH_2), 28.1, 28.0 (q, 2 $C(CH_3)_3$); mass spectrum (70 eV, 80 °C), m/z (relative intensity) 340 (0, M^+), 284 (3), 228 (28), 226 (100), 211 (56), 210 (51), 197 (34), 194 (28), 182 (31), 180 (58), 135 (20), 132 (15), 123 (20), 57 (58); exact mass calcd for $C_{10}H_{12}O_6$ 228.0633892, found 228.06325689. Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.45; H, 8.03.

Carboxylic acid **5m-B** was also allowed to react with diazomethane, giving the methyl ester, as a waxy, colorless solid.

General Procedure for the Dehydrative Dimerization of 2-(Hydroxyalkyl)-2-propenoic Acid Esters 5. To a solution of ester **5** (10 mmol) in absolute CH_2Cl_2 (20 mL) were added 1,4-diazabicyclo[2.2.2]octane (3.36 g, 30 mmol) and *p*-(dimethylamino)pyridine (180 mg, 1.5 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (1.34 g, 12 mmol) in CH_2Cl_2 (10 mL) was dropped in slowly, to give a colorless precipitate after a short time. The mixture was stirred for 1 day at room temperature, diluted with ether (200 mL), washed with 30 mL of water (3×), and dried ($MgSO_4$). After removal of the solvent the residue was chromatographed on silica gel as detailed.

Dimethyl 3-Methyl-4-(1-propenyl)-1-cyclohexene-1,4-dicarboxylate (6b). Alcohol **5b** (0.72 g, 5 mmol) was dehydrated as described and the mixture was worked up after 20 h. Chromatography (1:1 ether/petroleum ether) gave a colorless wax of two diastereomers **6b** which could not be separated. Yield 570 mg, 90%. Spectroscopic data of major/minor isomer: IR ($CHCl_3$) 3020 (w), 2960 (m), 2890 (w), 2860 (w), 1720 (vs), 1695 (m), 1455 (m), 1440 (s), 1370 (vs), 1275 (s), 1100 (s), 1045 (m), 980 (m), cm^{-1}; 200-MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (m, 1 H at C-2), 5.55 (dq, J = 16.0 Hz, J = 5.5 Hz, 1 H, =C*H*CH_3), 5.41 (dm, J = 16.0 Hz, 1 H, =CH at C-4), 3.72 [3.73] (s, 3 H, OCH_3), 3.66 [3.68] (s, 3 H, OCH_3), 3.00 (m, 1 H at C-3), 1.45–2.45 (m, 4 H at C-5, C-6); 50-MHz ^{13}NMR ($CDCl_3$) δ 175.3 [175.1] (s, C=O at C-4), 167.5 (s, C=O at C-1), 143.6 [142.0] (d, C-2), 131.5 [132.0] (d, =CH at C-4), 128.2 [128.7] (s, C-1), 126.5 [126.5] (d, =*C*H-CH_3), 52.0, 51.4 (q, 2 OCH_3), 50.3 [49.6] (s, C-4), 35.7 [37.0] (d, C-3), 25.3 [24.3] (t, C-5), 22.3 [21.7] (t, C-6), 18.2, 16.3 [16.9, 15.3] (q, 2 CH_3); mass spectrum (70 eV, room temperature), m/z (relative intensity) 253 (3), 252 (15, M^+), 221 (20), 220 (89), 193 (77), 188 (34), 161 (100), 133 (99), 126 (86), 111 (83), 105 (83), 91 (91), 66 (77); exact mass calcd for $C_{14}H_{20}O_4$ 252.1361602, found 252.1362414.

Dimethyl 4-(1-Butenyl)-3-ethyl-1-cyclohexene-1,4-dicarboxylate (6c). 5c (1.6 g, 10 mmol) was dehydrated as described and the mixture was worked up after 7 h. The crude product (1.25 g, 89%) was chromatographed (1:2 ether/petroleum ether) to give **6c**, colorless oil, as two diastereomers which could not be separated, yield 1.16 g (83%): IR (film) 2970 (s), 2880 (m), 1730 (vs), 1655 (m), 1480 (m), 1440 (s), 1385 (w), 1250 (vs), 1195 (s), 1170 (s), 1095 (s), 1060 (m), 980 (m) cm^{-1}; 200-MHz ^{1}H NMR ($CDCl_3$) δ 7.07 (m, 1 H at C-2), 5.59 [5.55] (dt, J = 16.0 Hz, J = 6.0 Hz, 1 H, =C*H*CH_2), 5.40 [5.32] (dm, J = 16.0 Hz, 1 H, =CH at C-4), 3.72 [3.73] (s, 3 H, OCH_3), 3.65 [3.68] (s, 3 H, OCH_3), 2.76 (m, 1 H at C-3), 2.37, 1.95–2.25, 1.61–1.95 (m, 2 + 4 + 2 H, 4 H at C-5 and C-6, CH_2 at C-3, CH_2CH=), 1.00 (t, J = 6.5 Hz, 3 H, CH_3), 0.97 (t, J = 7.0 Hz, 3 H, CH_3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 175.3 [175.1] (s, C=O at C-4), 167.4 (s, C=O at C-1), 142.1 [140.5] (d, C-2), 133.4 [133.1] (d, =$CHCH_2$), 129.4 [130.1] (d, =CH at C-4), 128.8 [129.4] (s, C-1), 52.0, 51.4 [51.6] (q, 2 OCH_3), 50.5 [50.1] (s, C-4), 42.7 [44.1] (d, C-3), 25.9, 25.6, 24.7, 22.3 [20.7] (t, 4 CH_2), 13.7, 12.4 (q, 2 CH_3); mass spectrum (70 eV, room temperature), m/z (relative intensity) 281 (8), 280 (30, M^+), 249 (18), 248 (66), 221 (50), 216 (25), 189 (70), 161 (53), 140 (56), 125 (100), 95 (39), 91 (58), 81 (45), 79 (47); exact mass calcd for $C_{16}H_{24}O_4$ 280.1674604, found 280.1672834.

Dimethyl 3-Isopropyl-4-(3-methyl-1-butenyl)-1-cyclohexene-1,4-dicarboxylate (6d). 5d (1.17 g, 6.8 mmol) gave 1.0 g (95%) of crude product, which was chromatographed (1:6 ether/petroleum ether) to give 550 mg of pure major isomer and 50 mg of pure minor isomer, colorless oils. Yield 770 mg, 77%. Major isomer: IR ($CHCl_3$) 3020 (w), 2970 (s), 2880 (w), 1720 (vs), 1655 (w), 1460 (w), 1455 (w), 1440 (m), 1390 (w), 1370 (w), 1270 (vs), 1175 (m), 1100 (m), 1060 (w), 1030 (w), 985 (w), 910 (w) cm^{-1}; 200-MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (m, 1 H at C-2), 5.40–5.59 (m, 2 H, CH=CH), 2.97 (m, 1 H at C-3), 3.72 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 1.70–2.51 (m, 4 H at C-5, C-6), 1.07 (d, J = 7.0 Hz, 3 H, CH_3), 0.98 (d, J = 6.4 Hz, 6 H, 2 CH_3), 0.78 (d, J = 6.6 Hz, 3 H, CH_3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 175.2 (s, C=O at C-4), 166.9 (s, C=O at C-1), 138.9, 137.8 (d, C-2, =*C*HCMe_2), 129.7 (s, C-1), 126.9 (d, =CH at C-4), 52.0, 51.4 (q, 2 OCH_3), 50.2 (s, C-4), 45.8 (d, C-3), 31.1, 28.3 (d, 2 $CHMe_2$), 26.3 (t, C-5), 23.6,22.4, 22.4, 19.6 (q, 4 CH_3), 21.6 (t, C-6); mass spectrum (70 eV, room temperature), m/z (relative intensity) 308 (8, M^+), 276 (43), 260 (19), 248 (49), 217 (88), 207 (26), 205 (28), 189 (25), 153 (33), 146 (46), 144 (38), 138 (100), 105 (67), 95 (81), 91 (93), 79 (85); exact mass calcd for $C_{18}H_{28}O_4$ 308.1987606, found 308.1987990. Minor isomer: 200-MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (m, 1 H at C-2), 5.47 (dd, J = 16.0 Hz, J = 6.4 Hz, 1 H, =C*H*CH), 5.22 (d, J = 16.0 Hz, 1 H, =CH at C-4), 3.74 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 1.68–2.49 (m, 4 H at C-5, C-6), 1.07 (d, J = 6.7 Hz, 3 H, CH_3), 0.92 (d, J = 7.0 Hz, 6 H, 2 CH_3), 0.79 (d, J = 6.7 Hz, 3 H, CH_3); 50 MHz ^{13}C NMR ($CDCl_3$) δ 175.7 (s, C=O at C-4), 167.4 (s, C=O at C-1), 137.9, 137.8 (d, C-2 =*C*H-$CHMe_2$), 130.8 (s, C-1), 129.6 (d, =CH at C-4), 51.5 (q, 2 OCH_3), 50.0 (s, C-4), 48.1 (d, C-3), 31.2, 30.7 (d, 2 $CHMe_2$), 25.5 (t, C-5), 23.9, 22.3, 22.3, 19.9 (q, 4 CH_3), 21.4 (t, C-6).

Dimethyl 3-*tert*-Butyl-4-(3,3-dimethyl-1-butenyl)-1-cyclohexene-1,4-dicarboxylate (6e). Alcohol **5e** (1.4 g, 7.5 mmol) was dehydrated as detailed and the mixture was worked up after 30 h to give crude **6e** (850 mg, 68%). Chromatography (1:8 ether/petroleum ether) gave the two diastereomers, colorless solids, without mixed fractions. Major isomer, 740 mg, mp 77–78 °C. Minor isomer, 80 mg. Total yield 820 mg, 65%. Major isomer: IR ($CHCl_3$) 3020 (w), 2950 (s), 2900 (m), 2870 (w), 1710 (vs), 1650 (w), 1470 (w), 1460 (w), 1435 (m), 1390 (w), 1360 (m), 1265 (s), 1240 (s), 1090 (m), 1070 (m) cm^{-1}; 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.08 (m, $J_{2,3}$ = 4.3 Hz, $J_{2,6}$ = 1.9 Hz, 1 H at C-2), 5.72 (d, J = 16.4 Hz, 1 H, =C*H*CMe_3), 5.52 (d, J = 16.4 Hz, 1 H, =CH at C-4), 3.76 (s, 3 H, CO_2CH_3 at C-1), 3.64 (s, 3 H, CO_2CH_3 at C-4), 3.04 (m, $J_{3,5a}$ = 1 Hz, $J_{3,6}$ = 2.5 Hz, 1 H at C-3), 2.33–2.40 (m, 2 H at C-6), 2.16 (m, 1 H at C-5), 1.97 (m, 1 H at C-5), 1.01 (s, 9 H, CMe_3 at C-3), 1.00 (s, 9 H, =CHC(CH_3)$_3$); 100-MHz ^{13}C NMR ($CDCl_3$) δ 176.5 (s, C=O at C-4), 167.4 (s, C=O at C-1), 141.4 (d, C-2), 141.1 (d, =*C*HCMe_3), 129.3 (s, C-1), 124.8 (d, =CH at C-4), 51.9, 51.5 (q, 2 OCH_3), 50.7 (s, C-4), 50.3 (d, C-3), 35.9 (s, *C*Me_3 at C-3), 33.2 (s, =CH*C*Me_3), 30.2 (q, C*Me*$_3$ at C-3), 29.4 (t, C-5), 29.3 (q, =CHC*Me*$_3$), 21.8 (t, C-6); mass spectrum (70 eV, 50 °C), m/z (relative intensity) 337 (9), 336 (39, M^+), 305 (13), 304 (33), 289 (17), 280 (36), 248 (72), 245 (43), 220 (100), 196 (42), 189 (77), 168 (45), 153 (65), 93 (39), 57 (78); exact mass calcd for $C_{20}H_{32}O_4$ 336.2300609, found 336.22992. Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.40; H, 9.60. Found: C, 71.51; H, 9.46. Minor isomer: 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.10 (m, $J_{2,3}$ = 5.9 Hz, $J_{2,6}$ = 1.9 Hz, 1 H at C-2), 5.61 (d, J = 16.2 Hz, 1 H, =C*H*CMe_3), 5.20 (d, J = 16.2 Hz, 1 H, =CH at C-4), 3.73 (s, 3 H, CO_2CH_3 at C-1), 3.62 (s, 3 H, CO_2CH_3 at C-4), 2.55 (m, $J_{3,6}$ = 2 Hz, 1 H at C-3), 1.96–2.41 (m, 4 H at C-5, C-6), 0.97 (s, 9 H, CMe_3 at C-3), 0.93 (s, 9 H, =CHC(CH_3)$_3$); 100-MHz ^{13}C NMR ($CDCl_3$) δ 176.8 (s, C=O at C-4), 167.6 (s, C=O at C-1), 140.2, 140.1 (d, C-2, =*C*HCMe_3), 130.6 (s, C-1), 129.1 (d, =CH at C-4), 53.0 (d, C-3), 51.9, 51.3 (q, 2 OCH_3), 48.1 (s, C-4), 36.4 (s, *C*Me_3 at C-3), 32.9 (s, =CH-C*Me*$_3$), 30.1 (q, C*Me*$_3$ at C-3), 29.3 (q, =CHC*Me*$_3$), 25.1 (t, C-5), 21.7 (t, C-6).

Dimethyl 3-(Methoxymethyl)-4-(3-methoxy-1-propenyl)-1-cyclohexene-1,4-dicarboxylate (6f). 5f (1.57 g, 9 mmol) was dehydrated and the mixture was worked up after 8 h. Chromatography (1:1 ether/petroleum ether) gave the two diastereomers, colorless oil, 1.30 g (92%): IR (film) 2990 (w), 2960 (m), 2940 (m), 2900 (m), 2840 (w), 1725 (s), 1655 (w), 1455 (m), 1440 (m), 1385 (w), 1260 (s), 1245 (s), 1195 (m), 1120 (s), 1095 (s), 1050 (w), 980 (w), 920 (w), cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.98 (m, 1 H at C-2), 5.55–5.82 (m, 2 H, CH=CH), 3.93 (d, J = 4.5 Hz, 2 H, =CHCH_2), 3.72 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, CO_2CH_3), 3.45 (m, 2 H, CH_2OCH$_3$), 3.32, 3.29 (s, 2 × 3 H, 2 OCH$_3$), 3.21 (m, 1 H at C-3), 2.25–2.45 (m, 2 H at C-6), 1.82–2.25 (m, 2 H at C-5); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.5 [174.0] (s, C=O at C-4), 167.0 (s, C=O at C-1), 139.5 [138.4] (d, C-2), 131.9, 128.1 [133.9, 127.5] (d, CH=CH), 129.8 [130.2] (s, C-1), 73.0, 72.8 (t, 2 CH_2OCH$_3$), 58.7, 57.8 [57.6] (q, 2 OCH$_3$), 52.2, 51.5 [53.8, 51.7] (q, 2 CO_2CH_3), 49.3 [48.4] (s, C-4), 41.6 [43.3] (d, C-3), 27.4 (t, C-5), 22.0 (t, C-6); mass spectrum (70 eV, room temperature), m/z (relative intensity) 312 (2, M^+), 281 (2), 280 (2), 249 (14), 236 (27), 221 (21), 214 (17), 189 (35), 177 (78), 176 (28), 145 (39), 137 (20), 129 (26), 117 (78), 91 (26), 71 (28), 59 (24), 45 (100).

Dimethyl 3-Phenyl-4-(2-phenylethenyl)-1-cyclohexene-1,4-dicarboxylate (6g). 5g (1.2 g, 5.8 mmol) was dehydrated, giving a viscous yellow oil (0.66 g, 61%), which was chromatographed (1:2 ether/petroleum ether). The two diastereomers were obtained as a solid, 490 mg (45%), mp 111–113 °C: IR ($CHCl_3$) 3040 (w), 2960 (w), 2860 (w), 1725 (s), 1660 (w), 1500 (w), 1460 (w), 1440 (m), 1390 (w), 1270 (s), 1200 (m), 1180 (m), 1095 (m), 1045 (w), 1005 (w), 970 (m) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 7.0–7.4 (m, 11 H, 1 H at C-2, 10 Ar H), 6.20 [6.24] (d, J = 16.4 Hz, 1 H, =CHPh), 5.76 (d, J = 16.4 Hz, 1 H, =CH at C-4), 4.41 (d, J = 5 Hz, 1 H at C-3), 3.74, 3.74 [3.75, 3.72] (s, 2 × 3 H, 2 OCH$_3$), 1.79–2.69 (m, 4 H at C-5, C-6); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.6 [173.7] (s, C=O at C-4), 167.4 (s, C=O at C-1), 139.6 (d, C-2), 139.2, 136.9 (s, 2 Ar), 131.5, 131.0, 130.7, 130.2, 130.0, 128.5, 128.1 [128.0, 127.8, 127.5, 126.5, 126.3] (s, C-1 and d, CH=CH, Ar), 52.4, 51.7 (q, 2 OCH$_3$), 51.4 (s, C-4), 47.8 [48.9] (d, C-3), 24.8 [23.6] (t, C-5), 22.3 [21.4] (t, C-6); mass spectrum (70 eV, 90 °C), m/z (relative intensity) 377 (2), 376 (7, M^+), 344 (8), 242 (4), 188 (37), 129 (100), 128 (27), 84 (19); exact mass calcd for $C_{24}H_{24}O_4$ 376.1674604, found 376.1673248. Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.70; H, 6.46.

Dimethyl 3-Benzyl-4-(3-phenyl-1-propenyl)-1-cyclohexene-1,4-dicarboxylate (6h). 5h (4.4 g, 20 mmol) was dehydrated following the general procedure. The crude product (3.92 g, 97%) was chromatographed (1:2 ether/petroleum ether), giving a colorless solid, 3.42 g (80%), mp 70–73 °C. Samples of the two separate diastereomers could be obtained. Major diastereomer (cf. X-ray crystal structure): IR (KBr) 3080 (m), 3040 (m), 2960 (m), 1730 (s), 1715 (s), 1650 (w), 1605 (w), 1500 (w), 1460 (m), 1435 (m), 1390 (w), 1300 (w), 1265 (m), 1250 (m), 1230 (m), 1095 (m), 1085 (w), 980 (w) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H, Ar), 6.77 (dt, J = 4.5 Hz, J = 1.5 Hz, 1 H at C-2), 5.83 (dt, J = 16.0 Hz, J = 6.8 Hz, 1 H, =CHCH$_2$), 5.61 (d, J = 16.0 Hz, 1 H, =CH at C-4), 3.67 (s, 6 H, 2 OCH$_3$), 3.43 (d, J = 6.5 Hz, 2 H, =CHCH_2), 3.20 (m, 1 H at C-3), 3.03 (dd, J = 13.0 Hz, J = 4.0 Hz, 1 H, CHHPh at C-3), 2.39 (m, 2 H at C-6), 2.31 (dd, J = 13.0 Hz, J = 11.0 Hz, 1 H, CHHPh at C-3), 2.18 (m, 1 H at C-5), 1.89 (m, 1 H at C-5); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.9 (s, C=O at C-4), 167.3 (s, C=O at C-1), 141.2 (d, C-2), 140.0, 139.7 (s, 2 Ar), 131.2, 129.1, 128.5, 126.2, 126.1 (d, CH=CH at C-4, Ar), 128.8 (s, C-1), 52.1, 51.5 (q, 2 OCH$_3$), 50.6 (s, C-4), 43.1 (d, C-3), 39.2, 37.9 (t, 2 CH_2Ph), 26.4 (t, C-5), 22.2 (t, C-6); mass spectrum (70 eV, 90 °C), m/z (relative intensity) 405 (2), 404 (6, M^+), 373 (3), 372 (11), 345 (4), 344 (4), 312 (8). 278 (12) 253 (8), 143 (25), 117 (20), 115 (18), 112 (100); exact mass calcd for $C_{26}H_{28}O_4$ 404.1987606, found 404.1986857. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.17; H, 6.94. Minor diastereomer: 200-MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H, Ar), 6.75 (m, 1 H at C-2), 5.71 (dt, J = 16.0 Hz, J = 6.6 Hz, 1 H, =CHCH$_2$), 5.48 (d, J = 16.0 Hz, 1 H, =CH at C-4), 3.69, 3.67 (s, 2 × 3 H, 2 OCH$_3$), 3.34 (d, J = 6.5 Hz, 2 H, =CHCH_2), 2.79 (dd, J = 16.0 Hz, J = 3.5 Hz, 1 H, CHHPh at C-3), 1.90–2.60 (m, 5 H, CH_2CH_2, CHHPh at C-3); 50-MHz ^{13}C NMR ($CDCl_3$) δ (subtractive) 174.0 (s, C=O at C-4), 167.3 (s, C=O at C-1), 140.1, 139.4 (d, C-2 and/or s, Ar), 132.5, 130.4 (d), 129.0 (s, C-1), 51.8, 51.5 (q, 2 OCH$_3$), 50.2 (s, C-4), 44.4 (d, C-3), 39.9, 39.8 (t, 2 CH_2Ph), 25.6 (t, C-5), 22.0 (t, C-6).

Anthrone Derivative 6hα. The major dimer, i.e., *endo*-**6h** (1.0 g, 2.47 mmol), and KOH (2.0 g, 37 mmol) in absolute methanol (7 mL) were refluxed for 4.5 h. The mixture was diluted with water and extracted with ether (3×). The aqueous phase was acidified with dilute HCl and extracted with ether (5×), and the combined organic phase was dried ($MgSO_4$). After removal of the solvent the dicarboxylic acid was isolated as a light yellow solid, 0.79 g (85%), mp 194–195 °C. A sample of the diacid (0.4 g, 1.06 mmol) was mixed with $SOCl_2$ (0.82 g, 6.8 mmol) and heated at 80 °C for 30 min. The diacid dissolved with evolution of gas and the solution turned brown. The excess of $SOCl_2$ was removed at an oil pump and the resulting dichlorocarbonyl derivative was used directly in the next stage. Bis(acid chloride) (180 mg, 4.0 mmol) was dissolved in 6 mL of absolute 1,2-dichloroethane. Anhydrous $AlCl_3$ (150 mg, 1.1 mmol) was added and the mixture was stirred for 17 h at room temperatre, turning dark. It was poured onto ice water, and half-concentrated HCl was added until the precipitate had dissolved. The aqueous phase was extracted several times with CH_2Cl_2, and the combined organic phase was washed once with cold saturated aqueous NaCl and dried. After removal of the solvent the crude acid (145 mg, 100% e remained as a yellow oil, which was methylated with ethereal diazomethane. Chromatography on silica gel (40 g, 1:3 ether/petroleum ether) gave **6hα**, light yellow oil, 60 mg (42%): IR ($CHCl_3$) 3025 (w), 2980 (m), 2940 (s), 2870 (m), 1720 (s), 1695 (s), 1655 (w), 1610 (m), 1500 (w), 1460 (m), 1445 (m), 1390 (w), 1285 (s), 1270 (s), 1105 (m), 990 (w), 905 (w), 705 (m) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 8.03 (dd, J = 8.0 Hz, J = 2.0 Hz, 1 H, Ar), 7.05–7.57 (m, 8 H, Ar), 6.83 (m, 1 H, =CHCH), 5.72 (d, J = 16.0 Hz, 1 H, CH=CHCH$_2$), 5.56 (dt, J = 16.0 Hz, J = 6.5 Hz, 1 H, CH=CHCH$_2$), 3.79 (s, 3 H, OCH$_3$), 3.24 (d, J = 6.5 Hz, 2 H, CH=CHCH_2), 1.73, 2.20–2.65, 3.00 (m, 7 H, =CHCHCH_2, CH_2CH_2); 50-MHz ^{13}C NMR ($CDCl_3$) δ 198.4 (s, C=O), 167.3 (s, CO_2CH_3), 141.5, 139.8, 132.4, 131.5 (s, 4 =C_{sp^2}), 139.3, 133.8, 133.0, 128.7, 128.3, 128.1, 128.0, 126.9, 126.2, 126.0 (d, =CHCHCCH=CH, aromatic and olefinic CH), 57.5 (q, OCH$_3$), 49.9 (s, =CH, -CHC_{quat}), 41.2 (d, =CHCC_{quat}), 39.1, 31.5, 29.4, 22.3 (t, 4 CH_2); mass spectrum (70 eV, room temperature), m/z (relative intensity) 375 (5), 373 (28), 372 (100, M^+), 354 (14), 341 (17), 340 (21), 312 (11), 281 (47), 263 (38), 253 (31), 249 (56), 221 (30), 203 (18), 194 (17), 177 (18), 165 (17), 118 (72), 117 (29), 91 (45), 84 (57); exact mass calcd for $C_{25}H_{24}O_3$ 372.1725456, found 372.1724652.

Dimethyl 4-(4-(Methoxycarbonyl)-1-butenyl)-3-(2-(methoxycarbonyl)ethyl)-1-cyclohexene-1,4-dicarboxylate (6i). 5i (1.6 g, 7.4 mmol) was dehydrated and the mixture was worked up after 25 h. The crude product (1.5 g, 100%) was chromatographed (1:1 ether/petroleum ether), giving a mixture of two diastereomers, colorless oil, 1.31 g (80%), which was submitted to spectroscopy: IR, ($CHCl_3$) 3010 (w), 2970 (m), 2840 (w), 1725 (vs), 1650 (m), 1435 (s), 1360 (m), 1270 (vs), 1170 (s), 1095 (m), 1050 (m), 1040 (m), 1015 (m), 980 (m), 900 (w) cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 6.99 (m, 1 H at C-2), 5.31–5.64 (m, 2 H, CH=CH), 3.74, 3.70, 3.67, 3.65 (s, 4 × 3 H, 4 OCH$_3$), 2.86 (m, 1 H at C-3), 1.34–2.57 (m, 12 H, 6 CH_2); 75-MHz ^{13}C NMR ($CDCl_3$) δ 174.6, 173.3, 172.9 [174.3, 173.1] (s, 3 C=O), 167.0 (s, C=O at C-1), 140.4 [138.8] (d, C-2), 132.1, 130.1 [132.0, 129.5] (d, CH=CH), 129.4 [129.9] (s, C-1), 52.0 51.4, 51.3 [51.7] (q, 4 OCH$_3$), 50.4 [49.9] (s, C-4), 39.7 [41.2] (d, C-3), 33.5, 32.0, 26.8, 25.2 [33.2, 32.2, 25.1] (t, 2 $CH_2CH_2CO_2CH_3$), 27.9 [27.8] (t, C-5), 22.0 [21.6] (t, C-6); mass spectrum (70 eV, 90 °C), m/z (relative intensity) 396 (5, M^+), 365 (19), 364 (60), 332 (11), 306 (19), 305 (100), 304 (53), 273 (31), 244 (18), 231 (22), 213 (19), 198 (25), 134 (56), 79 (31); exact mass calcd for $C_{20}H_{28}O_8$ 396.1784196, found 396.178437.

Dimethyl 4-(4-Oxo-1-pentenyl)-3-(2-oxopropyl)-1-cyclohexene-1,4-dicarboxylate (6j). 5j (0.62 g, 3.33 mmol) was dehydrated, giving crude dimer (0.5 g, 89%), which was purified by chromatography (1:3 ether/petroleum ether). The two diastereomers, colorless oil, could not be separated. Yield: 200 mg (36%): IR ($CHCl_3$) 3020 (w), 3000 (w), 2950 (w), 1720 (vs), 1655 (w), 1435 (w), 1400 (w), 1360 (m), 1270 (s), 1165 (m), 1095 (m), 1040 (w), 1020 (w), 980 (w) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.89 (m, 1 H at C-2), 5.71 (dt, J = 16 Hz, J = 7 Hz, 1 H, =CHCH$_2$), 5.46 (d, J = 16 Hz, 1 H, =CH at C-4), 3.70 (s, 3 H, OCH$_3$), 3.66 (s, 3 H, OCH$_3$), 3.56 (m, 1 H at C-3), 3.18 (d, J = 7 Hz, 2 H, =CHCH_2), 2.77 (dd, J = 18 Hz, J = 4.7 Hz, 2 H, CH_2COCH$_3$ at

C-3), 1.71–2.39 (m, 4 H at C-5, C-6), 2.14, 2.12 (s, 2 × 3 H, 2 $COCH_3$); 50-MHz ^{13}C NMR ($CDCl_3$) δ 206.1, 205.8 [205.7] (s, 2 C=O), 174.2 [175.3] (s, C=O at C-4), 167.1 [167.0] (s, C=O at C-1), 141.1 [140.0] (d, C-2), 134.0 [134.1] (d, C-7), 129.2 [129.5] (s, C-1), 124.7 (d, =*C*HCH$_2$), 52.3, 51.6 (q, 2 CO_2CH_3), 50.2 (s, C-4), 47.1, 45.3 [46.9, 43.6] (t, 2 CH_2COCH_3), 35.8 [37.3] (d, C-3), 30.1, 29.6 [30.3] (q, 2 $COCH_3$), 25.9 [27.6] (t, C-5), 22.0 [21.0] (t, C-6); mass spectrum (70 eV, 90 °C), *m/z* (relative intensity) 336 (2, M^+), 305 (5), 304 (27), 272 (21), 261 (13), 245 (19), 234 (20), 187 (20), 43 (100); exact mass calcd for $C_{17}H_{20}O_5$ 304.1310749, found 304.1286795.

Tricyclic Lactone 7a. In a flame-dried flask a solution of dimeric ester **6j** (200 mg, 0.595 mmol) in CH_2Cl_2 (7 mL) was cooled to −25 °C (methanol, dry ice). Potassium *tert*-butoxide (20 mg, 0.17 mmol) was added rapidly and the mixture was stirred for 25 min at −25 °C. The mixture was diluted with ether (50 mL), washed rapidly with ice water (3×), and dried ($MgSO_4$). The crude product was purified by chromatography (silica gel, 5:1 ether/petroleum ether), giving **7a**, colorless solid, 135 mg (74%), mp 143–144 °C (cf. X-ray crystal structure): IR ($CHCl_3$) 3010 (m), 2990 (w), 2980 (m), 2870 (w), 1780 (vs), 1710 (vs), 1675 (s), 1645 (m), 1625 (m), 1435 (m), 1390 (m), 1365 (m), 1315 (m), 1270 (s), 1250 (s), 1120 (s), 1085 (m), 910 (m) cm^{-1}; 300-MHz ^1H NMR ($CDCl_3$) δ 6.87 (br s, 1 H, =*CH*CHCH$_2$), 6.52 (dd, *J* = 16.0 Hz, *J* = 9.9 Hz, 1 H, CH=*CH*CH), 6.22 (d, *J* = 16.0 Hz, 1 H, *CH*=CHCH), 3.77 (s, 3 H, CO_2CH_3), 2.75 (m, 1 H, =CHC*H*CH$_2$), 2.63 (d, *J* = 9.9 Hz, 1 H, CH=CHC*H*), 2.61 (m, 1 H, *H*CHCH$_2$C$_{quat}$), 2.39 (dd, *J* = 13.2 Hz, *J* = 9.7 Hz, 1 H, =CHCHC*H*H), 2.28 (s, 3 H, $COCH_3$), 1.96, 1.83 (m, 3 H, HC*HH*$_2$C$_{quat}$), 1.72 (dd, *J* = 13.2 Hz, *J* = 5.0 Hz, 1 H, =CHCHCH*H*), 1.43 (s, 3 H, CH_3); ^1H–^1H NMR (the following signal groups couple) 2.63 (1 H)/6.52 (1 H), 6.52/6.22 (1 H), 2.75 (1 H)/2.39 (1 H), 2.75/1.72 (1 H), 2.39/1.72, 2.61 (1 H)/1.96 (1 or 2 H), 2.61/1.83 (1 or 2 H), 1.96/1.83; the signals at 6.87, 3.77, 2.28, 1.43 show no coupling; 75-MHz ^{13}C NMR ($CDCl_3$) δ 196.8 (s, *C*OCH$_3$), 177.0 (s, *C*O$_2$C$_{quat}$), 166.9 (s, =*C*CO$_2$CH$_3$), 138.5, 138.4, 137.1 (d, 3 =CH), 129.4 (s, =*C*CO$_2$CH$_3$), 90.0 (s, C$_{quat}$), 56.7, 37.6 (d, 2 =CH*C*H), 55.3 (s, C$_{quat}$), 51.9 (q, OCH$_3$), 41.1 (t, =CHCH*C*H$_2$), 27.1 (q, CO*C*H$_3$), 20.7, 19.1 (t, *C*H$_2$*C*H$_2$), 17.4 (q, CH_3); mass spectrum (70 eV, 60 °C), *m/z* (relative intensity) 304 (1, M^+), 303 (5), 276 (7), 273 (7), 272 (13), 218 (13), 201 (21), 159 (13), 131 (14), 129 (14), 115 (15), 109 (15), 108 (86), 91 (23), 57 (23), 44 (100); exact mass calcd for $C_{17}H_{20}O_5$ 304.1310749, found 304.1310233. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.04; H, 6.51.

Dimethyl 4-[4-[(Methylsulfonyl)oxy]-1-butenyl]-3-[2-[(methylsulfonyl)oxy]ethyl]-1-cyclohexene-1,4-dicarboxylate (6l). Diol **5l** (0.79 g, 4.54 mmol), DABCO (2.5 g, 22.3 mmol) and DMAP (0.3 g, 2.5 mmol) were dissolved in CH_2Cl_2 (10.5 mL). A solution of methanesulfonyl chloride (1.25 g, 11 mmol) in 10.5 mL of absolute CH_2Cl_2 was slowly dropped in at −30 °C. The mixture was stirred for 30 h at −20 °C, diluted in the cold with ether (200 mL), and extracted with ice water (3×). The crude product (0.7 g) was chromatographed on silica gel (ether/methanol 12:1), giving **6l**, light yellow oil, 0.62 g (59%), two diastereomers which were submitted to spectroscopy: IR ($CHCl_3$) 3040 (w), 2970 (w), 1725 (s), 1660 (w), 1445 (m), 1365 (s), 1350 (s), 1275 (s), 1180 (vs), 1000 (w), 980 (s), 960 (m), 930 (m), cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.98 (m, 1 H at C-2), 5.68–5.50 (m, 2 H, CH=CH), 3.73 (s, 3 H, OCH_3), 3.68 [3.70] (s, 3 H, OCH_3), 3.06, 3.01 [3.04, 2.99] (s, 2 × 3 H, SCH_3), 1.43–2.57 (m, 13 H, 6 CH_2, CH); 50-MHz ^{13}C NMR ($CDCl_3$) δ 174.3 [173.9] (s, C=O at C-4), 167.1 (s, C=O at C-1), 139.7 [130.4] (d, C-2), 133.6 [134.6] (d, =*C*HCH$_2$), 130.0 [130.2] (s, C-1), 126.7 [126.0] (d, =CH at C-4), 68.7, 68.1 [69.0, 67.8] (t, 2 CH_2OMs), 57.5, 57.4 (q, 2 SCH_3), 52.4, 51.7 [53.5, 52.1] (q, 2 OCH_3), 50.5 [50.2] (s, C-4), 37.1 [39.5] (d, C-3), 32.7, 31.5 [32.5, 32.0] (t, 2 *C*H$_2$CH$_2$OMs), 25.6 [25.5] (t, C-5), 22.1 [21.9] (t, C-6); mass spectrum (70 eV, 170 °C), *m/z* (relatively intensity) 467 (1, M^+), 436 (7), 404 (3), 377 (11), 372 (13), 341 (10), 340 (17), 313 (30), 281 (36), 217 (35), 185 (33), 157 (43), 138 (37), 137 (66), 129 (40), 91 (43), 80 (100); exact mass calcd for $C_{17}H_{25}O_9S_2$ 436.0861797, found 436.0868092.

Dimethyl 8-(1,3-Butadienyl)spiro[2.5]oct-4-ene-5,8-dicarboxylate (7b). Dimesylate **6l** (200 mg, 0.425 mmol), potassium *tert*-butoxide (250 mg, 2.2 mmol), and 18-crown-6 (15 mg, 0.05 mmol) were mixed in 8 mL of absolute CH_2Cl_2. The mixture was stirred at room temperature, turning yellow quickly. After 35 min CH_2Cl_2 was added and the mixture was washed with water, dried ($MgSO_4$), and chromatographed (silica gel, 1:2 ether/petroleum ether), giving **7b** as a colorless oil, 90 mg (75%): IR ($CHCl_3$) 3010 (m), 2960 (s), 2930 (s) 2860 (s), 1720 (s), 1705 (s), 1640 (m), 1600 (w), 1450 (m), 1435 (m), 1365 (w), 1350 (m), 1285 (s), 1170 (s), 1110 (s), 1080 (s), 1005 (m), 985 (m), 955 (m), 910 (m) cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.00–6.36 (m, 3 H at C-4, CH=C*HCH*=CH$_2$), 5.46 (d, *J* = 15.8 Hz, 1 H, C*H*=CHCH=CH$_2$), 5.05–5.26 (m, 2 H, =CH$_2$), 3.70, 3.65 (s, 2 × 3 H, 2 OCH_3), 2.33, 1.89 (m, 3 + 1 H at C-6, C-7), 0.66–1.25 (m, 4 H, CH_2CH_2 at C-3); 50-MHz ^{13}C NMR ($CDCl_3$) δ 173.9 (s, C=O at C-8), 167.2 (s, C=O at C-5), 147.0, 136.4, 132.7, 132.4 (d, 4 =CH), 127.5 (s, C-5), 117.7 (t, =CH$_2$), 52.0, 51.4 (q, 2 OCH_3), 50.5 (s, C-8), 30.2 (t, C-7), 24.4 (s, C-3), 21.6 (t, C-6), 13.8, 12.0 (t, C-1, C-2); mass spectrum (70 eV, room temperature), *m/z* (relative intensity) 277 (4), 276 (16, M^+), 240 (22), 217 (100), 185 (62), 157 (94), 142 (43), 129 (100), 128 (55), 115 (58), 105 (38), 91 (69), 79 (47), 77 (59); exact mass calcd for $C_{16}H_{20}O_4$ 276.1361602, found 276.1360434.

Ammonium Salts 5aβ and 5cβ. Mesylate **5aα** (prepared from the alcohol, EtN-*i*-Pr$_2$ and cat. DMAP in CH_2Cl_2 and dropwise addition of MsCl at −20 °C) (100 mg, 0.4 mmol) and, respectively, mesylate **5cα** (95 mg, 0.4 mmol) were dissolved separately in $CDCl_3$ (1 mL) in an NMR tube. After addition of equimolar DABCO (45 mg, 0.4 mmol), the ^1H NMR spectrum of the solution was recorded. The salts **5aβ**, and also **5cβ**, formed spontaneously as major products. Traces of the monomeric 1,3-dienes, and their respective dimers, could be recognized. **5aβ**: 200-MHz ^1H NMR ($CDCl_3$) δ 7.51 (q, *J* = 7.5 Hz, 1 H, =CH), 4.38 (s, 2 H, CH_2C=), 3.51, 3.24 (br t, 2 × 6 H, 6 NCH_2), 2.74 (s, 3 H, SCH_3), 2.19 (d, *J* = 7.5 Hz, 3 H, CH_3), 1.50 (s, 9 H, CMe_3). **5cβ**: 200-MHz ^1H NMR ($CDCl_3$) δ 7.51 (t, *J* = 8.0 Hz, 1 H, =CH), 4.45 (s, 2 H, CH_2C=), 3.83 (s, 3 H, OCH_3), 3.52, 3.22 (br t, 2 × 6 H, 6 NCH_2), 2.77 (s, 3 H, SCH_3), 2.10 (m, 2 H, =CHC*H*$_2$CH$_2$), 1.65 (m, 2 H, =CHCH$_2$C*H*$_2$), 0.98 (t, *J* = 7.5 Hz, 3 H, CH_3). The *Z*-configurated ammonium salt **5aβ** was detected in the 200-MHz ^1H NMR ($CDCl_3$) spectrum: δ inter al. 7.02 (q, *J* = 7.0 Hz, 1 H, =CH), 2.15 (d, *J* = 7.0 Hz, 3 H, CH_3).

***tert*-Butyl 2-methylene-3-butenoate (3A):** 200-MHz ^1H NMR ($CDCl_3$) δ 6.48 (ddd, *J* = 18.0 Hz, *J* = 11.5 Hz, *J* = 1.0 Hz, H$_2$C=C*H*), 6.01 (br s, 1 H, C=CH$_2$), 5.75 (br s, 1 H, C=CH$_2$), 5.64 (dd, *J* = 18.0 Hz, *J* = 1.5 Hz, 1 H, HC*H*=CH), 5.22 (dm, *J* = 11.5 Hz, 1 H, *H*CH=CH).

Methyl 5,5-Dimethyl-4-pyrrolidino-1-cyclohexene-1-carboxylate (3aα). Flash-vapor thermolysis (FVT) of methyl 3-acetoxy-2-methylenebutanoate at 500 °C in a stream of argon and trapping of the pyrolysate at −78 °C gave **3a**, of which 2 g (11.6 mmol) was mixed with freshly distilled pyrrolidinoisobutene (5 mL) at −78 °C. The mixture was allowed to slowly reach room temperature. After 1 h (GC control) volatile byproducts were pumped off and the residue was separated from the dimer of **3a** by treatment with 2 N HCl (50 mL) and extraction with ether (5×). The aqueous phase was made alkaline with 10% NaOH and extracted with ether (3×) after addition of NaCl. The organic phase was dried (Na_2SO_4), the solvent was evaporated, and the remaining oil was distilled (Kugelrohr, 90 °C, 0.05 Torr) to give **3aα** (1.1 g, 50%), pale yellow oil, sensitive to oxidation: IR ($CHCl_3$) 2960, 2805 (C—N), 1710 (C=O), 1650 (C=C), 1440, 1265, cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$) δ 6.87 (m, 1 H, olefin H), 3.63 (s, 3 H), 2.52 (m, 4 H), 2.49 (t, 1 H), 2.22 (m, 2 H), 2.05 (m, 2 H), 1.58 (m, 4 H), 0.9 (s, 3 H), 0.86 (s, 3 H); 50-MHz ^{13}C NMR ($CDCl_3$) δ 167.6 (s, C=O), 137.8 (d, CH=), 129.0 (s, C-1), 61.8 (d, CH), 51.1 (t, CH_2), 50.7 (q, OCH_3), 38.8 (2 CH_2, N-ring), 34.4 (s, C-5), 28.2 (q, 2 CH_3), 23.8 (t, 2 CH_2, N-ring), 23.1 (t, CH_2); mass spectrum (70 eV, 50 °C), *m/z* (relative intensity) 237 (12, M^+), 194 (100), 134 (44), 125 (27), 110 (13), 84 (18); exact mass calcd for $C_{14}H_{23}NO_2$ 237.1728798, found 237.1728264.

Methyl 6-(1-Propenyl)bicyclo[2.2.1]hept-2-ene-6-carboxylate (6b-A). 3-(Methoxycarbonyl)-5-methylbicyclo[4.3.0]nona-3,7-diene (6b-B). Coupling product **5b** (0.72 g, 5 mmol) was dissolved in 8 mL of CH_2Cl_2 together with DABCO (1.68 g, 15 mmol), DMAP (200 mg, 1.65 mmol), and cyclopentadiene (3.0 g, 50 mmol). A solution of methanesulfonyl chloride (0.68 g, 6 mmol) in 5 mL of CH_2Cl_2 was added dropwise at 0 °C. The mixture was stirred for 24 h at 0 °C, taking on a dark green coloration. Workup proceeded as usual, the crude product (660 mg) being chromatographed on silica gel (1:6 eth-

er/petroleum ether) to give two fractions: (1) dimer **6b** (210 mg, 34%) and (2) a mixture (3:2) of **6b-A** and **6b-B** (350 mg, 36%). The mixture was heated in benzene to 80 °C for 2 h. [2.2.1]Bicyclic **6b-A** was converted quantitatively into **6b-B**. **6b-A**: 90-MHz ^{1}H NMR ($CDCl_3$) δ 6.22, 5.98 (dd, J = 6 Hz, J = 3 Hz, 2 H, ring CH=CH), 5.34 (m, 2 H, C*H*=C*H*), 3.72 (s, 3 H, OCH_3), 3.27, 2.81 (m, 2 H, 2 bridgehead H), 1.20-3.00 (m, 4 H, 2 CH_2), 1.60 (m, 3 H, CH_3). ***cis*-Hydrindane 6b-B**: IR ($CHCl_3$) 3060 (w), 2980 (m), 2940 (m), 2880 (m), 2835 (m), 1710 (vs), 1655 (w), 1635 (w), 1400 (s), 1380 (w), 1375 (w), 1345 (w), 1310 (m), 1260 (vs), 1120 (m), 1085 (m), 1035 (w), 995 (w); 90-MHz ^{1}H NMR ($CDCl_3$) δ 6.86 (m, 1 H, C*H*=C), 5.44 (m, 2 H, CH=CH), 3.73 (s, 3 H, OCH_3), 1.8-2.2 (m, 7 H, 2 CH_2, 3 CH), 1.20 (d, J = 7.5 Hz, 3 H, CH_3); 20-MHz ^{13}C NMR ($CDCl_3$) δ 167.4 (s, C=O), 147.3 (d, =CH), 132.3, 130.6 (d, CH=CH), 131.0 (s, *C*=CH), 51.5 (q, OCH_3), 50.1, 35.3, 33.1 (d, 3 CH), 41.1, 27.9 (t, 2 CH_2), 17.7 (q, CH_3); mass spectrum (70 eV, room temperature), m/z (relative intensity) 192 (30, M^+), 160 (13), 133 (8), 127 (33), 126 (11), 121 (10), 115 (18), 91 (13), 67 (23), 66 (100); exact mass calcd for $C_{12}H_{16}O_2$ 192.1150304, found 192.1149426.

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Synthesis and Spectroscopic Analysis of Branched RNA Fragments: Messenger RNA Splicing Intermediates

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RNA splicing is now established as a major RNA processing reaction in eukaryotic cells. Splicing of messenger RNA precursors generates a lariat RNA structure containing a branched RNA core (Wallace J. C.; Edmons M. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 950-954) of the type A(2′p5′G)3′p5′X (A^G_X), where X is a pyrimidine residue. Understanding the mechanism which generates these molecules as well as the role they play in the splicing reaction are central issues in cell biology. Chemically synthesized branched RNA fragments of defined sequence and structure are likely to play a key role in understanding the full biological role of these molecules. Herein we describe the chemical synthesis of a series of trinucleotides (A^U_U, A^G_G, A^C_C, A^G_U, A^U_G, A^G_C, A^C_G, A^T_T, G^U_U, aA^U_U) and a tetranucleotide (UpA^U_U) with branched linkages. These molecules were fully characterized by UV, NMR (^{1}H, ^{13}C, ^{31}P), HPLC analyses of enzymatic digests, and gel electrophoresis.

Introduction[1]

In vivo and in vitro studies of the biosynthesis of messenger RNA precursors (pre-mRNA) have established that splicing of these primary transcripts proceeds via a novel RNA form, a lariat RNA.[2] This intermediate is an RNA branch with RNA chains linked to an adenosine residue by both 2′-5′ and 3′-5′ vicinal phosphodiester linkages. Analysis of branch structures in yeast and higher eukaryotes has indicated that the adenosine-branched nucleoside is usually linked to guanosine and a pyrimidine through the vicinal 2′-5′ and 3′-5′ phosphodiester linkages, respectively. The structure of the branch is A(2′p5′G)-3′p5′U (A^G_U) in the case of adenovirus 2 transcripts[2b] and A(2′p5′G)3′p5′C (A^G_C) in both β-globin[2c] and yeast[2d] actin RNA precursors. In spite of the remarkable advances made in the elucidation of the splicing process, many aspects of this reaction are still poorly understood. The exact mechanism of splice site and branch point selection is unknown as are the role and conformational properties of the lariat molecules. Some authors have speculated that the branch point sequences of the lariat molecules may serve as a recognition signal for achieving accurate splicing.[2c,3] Alternatively, the primary sequence and/or the three-dimensional structure of the branch may play a key role (e.g. may possess catalytic activity) in directing and regulating the splicing process. In order to gain a better understanding of the role of lariat RNA, the development of chemical synthesis and the study (e.g. conformational analysis) of branched nucleotide fragments is a prerequisite. In this report we describe the chemical synthesis and structural characterization of a series of trinucleotides and a tetranucleotide with branched linkages. A preliminary report of some of these results has appeared.[4]

Results and Discussion

Synthesis of Branched RNA. Branched RNA fragments were rapidly prepared by introducing both 2′-5′ and 3′-5′ vicinal phosphate linkages simultaneously. The basis of this strategy, as presently applied to the phosphite triester synthesis of oligonucleotides using nucleoside phosphoramidites, is summarized in Scheme II. The key

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(1) Abbreviations: the branched nucleotide sequence X(2′-p-5′Y)3′-p-5′Z where X is the branched nucleoside is abbreviated as X^Y_Z. The linear sequences X3′-p-5′Y3′-p-5′Z and X2′-p-5′Y2′-p-5′Z are written as XpYpZ and XpYpZ, respectively. The branched tetramer U3′-p-5′A-(2′-p-5′U)3′-p-5′U is abbreviated as UpA^U_U.

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