

Radical Additions of Alkyl 2-Haloalkanoates and 2-Haloalkanenitriles to Alkenes Initiated by Electron Transfer from Copper in Solvent-Free Systems

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Alkyl 2-iodoalkanoates **2**, and 2-iodoalkanenitriles **15** were added, with copper powder, to the 1-alkenes **1a**, **e**, **f**, and **h**, and to the alkenes **1b**, **c**, **d**, and **g** with a 1,2-dialkyl substituted double bond, to give, respectively, γ -lactones and 4-iodoalkanenitriles in very good yields. No solvent was used. The reaction is a free radical addition initiated by electron transfer from copper to the activated iodoalkane. Yields were lower using the respective bromo compounds. In situ formation of the iodo compounds, by addition of stoichiometric

amounts of sodium iodide to the reaction mixture, gave improved yields. In the case of the methyl bromomalonates **6**, the addition of sodium iodide proved to be unnecessary. The diastereoselectivity of the addition reaction by relative 1,3-asymmetric induction was rationalized by consideration of the steric interactions of the substituents in the transition state which is formed in the process of iodine transfer to the chiral adduct radical.

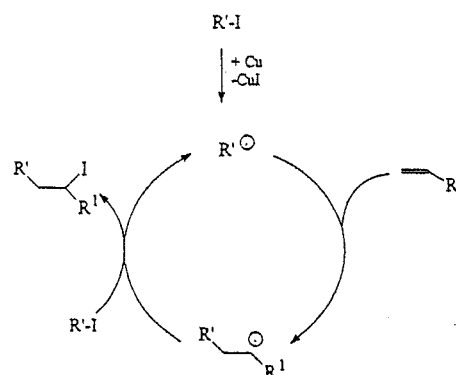
The need to reduce the amount of toxic waste and by-products arising from chemical processes requires an increasing emphasis on the use of less toxic and more environmentally compatible materials in the design of new synthetic methods.^[1] Within this context, the reduced use of ecologically suspect solvents is of considerable significance.

For some time now intermolecular radical addition reactions have been powerful tools in preparative organic chemistry,^[2] but the most widely used methods have a number of ecological disadvantages when deployed in widespread industrial use. This applies particularly to the frequently used organotin compounds.^[3] Transition metal complexes and salts that initiate radical reactions by electron transfer processes offer a viable alternative.^[4] We cyclized methyl 2-iodopetroselinate by using metallic silver in methanol.^[5] Metallic copper has been used in the Ullmann reaction for the synthesis of diaryls from aryl halides,^[6] and in the radical additions of highly activated bromomalonodinitrile^[7], 2,2-dibromo-1,3-diones^[8] and perfluoroalkyl iodides^[9] to alkenes.

We have reported recently on the radical additions of alkyl 2-iodoalkanoates and 2-iodoalkanenitriles to alkenes, initiated by electron transfer from copper metal (Scheme 1),^[10] in the absence of solvent. In the case of the addition of alkyl 2-iodoalkanoates the alkyl 4-iodoalkanoates, which are initially formed, cyclize to give γ -lactones. The alkenes most frequently used were the esters of unsaturated carboxylic acids, such as methyl 10-undecenoate (**1a**), methyl oleate (**1b**), methyl erucate (**1c**), and methyl petroselinate (**1d**) (Scheme 2), which are of considerable interest being, as they are, renewable raw materials.^[11] The reaction pro-

cedure is very simple: the alkene, iodo compound, and commercial copper powder are mixed without any pretreatment and heated to 100–130 °C in an inert atmosphere. After a simple work-up procedure, the products are obtained analytically pure and in satisfactory yields. We now report on the scope of this new reaction and give the experimental details. Furthermore, we give one of the first examples of diastereoselectivity by 1,3-induction in free radical reactions.

Scheme 1. Mechanism for the copper-initiated addition of activated iodoalkanes to alkenes. R'-I = alkyl 2-iodocarboxylate, 2-iodoalkanenitrile. R' = alkyl, (CH₂)₈COOMe



R'I = alkyl 2-iodocarboxylate, 2-iodoalkanenitrile; R' = alkyl, (CH₂)₈COOMe.

Scheme 2. Alkenes 1 used as substrates

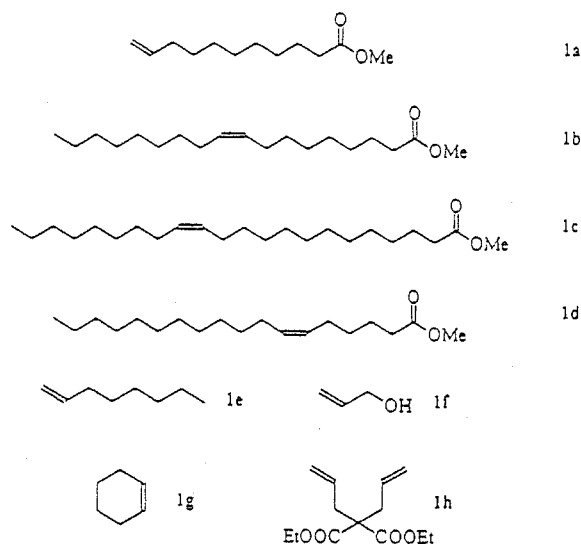


Table 1. Results of the copper-initiated additions of ethyl 2-haloalkanoates 2 to alkenes 1 to give γ -lactones 3

Entry	1	2	3	[(Z)-3]/[(E)-3]	Yield [%]
1	1a	2a	3a	—	78 ^[a] ; 60 ^[b]
2	1a	2b	3b	1.3:1	86 ^[a] ; 67 ^[b] ; 73 ^[c]
3	1a	2c	3c	1.3:1	80 ^[a] ; 41 ^[b] ; 72 ^[c]
4	1a	2d	3d	1.7:1	73 ^[a] ; 44 ^[b] ; 70 ^[c]
5	1a	2e	3e	1.4:1	79 ^[a] ; 43 ^[b] ; 72 ^[c]
6	1a	2f	3f	1.6:1	69 ^[c]
7	1a	2g	3g	2:1	63 ^[c]
8	1a	2h	3h	—	40 ^[a] [b]; 54 ^[c]
9	1a	2i	3i	1.1:1	46 ^[c]
10	1e	2a	3k	—	70 ^[a]
11	1e	2c	3l	1.4:1	88 ^[c]
12	1f	2b	3m	1.1:1	72 ^[a]
13	1f	2c	3n	1.3:1	72 ^[a]

^[a] 2 (X = I; R = Et); reaction temperature 130 °C; reaction time 4–8 h. — ^[b] 2 (X = Br, R = Et); 120 °C; 1–4 d. — ^[c] 2 (X = Br, R = Et) with added NaI; 120 °C, 5–9 h.

Results and Discussion

1. Copper-Initiated Additions of Alkyl 2-Haloalkanoates 2 to 1-Alkenes

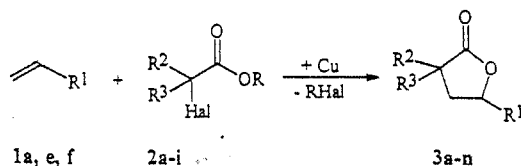
The addition of alkyl 2-iodoalkanoates 2 to 1-alkenes 1a, e and f affords γ -lactones 3 (Scheme 3) in high yields (Table 1). For example, the reaction of ethyl iodoacetate (2a) with 1-octene (1e), in the presence of copper, gave γ -decalactone (3k) in an isolated yield of 70% (entry 10). The addition product was formed regioselectively by radical addition to the terminal carbon of the alkene. Additions of ethyl 2-iodoalkanoates 2 to methyl 10-undecenoate (1a) gave substituted γ -lactones 3a–i with an ester functionality in the ω -position. Primary and secondary 2-iodoalkanoates gave very good isolated product yields of up to 86% (entries 1–7). Tertiary 2-iodoalkanoates gave only moderate isolated addition products yields of 40–50% (entries 8–9).

The influence of the molar ratio of the substrates, and of copper, on the yield of product 3c was investigated for the

addition of ethyl 2-iodobutanoate (2c) to the alkene 1a. Equimolar amounts of alkene 1a and iodobutanoate 2c, and a catalytic amount of copper, gave only 2% of the lactone 3c (Table 2, entry 1). Half molar and equimolar amounts of copper gave yields of 20% and 55%, respectively (entries 2.3). Improved yields were obtained using an excess of copper (80%, entry 4), the alkene 1a (86%, entry 5), and of the iodo compound 2c (60%, entry 6). Using a moderate excess of the iodoalkanoate 2c and copper almost quantitative yields, with respect to the charged alkene, could be obtained (entries 7,8). A higher excess of 2c and copper gave only a minor improvement in the yield (entry 9). Thus, the ratio of alkene 1/2-iodoalkanoate 2/Cu = 1:1.3:1.3 was used for the examples in Table 1.

The more readily available alkyl 2-bromoalkanoates 2 also undergo copper-initiated addition to alkene 1a (Table 1, entries 1–5). However, reaction times are much longer than with the corresponding iodo compounds, and yields are much lower because of the formation of the hydrogenated addition products. For example, in the addition of methyl 2-bromohexanoate (2d) to the alkene 1a, only 44% of the lactone 3d (entry 4) and 17% of dimethyl 2-butyltridecandioate were formed (Scheme 4). The reaction time was 36 h compared to 4 h with the respective iodo compound.

Scheme 3. Additions of alkyl 2-haloalkanoates 2 to 1-alkenes 1



1a, e, f

2a-i

3a-n

Hal = Br, I; R = Me, Et

Table 2. Addition of ethyl 2-iodobutanoate (2c) to methyl 10-undecenoate (1a): Influence of the molar ratios of the substrates on the yield of γ -lactone 3c

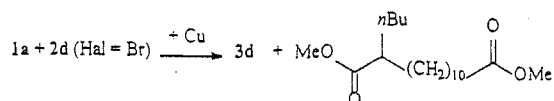
Entry	Molar ratios of the substrates [2c]/[1a]/[Cu]	Yield of γ -lactone 3c [%] ^[a]
1	1:1:0.1	2
2	1:1:0.5	20
3	1:1:1	55
4	1:1:2	80
5	0.51:1	43
6	2:1:1	60
7	1.3:1:1.5	94
8	1.5:1:1.5	94
9	3:1:3	95

^[a] Yields determined gas chromatographically based on charged 1a; the reaction temperature was 120 °C, the reaction time 4 h.

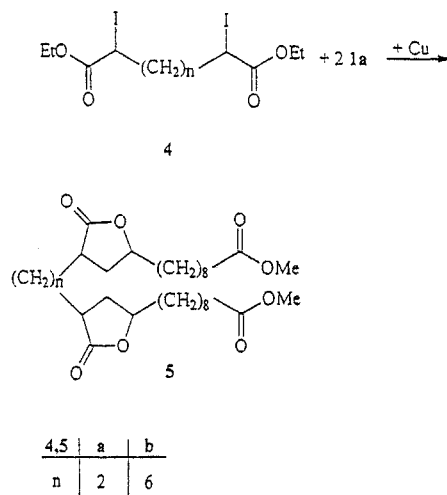
2a-i, 3a-n	a	b	c	d	e	f
R ¹		(CH ₂) ₈	COOMe	(3a-i)		
R ²	H	Me	Et	nBu	nC ₁₄ H ₂₉	iPr
R ³	H	H	H	H	H	H
g	h	i	k	l	m	n
tBu	Me	iPr	nC ₆ H ₁₃	nC ₆ H ₁₃	CH ₂ OH	CH ₂ OH
H	Me	Me	H	Et	Et	nBu
			H	H	H	H

If the iodo compound is formed from the corresponding bromo compound in situ, by the addition of a stoichiometric amount of sodium iodide to the reaction mixture, the products are obtained in high yields, which are similar to those obtained by direct use of the iodo derivatives **2** (Table 1, entries 2–5). Reaction times were also comparable. The products can be synthesized without problems on a multigram scale as was shown for the lactone **3f**. Ethyl chloroacetate, alkene **1a** and copper gave no addition product at 120 °C. However, addition of stoichiometric amounts of sodium iodide yielded 43% of the γ -lactone **3a**.

Scheme 4. Addition of methyl 2-bromohexanoate to methyl 10-undecenoate (**1a**)



Scheme 5. Addition of dimethyl α,α' -diiododialkanoates **4** to two equivalents of alkene **1a**



Of particular interest is the example of diethyl 2,5-diiodoadipate (**4a**), which can be added to two equivalents of **1a** to form the di- γ -lactone **5a** in a yield of 60% (Scheme 5). The equivalent reaction of diethyl 2,9-dibromosebacate (**4b**) with added sodium iodide gave the homologous di- γ -lactone **5b**.

Interestingly, the reaction procedure also worked well with the allyl alcohol **1f** as the alkene component. For example, addition of ethyl 2-haloalkanoates **2b** and **2c** to allyl alcohol gave the 3-alkyl-5-hydroxymethyl-tetrahydrofuran-2-one **3m** and **3n** in good yields (Table 1, entries 12,13).

The γ -lactones **3** with the exception of **3a** and **3k** were obtained as a mixture of diastereoisomers. The diastereomers could be assigned unambiguously from the ^1H - and ^{13}C -NMR spectra by comparison with the literature data.^[12] (*Z*)-**3** was formed preferentially with low diastereoselectivity. The diastereomeric ratio increases with the increasing steric effect of the alkyl group R^2 of γ -lactone **3** (Table 1) going from [(*Z*)-**3**]/[(*E*)-**3**] = 1.3:1 ($\text{R}^2 = \text{Me}$, entry 2) through 1.6:1 ($\text{R}^2 = i\text{Pr}$, entry 6) to 2:1 ($\text{R}^2 = t\text{Bu}$, entry 7). The diastereomeric ratio increases also with the increas-

ing steric effect of the alkyl group R of the haloalkanoate **2** (Table 3) going from [(*Z*)-**3d**]/[(*E*)-**3d**] = 1.7:1 ($\text{R} = \text{Me}$, entry 1) through 1.8:1 ($\text{R} = n\text{C}_{18}\text{H}_{37}$, entry 2) to 2:1 ($\text{R} = c\text{C}_6\text{H}_{11}$, entry 3) and to 2.5:1 ($\text{R} = (-)\text{-bornyl}$, entry 4). In contrast, the yield of the addition product **3d**, after a reaction time of 5 h, decreases when following the same trend in steric effects (Table 3, entries 1–4). The observed diastereoselectivities will be discussed in section 7.

Table 3. Copper-initiated additions of alkyl 2-bromohexanoates to 1-alkene **1a** with added sodium iodide^[a]. Influence of the alkyl component of the 2-bromohexanoate on diastereoselectivity and yield

Entry	Alkyl	γ -Lactone [(<i>Z</i>)- 3d]/[(<i>E</i>)- 3d]	Yield [%] ^[b]
1	methyl	1.7:1	70
2	octadecyl	1.8:1	40
3	cyclohexyl	2.0:1	38
4	(-)-bornyl	2.5:1	32

^[a] Reaction temperature 130 °C, reaction time 5 h. – ^[b] Isolated yield relative to starting **1a**.

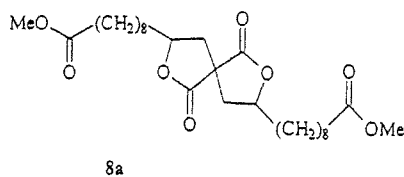
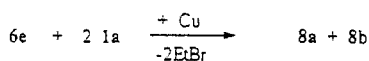
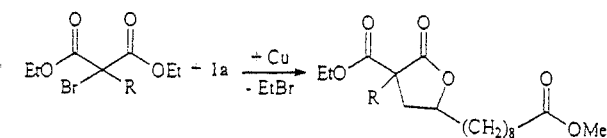
2. Copper-Initiated Additions of Diethyl Bromomalonates **6** to Alkene **1a**

Diethyl bromomalonates **6a–d**, which are strongly activated, can be added to the alkene **1a** (initiated by copper) in good to moderate yields (Scheme 6, Table 4). The addition of sodium iodide, as in the case of 2-bromoalkanoates **2** (Table 1), was not necessary. The γ -lactones **7** were obtained as diastereomeric mixtures. The diastereomers could be unambiguously assigned by the comparison of their ^1H - and ^{13}C -NMR spectra with the literature data.^[13] The thermodynamically more stable stereoisomer is formed preferentially with low stereoselectivity. The diastereomeric ratio was, in all examples investigated, $\text{dr} = 1.8:1$ – $2:1$.

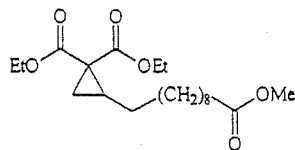
It seems to be remarkable that diethyl dibromomalonate **6a** could be added to the alkene **1a** to give the bromo- γ -lactone **7a** in high yields (72%). Product **7a** was added in a further step to the alkene **1a** to give a diastereomeric mixture of spiro-di- γ -lactones **8a**, in a yield of 61%. Thus, the reactivity of the dibromomalonate **6a** in the electron transfer reaction from copper is much higher than the reactivity of the bromo- γ -lactone **7a**. In contrast, the reaction of diethyl bromomalonate **6e** and the alkene **1a**, with copper, gave the spiro-di- γ -lactones **8a** directly, in a yield of 40%. The intermediate γ -lactone **7e** could not be detected. Instead, as minor product, cyclopropane-1,1-dicarboxylate **8b** was isolated in a yield of 5%. Interestingly, cyclopropane-1,1-dicarboxylates were obtained by reacting diethyl dibromomalonate **6a** with alkenes and copper with benzene as the solvent.^[8b]

Diethyl dibromomalonate (**7a**) could be added in a one pot reaction to two equivalents of alkene **1a** to also give spiro-di- γ -lactones **8a**, in yields of 43%^[14]. The synthesis of the same spiro-di- γ -lactone **8a** by manganese(III) acetate mediated addition of malonic acid to the alkene **1a** was described quite recently.^{[15][16]}

Scheme 6. Additions of diethyl bromomalonates 6 to alkene 1a



8a



8b

6,7	a	b	c	d	e
R	Br	Me	$n\text{C}_6\text{H}_{13}$	$c\text{C}_6\text{H}_{11}$	H

Table 4. Results of the copper-initiated additions of diethyl bromomalonates 7 to methyl 10-undecenoate (1a)^[a]

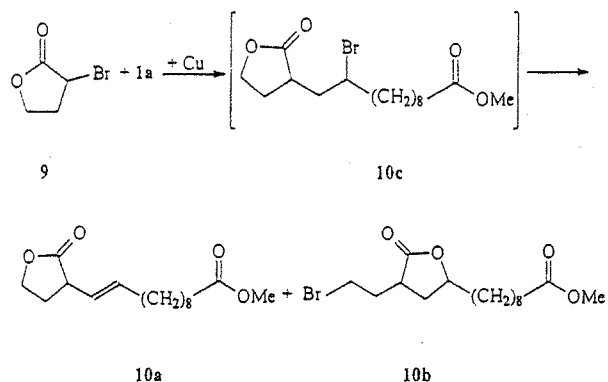
Entry	7	Reaction time[h]	γ -Lactone	[(E)-7]/[(Z)-7]	Yield ^[b]
1	a	4	7a	1.9:1	72
2	b	4	7b	1:1.8	87
3	c	5	7c	1:2	77
4	d	4	7d	1:2	52
5	e	4	8a	^[c]	40

^[a] Reaction temperature 130 °C. – ^[b] Isolated yield relative to starting 1a. – ^[c] $[u\text{-}8a]/[sa\text{-}8a]/[ss\text{-}8s] = 1.1:1:0.1$.

3. Copper-Initiated Addition of 2-Bromo- γ -butyrolactone (9) to Alkene 1a

2-Bromo- γ -butyrolactone (9) was also added to the alkene 1a. The main product is the unsaturated addition/elimination product 10a $\{[(E)\text{-}10a]/[(Z)\text{-}10a] = 2:1\}$, which was obtained in a yield of 50% (Scheme 7). The expected bromo- γ -lactone 10b, formed by intramolecular transacylation of the primary addition product 10c, was isolated as a minor product in a yield of 12%. The diastereoselectivity of $[(Z)\text{-}10b]/[(E)\text{-}10b] = 3.3:1$ is remarkable compared to that obtained by the addition of the acyclic 2-iodoalkanoates 2 (Table 1). Comparable results were obtained in reactions with added sodium iodide. Obviously,

the intramolecular transacylation of addition product 10c to 10b is relatively slow. Thus, the elimination of hydrogen bromide, which occurs in the examples given in Table 1 in only minor amounts, is observed as the main reaction.

Scheme 7. Addition of 2-bromo- γ -butyrolactone (9) to alkene 1a

4. Copper-Initiated Additions of Ethyl 2-Haloalkanoate 2b to Alkenes 1b, c, d with 1,2-Dialkyl Substituted Double Bonds

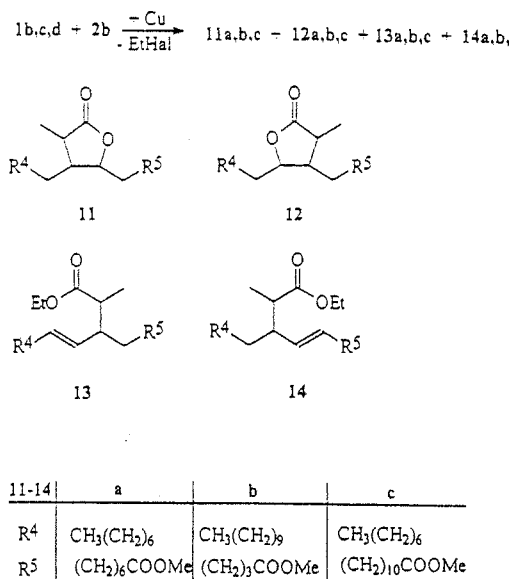
Radical additions using traditional methods, to alkenes containing 1,2-dialkyl substituted double bonds, such as methyl oleate (1b), frequently provide the products in only poor yields.^[2] Thus in the benzoyl peroxide initiated addition of ethyl bromoacetate (in a tenfold excess) to methyl oleate the product is obtained in a yield of only 10%.^[17] Moreover, using several variants of the tin procedure, we were still unable to achieve satisfactory additions. In contrast, with copper initiation we were able to achieve yields in excess of 50% without any difficulty, which could again be improved by the very slow addition of the halo compound 2b.

Ethyl 2-iodopropionate (2b) was added to methyl oleate (1b) to give the γ -lactones 11a and 12a in an isolated yield of 51% as a regioisomeric mixture, ca. 1:1. The unsaturated addition/elimination products 13a and 14a were obtained as minor products in a yield of 10% (Scheme 8). The analogous additions to methyl erucate (1c) and to methyl petroselinate (1d) gave the corresponding products in yield of 50% and 49%, respectively. It is remarkable, that in these reactions improved yields of the addition products of up to 60% were obtained by using ethyl 2-bromopropionate (2b) with stoichiometric amounts of sodium iodide added. The regioisomeric γ -lactones 11 and 12, respectively, were formed as a mixture of four diastereomers $\{[2\alpha, 3\alpha, 4\alpha\text{-}11]/[2\alpha, 3\beta, 4\alpha\text{-}11]/[2\alpha, 3\beta, 4\beta\text{-}11]/[2\alpha, 3\alpha, 4\beta\text{-}11] = 2:2:1:1\}$. The diastereomers could be assigned unambiguously from the ¹H- and ¹³C-NMR spectra by comparison with the literature data.^[18]

5. Copper-Initiated Additions of 2-Haloalkanenitriles 15 to Alkenes

Iodoacetonitrile (15a) was added to 1-alkenes such as 1a and 1e, and to alkenes with 1,2-dialkyl substituted double bonds such as cyclohexene (1g) and methyl erucate (1c), in an analogous manner (Scheme 9). In these cases the iodo functionality is retained in the addition products 16, offer-

Scheme 8. Addition of ethyl 2-haloalkanoate 2b to alkenes 1b, c, d



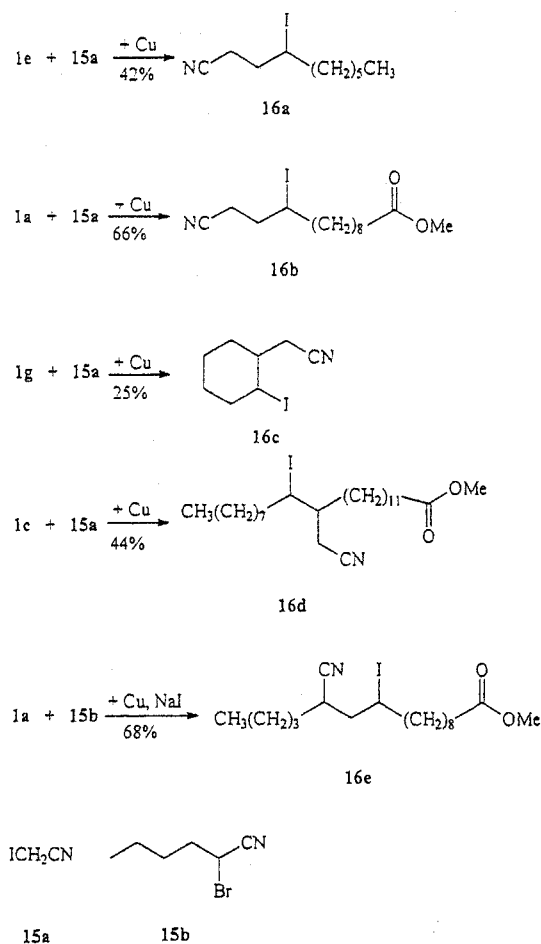
ing interesting possibilities for further transformations. Yields seem to be lower compared to those for the equivalent addition reactions of methyl iodoacetate (Table 1, entries 1 and 10). The very low yield of the addition product 16c may be due to the low reaction temperature of 90 °C. 2-Bromoalkanenitriles, such as 2-bromohexanenitrile 15b, were also added, with added sodium iodide to 1a, and afforded the iodinated addition product 16e in an isolated yield of 55%.

6. Mechanism of the Copper-Initiated Radical Addition of Activated Haloalkanes to Alkenes

We assume that the reaction is initiated by electron transfer from copper to the activated haloalkane. The electrophilic radical formed after cleavage of the halide adds to the electron-rich double bond of the alkene, and subsequent halogen abstraction yields the product (Scheme 1), which in the case of alkyl 2-haloalkanoates 2 cyclizes to a γ -lactone due to the well known thermal lactonization of 4-haloalkanoates.^{[19][20]} The respective alkyl 4-iodoalkanoates could be detected by GC-MS in the reaction mixture after a reaction time of 1 h. To provide proof for the free radical mechanism we reacted ethyl 2-iodobutanoate (2c) and diethyl diallylmalonate (1h), initiated by copper at 130 °C, and obtained the addition-cyclization product 20 in a yield of 73% (Scheme 10). The formation of product 20 can easily be explained. The α -ester radical 17 formed by electron transfer from copper to the iodo compound 2c is added to the alkene 1h. The adduct radical 18 is cyclized to the radical 19 and iodine transfer from 2c gives the product 20. Comparable free radical cyclizations of diallylmalonates have been described in the literature.^[21]

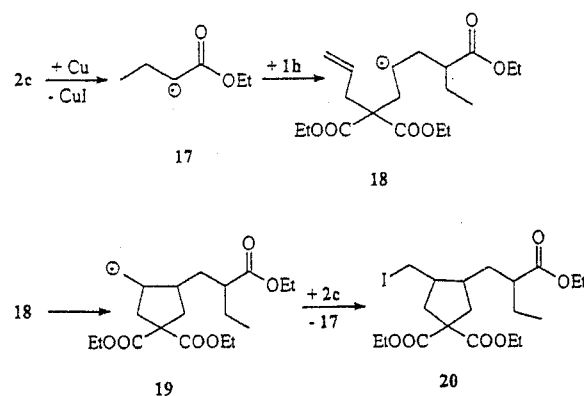
The mass balance of the Cu-initiated addition of octyl iodoacetate 2a (R = n C₈H₁₇) to methyl 10-undecenoate

Scheme 9. Additions of iodoacetoneitrile (15a) and 2-bromohexanenitrile (15b) to alkenes 1

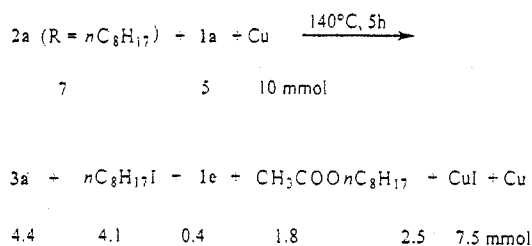


showed that about 25% of the copper is oxidized to copper(I) iodide during the reaction, and about 20% of the iodoacetate is reduced by halogen-hydrogen exchange to octyl acetate (Scheme 11). Approximately three moles of radicals per mol of transferred electrons are generated. It is thus a radical chain reaction with a relatively short chain-length.

Scheme 10. Mechanism of the addition of ethyl 2-iodobutanoate (2c) to alkene 1h



Scheme 11. Mass balance of the Cu-initiated addition of octyl iodoacetate to methyl 10-undecenoate



7. Diastereoselectivity: Relative 1,3-Asymmetric Induction

Tables 1 and 2 give the diastereomeric ratios of the products 3. (*Z*)-3 is formed preferentially. The diastereoselectivity increases with increasing steric effect of the substituents R^1 and R^2 . The *syn*-selectivity can easily be rationalized by considering the possible conformations of the diastereomeric transition states of iodine transfer (Scheme 12). Transition state I, leading to product *syn*-21, is energetically more favorable because of the minimal steric interactions of the substituents R , R^1 and R^2 . In contrast, transition state II, leading to product *anti*-21, is higher in energy because of the unfavorable steric interaction of the substituents R^1 and COOR. That also explains the increasing *syn*-selectivity, with increasing steric effect of the substituent R , of the ester functionality (Table 2). The same stereoisomeric ratio was also obtained using the corresponding benzoyl peroxide initiated addition^[20] and Curran's iodine atom transfer method.^[19] This confirms that, as in these two reactions, the iodoalkane is the iodine donor in the Cu-initiated addition. Comparable stereochemical results were found from the addition of 2-bromohexanenitrile to alkene 1a (diastereomeric product ratio of 14e = 1.6:1). The dia-

stereoselectivity of the additions of the haloalkanes 2 to alkenes 1b, c, d can be rationalized in an analogous fashion.^[22]

Conclusion

Alkyl 2-haloalkanoates and 2-haloalkanenitriles have been added efficiently to alkenes in a free radical reaction initiated by copper powder.

Key features of the reaction described here are: no solvent is used, the work-up procedure is simple in comparison to other methods since the copper powder initiator is unproblematic for both work-up and separation, the reagents are used in essentially stoichiometric quantities, the yields are comparably high, even with 1,2-dialkylethenes, the reaction can be performed without problems on a multigram scale, and the initiator can be reused (after total oxidation of the copper it is readily recovered by reduction). These interesting mechanistic features lead to a description of one of the first examples of 1,3-stereoinduction in free radical reactions.^{[10][23]}

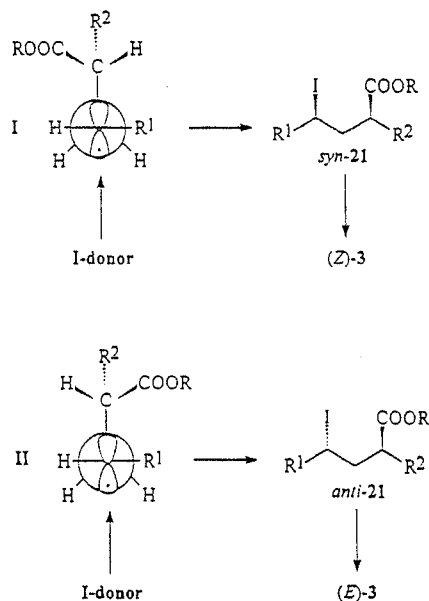
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Experimental Section

Melting points (uncorrected): Leitz Laborlux 12. – Refractive indices n_D : Zeiss-Abbé-Refraktometer. – Elemental analysis: Fisons Instruments FA 1108. – ^1H and ^{13}C NMR: Bruker AM 300 (300 MHz); solvent CDCl_3 ; TMS as internal standard, selected data are given. Full ^1H - and ^{13}C -NMR data are available from the authors on request. The ratio of the diastereomeric products was determined by evaluation of the ^1H - and ^{13}C -NMR spectra, respectively. – Mass spectra: Finnigan MAT 212 (for GC-MS coupled with Varian 3700) and Finnigan MAT 95. – Analytical GC: Carlo Erba GC 6000 Vega Series 2 with FID detector and Spectra Physics Data Jet Integrator, fused silica capillary column DB 1 30m. – Medium-pressure liquid chromatography (MPLC): Merck silica gel 60, 0.04–0.063 mm. – Thin-layer chromatography (TLC): Merck plates, silica gel 60 F; detection by treatment with a solution of 15% H_2SO_4 , followed by heating at 200°C . – Solvents were purified and dried in the usual way. – Petroselinic acid (81.3% petroselinic acid, 3.3% palmitic acid, 0.4% stearic acid, 13.5% $\text{C}_{18:2}$), oleic acid (82.8% oleic acid, 3.5% palmitic acid, 3.6% stearic acid, 8.4% $\text{C}_{18:2}$), erucic acid (ca. 90% erucic acid), Henkel KGaA, methyl 10-undecenoate, Elf Atochem, were used without further purification. Copper powder (Merck, > 230 mesh).

Reaction of Alkyl 2-Iodoalkanoates 2 and Alkenes. – General Procedure (Method A): A 50 ml, two necked flask equipped with a magnetic stirrer, reflux condenser, and a gas inlet tube was charged with 1.3 equiv of 2-iodoalkanoate, 1 equiv of alkene, and 1.3 equiv of copper powder. The mixture was heated with constant stirring at 130°C under nitrogen. The reaction was monitored by thin-layer chromatography and was usually complete within 3–7 h. The product was isolated by distillation; alternatively, the reaction mixture was taken up into diethylether and after removal of the copper salts by filtration and evaporation of the solvent on a rotary evaporator, the product was obtained by kugelrohr distillation or recrystallization or flash chromatography.

Scheme 12. Stereoselective formation of the *syn*-addition product by relative 1,3-asymmetric induction; transition state I of iodine transfer is more favorable compared to transition state II due to steric effects



Reaction of Alkyl 2-Bromoalkanoates 2 and Alkenes. – General Procedure (Method B): A 50 ml. two necked flask equipped with a magnetic stirrer, reflux condenser, and a gas inlet tube was charged with 1.3 equiv of bromoalkane, 1 equiv of alkene, and 1.3 equiv of copper powder. The mixture was heated with constant stirring at 120–130 °C under nitrogen. The reaction was monitored by thin-layer chromatography and was usually complete within 1–4 d. Work-up procedure was as for method A.

Reaction of Alkyl 2-Bromoalkanoates 2 and Alkenes with Added Sodium Iodide. – General Procedure (Method C): A 50 ml. two necked flask equipped with a magnetic stirrer, reflux condenser, and a gas inlet tube was charged with 1.3 equiv of bromoalkane, 1 equiv of alkene, 1.3 equiv of copper powder and 1 equiv of sodium iodide. The mixture was heated with constant stirring at 120–130 °C in an inert atmosphere. The reaction was monitored by thin-layer chromatography and was usually complete within 4–8 h. Work up procedure was as for method A.

5-Hexyltetrahydrofuran-2-one (3k). – Method A: 5.00 g (23.4 mmol) of ethyl iodoacetate (2a), 1.73 g (15.4 mmol) of 1e and 1.20 g (18.6 mmol) of copper powder were heated at reflux for 24 h. Kugelrohr distillation (70–140 °C/0.005 Torr) gave 1.82 g (70%) of 3k^{[20][24]}.

Methyl 9-(5-Oxotetrahydrofuran-2-yl)nonanoate (3a). – Method A: 4.00 g (18.7 mmol) of ethyl iodoacetate (2a), 3.00 g (15.1 mmol) of 1a and 1.00 g (15.7 mmol) of copper powder were heated for 24 h at 100 °C. After work-up, recrystallization from light petroleum (60/80) gave 3.00 g (78%) of 3a, m.p. 34 °C^[25].

Method B: 4.59 g (27.5 mmol) of ethyl bromoacetate (2a), 3.00 g (15.1 mmol) of 1a and 1.43 g (22.5 mmol) of copper were heated for 24 h at 120 °C, yield 2.30 g (60%).

Method C: 2.73 g (22.5 mmol) of ethyl chloroacetate (2a), 3.00 g (15.1 mmol) of 1a, 2.50 g (15.0 mmol) sodium iodide and 1.43 g (22.5 mmol) of copper were heated for 8 h at 120 °C, yield 1.78 g (43%).

Methyl 9-(4-Methyl-5-oxotetrahydrofuran-2-yl)nonanoate (3b). – Method A: 4.45 g (19.5 mmol) of ethyl 2-iodopropanoate (2b), 3.00 g (15.1 mmol) of 1a, and 1.43 g (22.5 mmol) of copper were heated for 4 h to 130 °C. After work-up kugelrohr distillation gave 3.50 g (86%) of 3b.

Method B: 5.40 g (29.8 mmol) of ethyl 2-bromopropionate (2b), 6.00 g (30.2 mmol) of 1a, and 2.00 g of copper were heated for 24 h at 120°. Yield 5.50 g (67%) of 3b. As minor product 0.70 g (8%) of methyl 12-ethoxycarbonyltridecanoate was isolated.

Method C: 4.00 g (20.5 mmol) of ethyl 2-bromopropionate (2b), 2.25 g (15.0 mmol) of sodium iodide, 3.00 g (15 mmol) of 1a and 1.43 g (22.5 mmol) of copper were heated for 5 h at 120 °C. Yield 2.99 g (73%) of 3b: [(Z)-3b]/[(E)-3b] = 1.3:1, colourless liquid, $n_D^{25} = 1.4560$. – ¹H NMR (CDCl₃): δ = 4.50 [tt, J = 7.6, 5.2 Hz, 1 H, H-2, (E)], 4.33 [tdd, J = 10.4, 7.4, 5.4 Hz, 1 H, H-2, (Z)], 2.78–2.61 (m, 1 H, H-4), 2.49 [ddd, J = 12.3, 8.5, 5.4 Hz, 1 H, H-3α, (Z)], 2.13 [ddd, 12.8, 8.9, 5.2 Hz, 1 H, H-3α, (E)], 2.01 [td, 12.8, 7.6 Hz, 1 H, H-3β, (E)], 1.46 [td, 12.3, 10.4 Hz, 1 H, H-3β, (Z)]. – ¹³C NMR (CDCl₃): δ = 179.8 [C-5, (E)], 179.4 [C-5, (Z)], 78.4 [C-2, (Z)], 78.2 [C-2, (E)], 37.1 [C-3, (Z)], 35.7 [C-3, (E)], 35.3 [C-4, (E)], 35.2 [C-4, (Z)]. – MS(70 eV): m/z (%): 270 [M⁺] (14), 239 (10), 99 (100), 98 (40), 81 (36), 74 (41), 69 (43), 56 (48). – MS/CI (isobutane): m/z (%): 271 (100) [MH⁺]. – C₁₅H₂₆O₄ (270.4): calcd. C 66.64, H 9.69; found C 66.53, H 9.66.

Methyl 9-(4-Ethyl-5-oxotetrahydrofuran-2-yl)nonanoate (3c). – Method A: 7.50 g (31.0 mmol) of ethyl 2-iodobutanoate (2c), 6.00

g (30.2 mmol) of 1a, and 2.00 g (31.5 mmol) of copper were heated for 6 h at 130 °C. Kugelrohr distillation gave 6.83 g (80%) of 3c.

Method B: 5.40 g (29.8 mmol) of ethyl 2-bromobutanoate (2c), 6.00 g (30.2 mmol) of 1a, and 2.00 g of copper were heated for 24 h at 120 °C. Yield 3.50 g (41%) of 3c. As minor product methyl 12-ethoxycarbonyltridecanoate (4c) was identified by GC-MS.

Method C: 4.39 g (22.5 mmol) of ethyl 2-bromobutanoate (2c), 2.25 g (15.0 mmol) of sodium iodide, 3.00 g (15.1 mmol) of 1a and 1.43 g (22.5 mmol) of copper were heated for 5 h to 120 °C. Yield 3.10 g (72%) of 3c: [(Z)-3c]/[(E)-3c] = 1.3:1, colourless liquid, $n_D^{25} = 1.4597$. – ¹H NMR (CDCl₃): δ = 4.48 [m, 1 H, H-2, (E)], 4.34 [tdd, J = 10.2, 7.4, 5.4 Hz, 1 H, H-2, (Z)], 2.62–2.50 (m, 1 H, H-4), 2.47 [ddd, J = 12.1, 8.6, 5.4 Hz, 1 H, H-3α, (Z)], 2.14–2.10 [m, 2 H, H-3, (E)], 1.48 [td, 12.3, 12.1, 10.2 Hz, 1 H, H-3β, (Z)]. – ¹³C NMR (CDCl₃): δ = 178.8 [C-5, (E)], 178.4 [C-5, (Z)], 78.4 [C-2], 42.0 [C-3, (Z)], 41.3 [C-3, (E)], 35.3 [C-4, (E)], 35.2 [C-4, (Z)]. – MS(70 eV); m/z (%): 284 [M⁺] (12), 253 (10), 113 (100), 98 (38), 81 (26), 74 (26), 69 (34), 56 (71). – MS/CI (isobutane); m/z (%): 285 (100) [MH⁺]. – C₁₆H₂₈O₄ (284.4): calcd. C 67.57, H 9.92; found C 67.61, H 9.96.

Methyl 9-(4-Butyl-5-oxotetrahydrofuran-2-yl)nonanoate (3d). – Method A: 4.99 g (19.5 mmol) of methyl 2-iodohexanoate (2d), 3.00 g (15.1 mmol) of 1a, and 1.43 g (22.5 mmol) of copper were heated for 4 h at 130 °C. After work-up recrystallization from cold light petroleum (60/80) gave 3.43 g (73%) of 3d: [(Z)-3d]/[(E)-3d] = 1.6:1; m.p. 37 °C.

Method B: 5.90 g (30.2 mmol) of methyl 2-bromohexanoate (2d), 6.00 g (30.2 mmol) of 1a, and 2.00 g of Cu were heated for 24 h at 120°. Yield 3.20 g (34%) of 3d. As minor product 0.8 g (17%) of dimethyl 2-butyiltridecandioate was isolated.

Method C: 4.15 g (19.9 mmol) of methyl 2-bromohexanoate (2d), 3.00 g (20.0 mmol) of sodium iodide, 3.00 g (15.1 mmol) of 1a and 1.43 g (22.5 mmol) of copper were heated for 5 h at 120 °C. Yield 3.28 g (70%) of 3d. – ¹H NMR (CDCl₃): δ = 4.46 [tt, J = 7.5, 5.5 Hz, 1 H, H-2, (E)], 4.31 [tdd, J = 10.2, 7.4, 5.4 Hz, 1 H, H-2, (Z)], 2.59–2.52 (m, 1 H, H-4), 2.42 [ddd, J = 12.2, 8.6, 5.4 Hz, 1 H, H-3α, (Z)], 2.04–2.00 [m, 2 H, H-3, (E)], 1.47 [td, 12.2, 10.2 Hz, 1 H, H-3β, (Z)]. – ¹³C NMR (CDCl₃): δ = 179.3 [C-5, (E)], 178.9 [C-5, (Z)], 78.6 [C-2, (Z)], 78.5 [C-2, (E)], 40.8 [C-3, (Z)], 39.1 [C-3, (E)], 35.4 [C-4]. – MS(70 eV); m/z (%): 281 [M⁺ – CH₃O] (6), 141 (100), 98 (90), 95 (82), 81 (37), 74 (38), 69 (70), 56 (94). – MS/CI (isobutane); m/z (%): 313 (100) [MH⁺]. – C₁₈H₃₂O₄ (312.4): calcd. C 69.19, H 10.32; found C 69.05, H 10.26.

Methyl 9-(5-Oxo-4-tetradecyltetrahydrofuran-2-yl)nonanoate (3e). – Method A: 6.50 g (16.5 mmol) of methyl 2-iodopalmitate (2e), 2.50 g (12.6 mmol) of 1a, and 1.43 g (22.5 mmol) of copper were heated for 4 h at 130 °C. Recrystallization from cold light petroleum (60/80) gave 4.50 g (79%) of 3e: [(Z)-3e]/[(E)-3e] = 1.4:1, m.p. 64 °C.

Method B: 6.70 g (20.0 mmol) of methyl 2-bromopalmitate (2e), 3.00 g (15.1 mmol) of 1a, and 1.43 g (22.5 mmol) of copper were heated for 24 h at 120°. Yield 1.30 g (19%) of 3e.

Method C: 3.50 g (10.0 mmol) of methyl 2-bromopalmitate (2e), 1.50 g (10.0 mmol) of sodium iodide, 1.70 g (8.6 mmol) of 1a and 0.73 g (11.3 mmol) of copper were heated for 5 h at 120 °C. Yield 2.80 g (72%) of 3e. – ¹H NMR (CDCl₃): δ = 4.48 [m, 1 H, H-2, (E)], 4.32 [tdd, J = 10.2, 7.3, 5.4 Hz, 1 H, H-2, (Z)], 2.65–2.52 (m, 1 H, H-4), 2.43 [ddd, J = 12.2, 8.6, 5.4 Hz, 1 H, H-3α, (Z)], 2.06–2.00 [m, 2 H, H-3, (E)], 1.47 [td, 12.2, 10.2 Hz, 1 H, H-3β, (Z)]. – ¹³C NMR (CDCl₃): δ = 179.4 [C-5, (E)], 179.0 [C-5, (Z)],

78.8 [C-2, (Z)], 78.7 [C-2, (E)], 41.0 [C-3, (Z)], 39.4 [C-3, (E)], 35.7 [C-4, (E)], 35.6 [C-4, (Z)]. - MS(70 eV): m/z (%): 421 [$M^+ - CH_3O$] (3.8), 323 (3), 281 (12), 256 (11), 224 (14), 123 (20), 109 (17), 98 (100), 74 (7), 69 (47), 56 (68), 43 (81). - MS/CI (isobutane): m/z (%): 453 (100) [MH^+]. - $C_{28}H_{32}O_4$ (452.7): calcd. C 74.29, H 11.58; found C 74.21, H 11.58.

Methyl 9-(5-Oxo-4-isopropyltetrahydrofuran-2-yl)nonanoate (3f). - *Method C*: 11.8 g (60.6 mmol) of ethyl 2-bromo-3-methylbutanoate (2f), 9.09 g (61.0 mmol) of sodium iodide, 12.0 g (60.6 mmol) of 1a and 3.85 g (61.0 mmol) of copper were heated for 9 h at 130 °C. Kugelrohr distillation (70–230 °C/0.1 mbar) gave 12.5 g (69%) of 3f: [(Z)-3f]/[(E)-3f] = 1.6:1, colourless liquid. $n_D^{26} = 1.4576$. - 1H NMR ($CDCl_3$): $\delta = 4.39$ [tt, $J = 7.5, 5.3$ Hz, 1 H, H-2, (E)], 4.26 [tdd, $J = 10.3, 6.9, 5.6$ Hz, 1 H, H-2, (Z)], 2.58–2.47 (m, 1 H, H-4), 2.25–2.05 [m, 2 H, H-3], 1.86 [ddd, 13.1, 9.7, 5.3 Hz, 1 H, H-3 β (E)], 1.68–1.22 [m, 1 H, H-3 β (Z)]. - ^{13}C NMR ($CDCl_3$): $\delta = 178.6$ [C-5, (E)], 178.0 [C-5, (Z)], 78.7 [C-2, (E)], 78.3 [C-2, (Z)], 46.9 [C-3, (Z)], 45.3 [C-3, (E)], 35.9 [C-4, (E)], 35.4 [C-4, (Z)]. - MS(70 eV): m/z (%): 298 [M^+] (0.2), 267 (12), 238 (8), 224 (10), 127 (100), 98 (57), 81 (62), 74 (14), 69 (38), 56 (37). - MS/CI (isobutane): m/z (%): 299 (100) [MH^+]. - $C_{17}H_{30}O_4$ (298.4): calcd. C 68.42, H 10.13; found C 68.37, H 10.05.

Methyl 9-(4-tert-Butyl-5-oxotetrahydrofuran-2-yl)nonanoate (3g). - *Method A*: 1.50 g (5.5 mmol) of ethyl 2-iodo-3,3-dimethylbutanoate (2g), 1.00 g (5.0 mmol) of 1a, and 0.70 g (1.1 mmol) of copper were heated for 6 h at 130 °C. Recrystallization from cold light petroleum (60/80) gave 0.98 g (63%) of 3g: [(Z)-3g]/[(E)-3g] = 2:1, m.p. 38 °C. - 1H NMR ($CDCl_3$): $\delta = 4.37$ [tt, $J = 7.6, 5.1$ Hz, 1 H, H-2, (E)], 4.21 [tdd, $J = 10.2, 7.0, 5.3$ Hz, 1 H, H-2, (Z)], 2.44 (dd, $J = 12.7, 8.9, 1$ H, H-4, (Z)), 2.42 (dd, $J = 10.2, 7.6, 1$ H, H-4, (E)), 2.25 [ddd, $J = 12.7, 8.9, 5.3$ Hz, 1 H, H-3 α (Z)], 2.22 [ddd, 13.4, 10.2, 5.1 Hz, 1 H, H-3 α (E)], 1.92 [td, 13.4, 7.6 Hz, 1 H, H-3 β (E)], 1.63 [td, 12.7, 10.2 Hz, 1 H, H-3 β (Z)]. - ^{13}C NMR ($CDCl_3$): $\delta = 177.3$ [C-5, (E)], 176.7 [C-5, (Z)], 77.8 [C-2, (E)], 77.2 [C-2, (Z)], 50.6 [C-3, (Z)], 48.9 [C-3, (E)], 36.0 [C-4, (E)], 35.4 [C-4, (Z)]. - MS(70 eV): m/z (%): 281 [$M^+ - OCH_3$] (8), 265 (3), 256 (9), 224 (14), 206 (14), 141 (100), 98 (82), 95 (48), 74 (11), 69 (40), 58 (68), 43 (95). - MS/CI (isobutane): m/z (%): 313 (100) [MH^+]. - $C_{18}H_{32}O_4$ (312.4): calcd. C 69.19, H 10.32; found C 69.00, H 11.06.

Methyl 9-(4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)nonanoate (3h). - *Method A*: 0.94 g (3.90 mmol) of ethyl 2-iodo-2-methylpropanoate (2h), 0.59 g (3.00 mmol) of 1a, and 0.29 g (4.56 mmol) of copper powder were heated for 8 h at 130 °C. Kugelrohr distillation (150–220 °C/0.07 mbar) gave 0.34 g (40%) of 3h.

Method B: 5.90 g (30.2 mmol) of ethyl 2-bromo-2-methylpropanoate (2h), 6.00 g (30.2 mmol) of 1a, and 2.00 g (31.5 mmol) of copper were heated for 120 h at 120 °C. Flash chromatography [light petroleum (60/80)/ether, 7:3 and 9:1] gave 3.44 g (67%) of 3h.

Method C: 4.39 g (22.5 mmol) of ethyl 2-bromo-2-methylpropanoate (2h), 2.25 g (15.0 mmol) of sodium iodide, 3.00 g (15.1 mmol) of 1a and 1.43 g (22.5 mmol) of copper were heated for 9 h at 120 °C. Kugelrohr distillation (70–230 °C/0.07 mbar) gave 2.30 g (54%) of 3h: $n_D^{25} = 1.4520$. - 1H NMR ($CDCl_3$): $\delta = 4.41$ (tdd, $J = 9.9, 7.4, 5.8$ Hz, 1 H, H-2), 2.16 (dd, 12.7, 5.8 Hz, 1 H, H-3 α), 1.72 (dd, 12.7, 9.9 Hz, 1 H, H-3 β), 1.24 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3). - ^{13}C NMR ($CDCl_3$): $\delta = 182.0$ (C-5), 77.0 (C-2), 43.5 (C-3), 40.3 (C-4), 25.0 (CH_3), 24.3 (CH_3). - MS(70 eV): m/z (%): 253 [$M^+ - CH_3O$] (9), 113 (66), 85 (78), 74 (36), 69 (100), 57 (63), 56 (55). - MS/CI (isobutane): m/z (%): 285 (100) [MH^+]. - $C_{16}H_{28}O_4$ (284.4): calcd. C 67.57, H 9.92; found C 67.52, H 9.87.

Methyl 9-(4-Methyl-5-oxo-4-propyltetrahydrofuran-2-yl)nonanoate (3i). - *Method C*: 2.00 g (9.0 mmol) of methyl 2-bromo-2-methylpropanoate (2i), 2.25 g (15.0 mmol) of sodium iodide, 3.00 g (15.1 mmol) of 1a, and 1.43 g (22.5 mmol) of copper were heated for 9 h at 130 °C. Yield 1.30 g (46%) of 3i: [(Z)-3i]/[(E)-3i] = 1.1:1. - 1H NMR ($CDCl_3$): $\delta = 4.36$ –4.25 (m, 1 H, H-2), 2.28–2.20 [m, 1 H, H-3 α (Z)], 1.92 [dd, $J = 12.6, 5.9$ Hz, 1 H, H-3 α (E)], 1.71 [dd, $J = 12.6, 9.9$ Hz, 1 H, H-3 β (E)], 1.68–1.18 [m, 1 H, H-3 β (Z)]. - ^{13}C NMR ($CDCl_3$): $\delta = 181.5$ (C-5), 77.1 (C-2), 44.0 [C-3, (Z)], 43.9 [C-3, (E)], 41.4 [C-4, (E)], 40.4 [C-4, (Z)]. - MS(70 eV): m/z (%): 281 (2.8) [$M^+ - OCH_3$], 238 (10), 165 (8), 141 (18), 113 (22), 97 (36), 95 (38), 84 (38), 74 (14), 69 (93), 56 (100). - MS/CI (isobutane): m/z (%): 313 (100) [MH^+]. - $C_{18}H_{32}O_4 \times H^+$: calcd. 313.2378; found 313.2290.

3-Ethyl-5-hexyltetrahydrofuran-2-one (3l).^[17] - *Method C*: 2.93 g (15.0 mmol) of ethyl 2-bromobutanoate (2c), 1.50 g (10.0 mmol) of sodium iodide, 3.30 g (20.0 mmol) of 1-octene (1e), and 0.95 g (15.0 mmol) of copper powder were heated for 9 h at 120 °C. Kugelrohr distillation (90–120 °C/0.1 mbar) gave 2.62 g (88%) of 3l: [(Z)-3l]/[(E)-3l] = 1.4:1. - 1H NMR ($CDCl_3$): $\delta = 4.43$ [tt, $J = 7.0, 6.4$ Hz, 1 H, H-5, (E)], 4.29 [tdd, $J = 10.2, 7.0, 5.7$ Hz, 1 H, H-5, (Z)], 2.54–2.46 (m, 1 H, H-3), 2.38 [ddd, $J = 12.1, 8.9, 5.7$ Hz, 1 H, H-4 α (Z)], 2.03–1.97 [m, 2 H, H-4, (E)], 1.50–1.40 [m, 1 H, H-4 β (Z)]. - ^{13}C NMR ($CDCl_3$): $\delta = 179.2$ [C-2, (E)], 178.7 [C-2, (Z)], 78.7 (C-5), 42.3 [C-4, (Z)], 40.6 [C-4, (E)], 35.6 [C-3, (E)], 35.5 [C-3, (Z)].

5-Hydroxymethyl-3-methyltetrahydrofuran-2-one (3m). - *Method A*: 4.16 g (18.2 mmol) of ethyl 2-iodopropanoate (2b), 5.00 g (83.3 mmol) of allyl alcohol (1f), and 1.58 g (24.2 mmol) of copper were heated for 5 h at 110 °C. Yield of crude product 1.90 g (72%) of 3m: [(Z)-3m]/[(E)-3m] = 1.1:1. - ^{13}C NMR ($CDCl_3$): $\delta = 180.9$ [C-2, (E)], 180.0 [C-2, (Z)], 78.8 [C-5, (Z)], 78.4 [C-5, (E)], 63.6 [CH_2OH , (Z)], 63.0 [CH_2OH , (E)], 35.2 [C-4, (Z)], 34.0 [C-4, (E)], 31.4 [C-3, (Z)], 31.3 [C-3, (E)], 15.8 [CH_3 , (E)], 14.8 [CH_3 , (Z)].

3-Ethyl-5-hydroxymethyltetrahydrofuran-2-one (3n). - *Method A*: 4.60 g (19.0 mmol) of ethyl 2-iodobutanoate (2c), 5.00 g (83.3 mmol) of allyl alcohol (1f), and 1.58 g (24.2 mmol) of copper were heated for 5 h at 110 °C. Yield of crude product 1.90 g (72%) of 3n: [(Z)-3n]/[(E)-3n] = 1.3:1. - ^{13}C NMR ($CDCl_3$): $\delta = 179.9$ [C-2, (E)], 179.0 [C-2, (Z)], 78.8 [C-5, (Z)], 78.6 [C-5, (E)], 63.6 [CH_2OH , (E)], 63.0 [CH_2OH , (Z)], 41.6 [C-4, (Z)], 40.5 [C-4, (E)], 28.8 [C-3, (E)], 28.7 [C-3, (Z)], 23.8 [CH_2CH_3 , (E)], 22.9 [CH_2CH_3 , (Z)], 11.1 (CH_3).

1,2-Bis[5-(8-methoxycarbonyloctyl)-2-oxotetrahydrofuran-3-yl]ethane (5a). - *Method A*: 1.05 g (2.30 mmol) of dimethyl α,α' -diiodoadipate (4a), 3.00 g (15.1 mmol) of 1a and 0.70 g (11.2 mmol) of copper were heated for 6 h at 130 °C. Recrystallization from ether gave 0.75 g (60%) of 5a as a mixture of diastereomers. 5a was identified by 1H NMR and ^{13}C NMR. - MS/CI (isobutane): m/z : 539 [MH^+]. - $C_{34}H_{58}O_8$ (538.7): calcd. C 66.89, H 9.36; found C 66.33, H 10.07.

1,6-Bis[5-(8-methoxycarbonyloctyl)-2-oxotetrahydrofuran-3-yl]hexane (5b). - *Method C*: 2.00 g (4.80 mmol) of diethyl α,α' -dibromosebacinate (4b), 2.02 g (13.5 mmol) sodium iodide, 3.98 g (20.0 mmol) of 1a and 3.32 g (52.2 mmol) of copper were heated for 6 h at 150 °C. Recrystallization from light petroleum (60/80) gave 0.28 g (10%) of 5b as a mixture of diastereomers. - MS(70 eV): m/z (%): 563 (0.9), 531 (3.2), 489 (3.6), 391 (37), 307 (21), 289 (16), 95 (52), 81 (75), 67 (62), 56 (94), 43 (100). - MS/CI (isobutane): m/z : 595 [MH^+]. - $C_{34}H_{58}O_8$ (594.8): calcd. C 68.65, H 9.83; found C 68.47, H 9.68.

Methyl 9-(4-Bromo-4-ethoxycarbonyl-5-oxotetrahydrofuran-2-yl)nonanoate (7a). — Method B: 9.54 g (30.0 mmol) of diethyl dibromomalonate (6a), 3.00 g (15.1 mmol) of **1a** and 1.43 g (22.5 mmol) of copper were heated for 4 h at 130 °C. Flash chromatography [light petroleum (60/80)/ether, 8:2] gave 5.13 g (72%) of **7a**: [(*E*-**7a**)/[(*Z*-**7a**)] = 1.9:1; $n_D^{20} = 1.4714$. — ¹H NMR (CDCl₃): δ = 4.65–4.58 [m, 1 H, H-2, (*E*)], 4.52–4.44 [m, 1 H, H-2, (*Z*)], 3.26 [dd, *J* = 13.9, 6.0 Hz, 1 H, H-3α, (*Z*)], 2.72–2.63 [m, 2 H, H-3, (*E*)], 2.40 [dd, *J* = 13.9, 8.5 Hz, 1 H, H-3β, (*Z*)]. — ¹³C NMR (CDCl₃): δ = 169.3 [C-5, (*Z*)], 169.1 [C-5, (*E*)], 165.5, [COOC₂H₅, (*Z*)], 164.9 [COOC₂H₅, (*E*)], 79.0 [C-2, (*Z*)], 78.9 [C-2, (*E*)], 54.3 [C-4, (*E*)], 53.2 [C-4, (*Z*)], 44.2 [C-3, (*E*)], 44.0 [C-3, (*Z*)]. — MS(70 eV): *m/z* (%): 295(0.3) [M⁺ – CH₃O – HBr], 251(8), 158(16), 128(40), 111(46), 96(66), 81(70), 74(46), 69(40), 56(100). — C₁₇H₂₇O₆Br × H⁺: calcd. 407.1069; found 407.1070 (MS/CI).

Methyl 9-(4-Ethoxycarbonyl-4-methyl-5-oxotetrahydrofuran-2-yl)nonanoate (7b). — Method B: 7.59 g (29.9 mmol) of diethyl 2-bromo-2-methylmalonate (6b), 3.00 g (15.1 mmol) of **1a** and 1.43 g (22.5 mmol) of copper were heated for 4 h at 130 °C, yield 4.50 g (87%) of **7b**: [(*E*-**7b**)/[(*Z*-**7b**)] = 1:1.8; $n_D^{20} = 1.4558$. — ¹H NMR (CDCl₃): δ = 4.50–4.33 [m, 1 H, H-2], 2.67 [dd, *J* = 13.2, 5.9 Hz, 1 H, H-3α, (*E*)], 2.38 [dd, *J* = 13.0, 6.6 Hz, 1 H, H-3α, (*Z*)], 2.14 [dd, *J* = 13.0, 8.7 Hz, 1 H, H-3β, (*Z*)], 1.68 [dd, *J* = 13.2, 10.1 Hz, 1 H, H-3β, (*E*)]. — ¹³C NMR (CDCl₃): δ = 170.5 [C-5, (*Z*)], 170.3 [C-5, (*E*)], 78.2 [C-2, (*E*)], 77.9 [C-2, (*Z*)], 51.5 [C-4, (*E*)], 51.0 [C-4, (*Z*)], 41.2 [C-3, (*E*)], 40.0 [C-3, (*Z*)]. — MS(70 eV): *m/z* (%): 311 [M⁺ – CH₃O] (10), 297 [M⁺ – CH₂CH₃O] (4), 171 (36), 143 (50), 95 (100), 87 (74), 74 (36), 69 (86), 57 (92). — MS/CI (isobutane): *m/z* (%): 343 (100) [MH⁺]. — C₁₈H₃₀O₆ (342.4): calcd. C 63.14, H 8.83; found C 62.83, H 8.62.

Methyl 9-(4-Ethoxycarbonyl-4-hexyl-5-oxotetrahydrofuran-2-yl)nonanoate (7c). — Method B: 20.0 g (62.0 mmol) of diethyl 2-bromo-2-hexylmalonate (8c), 12.4 g (62.5 mmol) of **1a** and 3.95 g (62.2 mmol) of copper were heated for 5 h at 130 °C. Flash chromatography [light petroleum (60/80)/ether, 8:2] gave 19.7 g (77%) of **7c**: [(*E*-**7c**)/[(*Z*-**7c**)] = 1:2; $n_D^{20} = 1.4623$. — ¹H NMR (CDCl₃): δ = 4.47–4.33 [m, 1 H, H-2], 2.71 [dd, *J* = 13.2, 5.6 Hz, 1 H, H-3α, (*E*)], 2.41 [dd, *J* = 13.4, 7.7 Hz, 1 H, H-3α, (*Z*)], 2.26 [dd, *J* = 13.4, 9.2 Hz, 1 H, H-3β, (*Z*)], 1.90–1.18 [m, 1 H, H-3β, (*E*)]. — ¹³C NMR (CDCl₃): δ = 170.3 [C-5, (*Z*)], 169.6 [C-5, (*E*)], 78.7 [C-2, (*E*)], 78.1 [C-2, (*Z*)], 56.2 [C-4, (*E*)], 55.3 [C-4, (*Z*)], 38.1 [C-3, (*E*)], 37.0 [C-3, (*Z*)]. — MS(70 eV): *m/z* (%): 381 [M⁺ – CH₃O] (6), 339 (4), 297 (10), 241 (21), 219 (26), 199 (23), 165 (47), 98 (54), 81 (63), 74 (18), 56 (79), 43 (100). — MS/CI (isobutane): *m/z* (%): 413 (100) [MH⁺]. — C₂₃H₄₀O₆ (412.6): calcd. C 66.96, H 9.77; found C 66.81, H 9.86.

Methyl 9-(4-Cyclohexyl-4-ethoxycarbonyl-5-oxotetrahydrofuran-2-yl)nonanoate (7d). — Method B: 1.50 g (4.70 mmol) of diethyl 2-bromo-2-cyclohexylmalonate (8d), 0.92 g (4.60 mmol) of **1a** and 0.30 g (4.70 mmol) of copper were heated for 5 h at 130 °C. Flash chromatography [light petroleum (60/80)/ether, 8:2] gave 0.98 g (52%) of **7d**: [(*E*-**7d**)/[(*Z*-**7d**)] = 1:2; $n_D^{20} = 1.4711$. — ¹H NMR (CDCl₃): δ = 4.40–4.25 [m, 1 H, H-2], 2.62 [dd, *J* = 13.0, 5.7 Hz, 1 H, H-3α, (*E*)], 2.47 [dd, *J* = 13.8, 6.4 Hz, 1 H, H-3α, (*Z*)], 2.31 [dd, *J* = 13.8, 8.1 Hz, 1 H, H-3β, (*Z*)], 1.79–0.87 [m, 1 H, H-3β, (*E*)]. — ¹³C NMR (CDCl₃): δ = 169.7 [C-5, (*Z*)], 169.0 [C-5, (*E*)], 78.5 [C-2, (*E*)], 78.3 [C-2, (*Z*)], 61.0 [C-4, (*E*)], 59.8 [C-4, (*Z*)], 42.9 [C-3, (*Z*)], 41.1 [C-3, (*E*)]. — MS(70 eV): *m/z* (%): 380(10), 297(4) [M⁺ – CH₃O], 171 (36), 143 (50), 95 (100), 87 (74), 74 (36), 69 (86), 56 (92). — MS/CI (isobutane): *m/z* (%): 411(100) [MH⁺]. — C₂₃H₃₈O₆ (410.5): calcd. C 67.29, H 9.33; found C 66.40, H 9.81.

Di(8-methoxycarbonyloctyl)-1,6-dioxo-2,7-dioxo-spiro-(4,4)-nonane (8a) and Diethyl 2-(8-Methoxycarbonyloctyl)cyclopropane-

1,1-dicarboxylate (8b). — Method B: 7.17 g (30.0 mmol) of diethyl bromomalonate (6e) and 3.00 g (15.1 mmol) of **1a** and 1.91 g (30.0 mmol) of copper were heated for 4 h to 130 °C. The reaction mixture was taken up into dichloromethane and filtrated. The solvent was removed. Recrystallization [light petroleum (60/80)] gave 1.5 g (40%) of **8a**: [*u*-**8a**]/[*sa*-**8a**]/[*ss*-**8a**] = 1.2:1:0.1. *u*-**8a** and *sa*-**8a** could be separated and isolated by MPLC [light petroleum (60/80)/diethyl ether, 91:9]. *u*-**8a**, m.p. 84 °C. — *sa*-**8a**, m.p. 90 °C. — ¹H NMR, ¹³C NMR, MS were identical with data given in ref.^[15]. Flash chromatography of the mother liquor gave 0.26 g (5%) of **8b**, which was identified by ¹H NMR, ¹³C NMR and MS. — C₁₉H₃₂O₆ (356.5): calcd. C 64.02, H 9.05; found C 63.93, H 9.03.

Methyl 11-(2-Oxotetrahydrofuran-3-yl)undec-9-enoate (10a) and Methyl 9-[4-(2-Bromoethyl)-5-oxotetrahydrofuran-2-yl]nonanoate (10b). — Method B: 3.30 g (19.8 mmol) of 2-bromobutyrolactone (9), 3.00 g (15.1 mmol) of **1a** and 1.91 g (30.0 mmol) of copper were heated for 14 h to 130 °C. Flash chromatography [light petroleum (60/80)/ether, 8:2 and 6:4] gave 2.12 g (50%) of **10a** [(*E*-**10a**)/[(*Z*-**10a**)] = 2:1] and 0.65 g (12%) of **10b**: [(*Z*-**10b**)/[(*E*-**10b**)] = 3.3:1; $n_D^{20} = 1.4804$. — **10b**: ¹H NMR (CDCl₃): δ = 4.19 [tdd, *J* = 10.4, 7.3, 5.5 Hz, 1 H, H-2, (*Z*)], 2.69 [tdd, *J* = 12.2, 8.4, 5.9 Hz, 1 H, H-4, (*Z*)], 2.45–2.20 [m, 1 H, H-3α, (*Z*)], 1.49 [td, *J* = 12.2, 10.4 Hz, 1 H, H-3β, (*Z*)]. — ¹³C NMR (CDCl₃): δ = 178.0 [C-5, (*Z*)], 79.0 [C-2, (*Z*)], 39.7 [C-3, (*Z*)], 35.4 [C-3, (*Z*)]. — MS(70 eV): *m/z* (%): 331, 333 [M⁺ – CH₃O] (3), 256 (7), 224 (8), 191, 193 (40), 98 (77), 81 (38), 74 (40), 69 (35), 56 (100), 42 (87). — MS/CI (isobutane): *m/z*: 363, 365 [MH⁺].

Methyl 8-(4-Methyl-3-octyl-5-oxotetrahydrofuran-2-yl)octanoate (11a) and Methyl 8-(4-Methyl-2-octyl-5-oxotetrahydrofuran-3-yl)octanoate (12a). — Method A: 4.56 g (20.0 mmol) of ethyl 2-iodopropanoate (**2b**) was added slowly to a mixture of 2.00 g (6.70 mmol) of **1b** and 1.90 g (30.0 mmol) of copper at 130 °C and heated for 8 h. The unreacted starting compounds were evaporated by kugelrohr distillation (190 °C), MPLC [light petroleum (60/80)/ether, 8:2] gave 1.28 g (51%) of a mixture (≈ 1:1) of **11a** and **12a**.

Method C: 2.00 g (6.70 mmol) of **1b**, 3.00 g (20.0 mmol) sodium iodide, 1.90 g (30.0 mmol) of copper and 4.56 g (20.0 mmol) ethyl 2-bromopropanoate (**2b**) were heated for 8 h at 130 °C, yield 1.49 g (58%). As minor product 0.37 g (14%) of a mixture of **13a** and **14a** was obtained. **11a**: ¹H NMR (CDCl₃): δ = 4.45 [ddd, *J* = 10.2, 7.6, 3.2 Hz, 1 H, H-2, (2α,3α,4α)], 4.35 [ddd, *J* = 9.4, 6.0, 4.2 Hz, 1 H, H-2, (2α, 3β, 4β)], 3.95 [td, *J* = 8.8, 3.1 Hz, 1 H, H-2, (2α, 3β, 4β)], 2.48–2.38 [m, 1 H, H-3, (2α, 3β, 4β)], 2.11–2.04 [m, 1 H, H-3, (2α, 3α, 4α)], 1.72–1.51 [m, 1 H, H-3, (2α, 3β, 4α)], 1.70–1.20 [m, 1 H, H-4]. — ¹³C NMR (CDCl₃): δ = 179.9 [C-5, (2α, 3β, 4β)], 179.4 [C-5, (2α,3α,4α)], 179.2 [C-5, (2α, 3β, 4α)], 83.5 [C-2, (2α, 3β, 4α)], 83.0 [C-2, (2α, 3α, 4β)], 82.5 [C-2, (2α, 3β, 4β)], 80.6 [C-2, (2α, 3α, 4α)], 48.7 [C-3, (2α, 3β, 4α)], 46.2 [C-3, (2α, 3α, 4α)], 43.9 [C-3, (2α, 3α, 4β)], 41.5 [C-3, (2α, 3β, 4β)], 29.3–24.0 [C-4]. — MS(70 eV): *m/z* (%): 281 (1.4), 255 (1), 223 (14), 213 (7), 195 (6), 95 (39), 81 (55), 74 (14), 69 (54), 56 (100), 43 (99). — C₂₂H₄₀O₄ × H⁺: calcd. 369.3004; found 369.2849 (MS/CI).

Methyl 13-(4-Methyl-3-octyl-5-oxotetrahydrofuran-2-yl)dodecanoate (11b) and Methyl 13-(4-Methyl-2-octyl-5-oxotetrahydrofuran-3-yl)dodecanoate (12b). — Method A: 2.00 g (5.70 mmol) of **1c**, 1.90 g (30.0 mmol) of copper and 4.56 g (20.0 mmol) of ethyl 2-iodopropanoate (**2b**) were heated for 8 h at 130 °C yielding 1.21 g (50%) of a mixture of **11b** and **12b**.

Method C: 2.00 g (5.70 mmol) of **1c**, 3.00 g (20.0 mmol) sodium iodide, 1.90 g (30.0 mmol) of copper and 5.34 g (30.0 mmol) ethyl 2-bromopropanoate (**2b**) were heated for 8 h at 130 °C. Yield 1.41 g (59%) of **11b/12b**. As a minor product 0.19 g (7%) of **13b/14b** was

isolated. — MS (70 eV); m/z (%): 393 [$M^+ - CH_3O$] (0.8), 375 (0.8), 279 (20), 251 (14), 211 (16), 97 (59), 83 (56), 74 (33), 69 (82), 56 (100), 43 (86). — $C_{26}H_{48}O_4 \times H^+$: calcd. 425.3631; found 425.3633 (MS/CI).

Methyl 5-(4-Methyl-5-oxo-3-undecyltetrahydrofuran-2-yl)pentanoate (11c) and *Methyl 5-(4-Methyl-5-oxo-2-undecyltetrahydrofuran-3-yl)pentanoate* (12c). — *Method A*: 2.00 g (6.70 mmol) of 1d, 1.90 g (30.0 mmol) of copper and 4.56 g (20.0 mmol) of ethyl 2-iodo-propanoate (2b) were heated for 8 h at 130 °C, yielding 1.22 g (49%) of a mixture of 11c and 12c.

Method C: 2.00 g (6.70 mmol) of 1d, 3.00 g (20.0 mmol) sodium iodide, 5.43 g (20.0 mmol) ethyl 2-bromopropanoate (2b) and 1.90 g (30.0 mmol) of copper were heated for 8 h at 130 °C, yield 1.54 g (60%) of 12c. As minor product 0.28 g (10%) of 13c/14c was isolated. — MS(70 eV); m/z (%): 337 [$M^+ - CH_3O$] (2.5), 263 (2), 223 (18), 213 (39), 181 (7), 179 (12), 95 (41), 81 (45), 74 (18), 69 (65), 56 (95), 43 (100). — $C_{22}H_{40}O_4 \times H^+$: calcd. 369.3004; found 369.2979 (MS/CI).

4-Iododecanenitrile (16a). — *Method A*: 4.00 g (23.9 mmol) 2-iodoacetone nitrile (15a), 2.24 g (20.0 mmol) 1e and 1.27 g (20.0 mmol) of copper were heated for 24 h at 80 °C. Flash chromatography [light petroleum (60/80)/ether, 8:2] gave 2.34 g (42%) of 16a; $n_D^{20} = 1.4849$. — ^{13}C NMR ($CDCl_3$): $\delta = 118.3$ (CN), 40.0 (C-4), 35.6 (C-5), 35.4 (C-3), 17.8 (C-2). — MS(70 eV); m/z (%): 279 [M^+] (0.4), 153 (100), 110 (23), 96 (36), 69 (78), 56 (78), 42 (100). — MS/CI (isobutane); m/z (%): 280 (8) [MH^+], 153 (100) [$MH^+ - I$].

Methyl 10-Iodo-12-cyanododecanoate (16b). — *Method A*: 2.50 g (15.0 mmol) of 2-iodoacetone nitrile (15a), 3.00 g (15.1 mmol) of 1a and 1.00 g (15.7 mmol) of copper were heated for 18 h at 100 °C. Flash chromatography [light petroleum (60/80)/ether, 9:1] gave 3.60 g (66%) of 16b; $n_D^{20} = 1.4990$. — ^{13}C NMR ($CDCl_3$): $\delta = 118.3$ (CN), 40.0 (C-10), 35.7 (C-9), 35.3 (C-11), 17.9 (C-12). — MS(70 eV); m/z (%): 334 [$M^+ - CH_3O$] (4), 206 (100), 188 (14), 178 (19), 122 (12), 97 (20), 81 (34), 74 (5), 69 (47), 56 (72), 42 (88). — $C_{14}H_{24}O_2IN$ (365.2): calcd. C 46.04, H 6.62, I 34.74, N 3.83; found C 46.55, H 6.58, I 34.92, N 4.03.

2-Iodo-1-cyanomethylcyclohexane (16c). — *Method A*: 4.00 g (23.9 mmol) 2-iodoacetone nitrile (15a), 4.78 g (58.3 mmol) 1g and 1.67 g (26.3 mmol) of copper were heated for 48 h at 90 °C. Flash chromatography [light petroleum (60/80)/ether, 9:1] gave 1.50 g (25%) of 16c; [(Z)-16c]/[(E)-16c] = 1.4:1; the diastereomers were separated by MPLC [light petroleum (60/80)/ether, 95:5]. (Z)-16c: $n_D^{20} = 1.5412$. — ^{13}C NMR ($CDCl_3$): $\delta = 117.9$ (CN), 42.7 (C-2), 39.8 (C-6), 36.0 (C-1), 22.0 (CH_2CN). — MS(70 eV); m/z (%): 249 [M^+] (0.5), 122 (30), 105 (5), 95 (4), 81 (100), 79 (11), 67 (87), 54 (12). — $C_8H_{12}NI$ (249.1): calcd. C 38.57, H 4.86, I 50.95, N 5.62; found C 38.77, H 4.84, I 50.75, N 5.65. (E)-16c: $n_D^{20} = 1.5336$. — ^{13}C NMR ($CDCl_3$): $\delta = 117.7$ (CN), 43.6 (C-2), 41.0 (C-6), 36.1 (C-1), 25.3 (CH_2CN). — $C_8H_{12}NI$ (249.1): calcd. C 38.57, H 4.86, I 50.95, N 5.62; found C 38.70, H 4.70, I 50.99, N 5.65.

Methyl 14(13)-Iodo-13(14)-cyanomethyl-docosanoate (16d). — *Method A*: 3.00 g (18.0 mmol) of 2-iodoacetone nitrile (15a), 4.23 g (12.0 mmol) of 1c and 0.97 g (11.3 mmol) of copper were heated for 12 h at 100 °C. Flash chromatography [light petroleum (60/80)/ether, 9:1] gave 1.37 g (44%) of 16d; $n_D^{20} = 1.4839$. — ^{13}C NMR ($CDCl_3$): $\delta = 118.3$, 118.2 (CN), 43.9, 43.5 (CHI), 42.1, 41.1 ($CHCH_2CN$), 38.4, 37.3 (CH_2CHI), 26.7, 26.2 (CH_2CN). — MS(70 eV); m/z (%): 360 [$M^+ - CH_3O - HI$] (100), 332 (24), 276 (6), 262 (6), 248 (4), 97 (27), 83 (38), 74 (28), 69 (65), 56 (100), 42 (88). — $C_{25}H_{46}O_2NI$ (519.5): calcd. C 57.80, H 8.92, N 2.70; found C 58.65, H 9.79, N 2.65.

Methyl 10-Iodo-12-cyanohexadecanoate (16e). — *Method C*: 6.00 g (34.2 mmol) of 2-bromohexanenitrile (15b), 5.1 g (32.2 mmol) of sodium iodide, 6.78 g (34.2 mmol) of 1a and 2.16 g (32.2 mmol) of copper were heated for 5 h at 130 °C. Flash chromatography [light petroleum (60/80)/ether, 85:15] gave 9.8 g (68%) of 16e; diastereomeric mixture = 1.6:1; $n_D^{20} = 1.4839$. — ^{13}C NMR ($CDCl_3$): $\delta = 121.0$, 121.1 (CN), 42.9, 42.3 (C-10), 40.7, 39.4 (C-9), 35.4 (C-11), 32.9, 33.1 (C-12). — MS(70 eV); m/z (%): 390 [$M^+ - CH_3O$] (0.5), 262 (60), 244 (14), 234 (10), 97 (30), 81 (44), 74 (32), 69 (53), 56 (74), 43 (100). — $C_{18}H_{32}O_2NI$ (421.4): calcd. C 51.31, H 7.65, N 3.32; found C 51.55, H 8.18, N 4.17.

Diethyl 3-(2-Ethoxycarbonylbutyl)-4-iodomethylcyclopentane-1,1-dioate (20). — *Method A*: 4.56 g (20.0 mmol) of ethyl 2-iodobutanoate (2c), 3.10 g (12.9 mmol) of diethyl diallylmalonate 1h and 1.29 g (20.3 mmol) of copper were heated for 6 h at 90 °C. Flash chromatography [light petroleum (60/80)/ether, 9:1] gave 4.53 g (73%) of 20; [(Z)-20]/[(E)-20] = 1.1:1; $n_D^{20} = 1.4742$ and was identified unambiguously by 1H - and ^{13}C -NMR spectra. — MS(70 eV); m/z (%): 482 [M^+] (1), 437 (3), 309 (24), 235 (100), 207 (81), 133 (78), 93 (50), 79 (50), 56 (39). — MS/CI (isobutane); m/z (%): 483 (100) [MH^+]. — $C_{19}H_{31}O_6I$ (482.3): calcd. C 47.31, H 6.48; found C 46.82, H 6.08.

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