DOI: 10.1002/ejoc.200901513

Thione Esters as Substrates for the Stereoselective Alkylation of Model Compounds of Nonactic Acids

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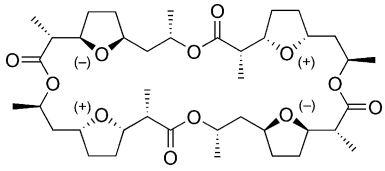
Keywords: Heterocycles / Diastereoselectivity / Retro reactions / Alkylation

The naturally occurring macrotetrolide antibiotic nonactin is used in ammonium ion selective electrodes. To increase the lifetime of nonactin in the semipermeable membrane of these sensors we have developed methods for the introduction of hydrophobic side-chains. Simple model compounds for nonactic acid such as **5** and **7** were synthesised. Maintaining the *cis* arrangement of the substituents in the 2,5-disubstituted tetrahydrofurans proved to be difficult. Three different routes were studied. The enolates obtained by treatment with NaHMDS or KHMDS could be alkylated with benzyl or allyl iodide as electrophiles. Under these conditions a *cis*/*trans* isomerisation of the substituents on the tetrahydrofuran ring occurred. A multistep methodology was developed as a synthetic alternative. The sequence consisted of a selective retro-Michael reaction, a 5-*exo*-*tet* iodocyclisation and a radical substitution. The products obtained by the two methodologies could be correlated, and thereby a tentative assignment of the relative configurations could be achieved. In the third route the thione ester **18** was deprotonated with *t*BuOK. At temperatures below –78 °C, the enolate maintained the *cis* configuration of the substituents at the tetrahydrofuran ring. The alkylated product **12** could be isolated with a satisfactory *cis*/*trans* ratio of 85:15. The model compound **12** could be successfully transformed into more hydrophobic derivatives by using either the Heck coupling or the cross-coupling metathesis transformation.

Introduction

Nonactin (**1**), an ionophore isolated from *Streptomyces* shows interesting antibiotic properties. The macrotetrolide **1** selectively mediates ammonium and potassium transport through lipophilic natural and artificial membranes,[1] and it is used as an additive in semipermeable membranes in ammonium sensors.[2] To increase the lifetime of this additive in the semipermeable membranes more lipophilic derivatives of the natural macrotetrolide **1** are needed. We report our efforts to modify model compounds of nonactic acid (**2**) with the goal of introducing lipophilic side-chains at the α-position to the carboxylic acid. First described in 1955,[3] **1** is the smallest homologue of the nactin family. Nonactin (**1**), an achiral *meso* compound, is composed of four constitutionally identical chiral nonactic acid (**2**) molecules (Figure 1). Two molecules of (+)-**2** are condensed with two molecules of (–)-**2** in an alternating (+)(–)(+)(–) sequence, which confers the unusual S_4 symmetry on nonactin (**1**). About 30 syntheses of nonactic acid and its derivatives have been reported.[4] Nonactic acid was considered to be a good model structure for measuring the progress of modern synthetic methodologies.[5] However, despite the impressive progress, tricky separations of stereoisomers have to be performed in all reported syntheses. Six total syntheses of the macrotetrolide **1** have been described in the literature,[6–11] but isolation of the natural product from fermentation is still the most efficient way to obtain **1**.[12] Major difficulties are encountered during the synthesis of enantiopure (+)- and (–)-nonactic acids (**2**) and during the assembly process. Racemic nonactic acid can be resolved on a gram scale by using mandelic acid derivatives[13–15] or *Rhodococcus erythropolis*.[12] Nonactin (**1**) is expensive and available in gram quantities only, and therefore structurally simpler ionophores, like depsipeptides[16] or tripodants,[17] have been tested as selective ionophores for the transport of ammonium ions. However, nonactin (**1**) is still used commercially as the standard ammonium-selective ionophore.



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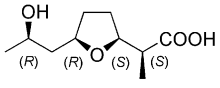

(+)-**2**

Figure 1. Structures of nonactin (**1**) and (+)-nonactic acid (**2**).

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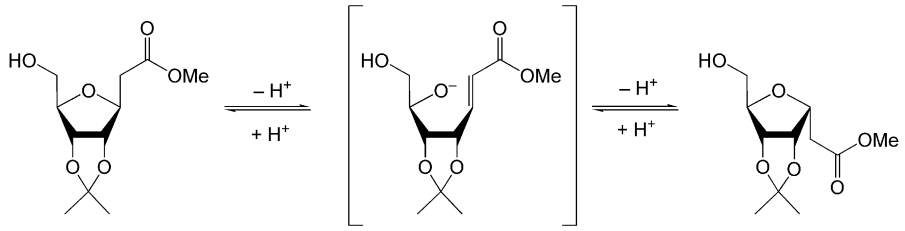
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901513.



Scheme 1. Reported *cis*/*trans* epimerisation induced by the retro-Michael reaction of the ester enolate.[26,27]

The lipophilicity of the ionophores used in sensors is the crucial factor determining the lifetime of ammonium-sensitive electrodes using nonactin (**1**).[18] We have recently reported short and scalable routes to generate 2,5-disubstituted furans and tetrahydrofurans, analogues of nonactic acid.[4,5d,19,20] We planned to introduce one to four lipophilic chains into nonactin to increase its lifetime in the membranes. The *cis* arrangement of the substituents on the tetrahydrofuran rings must be maintained during functionalisation to preserve the capacity of optimal binding of the cations.[21–23] We report herein a method for diastereoselectively introducing lipophilic side-chains (Figure 2) at the α-position of the ester function of our model compounds avoiding the undesired retro-Michael reaction.

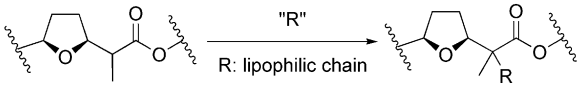


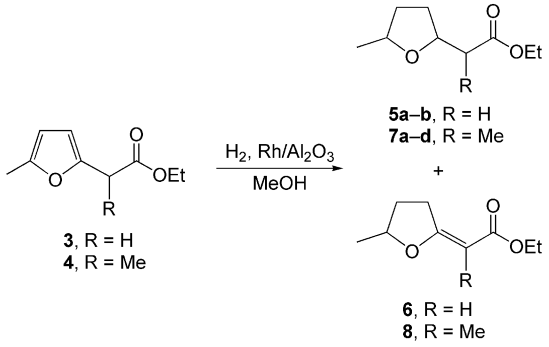
Figure 2. Goal of our studies: to increase the lipophilicity of the nonactin model compounds by alkylation.

Deprotonating the α-position of esters of this type induces *cis*/*trans* epimerisation at the tetrahydrofuran ring by an intramolecular retro-Michael reaction/recyclisation sequence (see Scheme 1).[24,25] The only method reported in the literature to maintain the *cis* arrangement blocks the epimerisation by intramolecular lactone formation.[26,27]

Results and Discussion

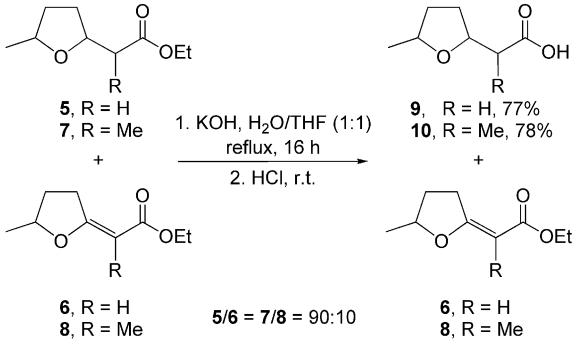
Synthesis and Structure Assignment of the Model Compounds

We attempted the introduction of lipophilic side-chains by using the two model compounds **5** and **7**. The molecules **5** and **7** preserve the essential features of nonactic acid, especially the crucial relative configuration of the two side-chains on the tetrahydrofuran ring. Compounds **5** and **7** were synthesised by catalytic hydrogenation of the two 2,5-disubstituted furans **3** and **4**, respectively, with rhodium on alumina as catalyst (Scheme 2).[5,28] During the catalytic reduction we obtained reproducibly **6** and **8** as minor, so far unknown, side-products, which were difficult to separate from the tetrahydrofurans **5** and **7**.[29,30] Different approaches to separating the side-products from the desired products were tried. A second hydrogenation converted the furylidenes into the tetahydrofurans but also led to partial transesterification so that mixtures of methyl and ethyl esters were obtained. Use of ethanol as solvent for the second hydrogenation slowed reaction too much so that the transformation became inefficient.



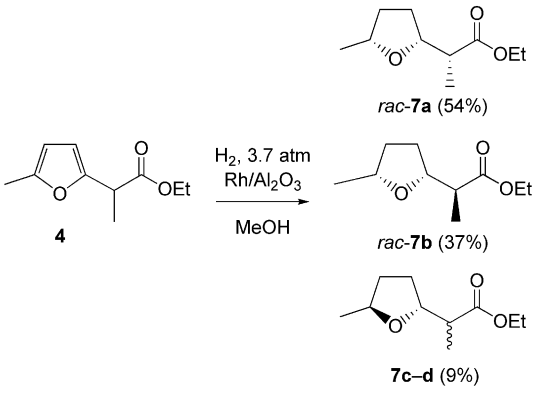
Scheme 2. Catalytic hydrogenation of the furans **3** and **4**.

In the end, differences in their reactivities were used for their separation. Treatment of the mixtures of tetrahydrofuran and furylidene with KOH in the solvent mixture water/THF (1:1) at reflux[28,31] led to the exclusive saponification of **5** and **7**, the furylidenes **6** and **8** remaining unchanged due to resonance stabilisation (Scheme 3). The acids were easily separated by silica gel chromatography. The furylidenes **6** and **8** were obtained in pure form and could be fully characterised. The ratio of the diastereoisomers remained unchanged during saponification. This observation is compatible with the assumption that no epimerisation of the chiral centre at the α-position of the ester had occurred.[24]



Scheme 3. Selective saponification of tetrahydrofurans **5** and **7** in the presence of furylidenes **6** and **8**.

Catalytic hydrogenation has been reported to yield mainly the desired *cis* diastereoisomers.[29,30] The *cis* isomer of **5**, obtained by catalytic reduction of the furan **3**, could be partially separated from the *trans* isomer by chromatography using a silica gel column. NOESY experiments confirmed the *cis* configuration of the major isomer of **5**. Two fractions were obtained by silica gel chromatography of the product **7** obtained by catalytic reduction of **4**. Each fraction contained a *cis* diastereoisomer as the major component and one of the *trans* diastereoisomers as an impurity. The major, more polar diastereoisomer was saponified. The acid **10a** crystallised from diethyl ether. Its relative configuration was determined with the help of X-ray diffraction.[28] The relative configuration of **10a** is *cis*/*anti*. (The *cis*/*trans* nomenclature is used to indicate the relative configuration of the side-chains on the five membered ring, whereas the *syn*/*anti* nomenclature follows the definition given by Evans et al. to characterise the relative configuration of aldol products at the α- and β-positions of the ester;[32] see also the Supporting Information.) The other *cis* diastereoisomer **7b** has therefore the relative configuration *cis*/*syn* (Scheme 4).

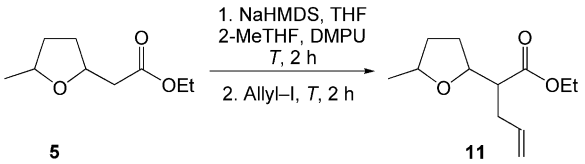


Scheme 4. Structures of the diastereoisomers of **7** obtained by catalytic hydrogenation.

Alkylation Using Enolate Chemistry

Alkylation of the α-position of esters by enolate chemistry has been widely studied. We decided to study this chemistry despite the reports of β-elimination in reactions involving tetrahydrofuran-containing substrates. We started our study by using the model compound **5**. NaHMDS, which is less aggregated than LDA,[33] gave encouraging results in the solvent mixture THF/DMPU (Entry 1 in Table 1). Two out of four possible stereoisomers were obtained. This result is compatible with the assumption that either the ring junction (*cis*/*trans*) or the chiral centre next to the ester (α/β) is preserved or highly stereocontrolled during this process. If the retro-Michael reaction can be avoided, the formation of the two stereoisomers could only be due to the newly introduced R group at the α-position of the ester. Our group has previously reported that by working below –110 °C using 2-methyltetrahydrofuran (2-Me-THF)/THF as the solvent mixture, a facile β-elimination can be avoided.[34,35] By applying these conditions a slightly higher diastereotopic ratio (*dr*) but lower yield was obtained (Entry 2 in Table 1). This result does not allow an unequivocal interpretation. For additional information, see the Supporting Information.

Table 1. Attempts to alkylate **5** by using NaHMDS as base.



5 **11**

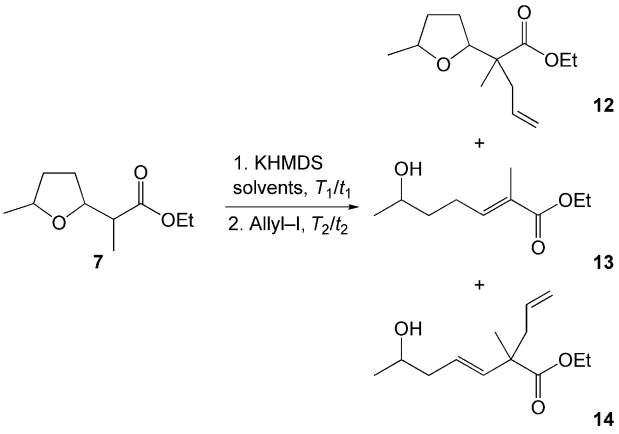
Entry	*T* [°C]	Yield [%]	*dr*[a]
1	–78	55	55:45
2	–115	38	75:25

[a] Ratio of diastereoisomers, according to ^{1}H NMR spectroscopy.

Not surprisingly the substituted compound **7** was considerably less reactive than **5** under the same conditions. The yield of **12** was below 10% in all our attempts (experiments not reported). To obtain acceptable yields of product the stronger base KHMDS had to be used, which afforded enolates with more ionic character. In our first attempt, **12** was obtained in 16% yield together with 44% of the ring-opened compound **14** (Entry 1, Table 2). Shorter deprotonation times increased the yield of **12** (Entries 2 and 3, Table 2). In an effort to optimise the yield of compound **12**, we changed the solvent mixture from toluene/THF (Entries 1–3 in Table 2) to THF/2-Me-THF without success (Entries 4–6, Table 2). The use of 2-methyl-THF enabled the reaction mixture to be stirred at temperatures below –87 °C. Lowering the temperature for the deprotonation and alkylation reactions from –78 to –90 °C and finally to –100 °C lowered the overall yield without improving significantly the ratio between the furan-containing product and the ring-opened products (Entries 4–6, Table 2; see also the Supporting Information). The isolation of compounds **13** and **14** was compatible with a retro-Michael process. In most of the reactions **13** is a minor product (exception: Entry 6, Table 2). The ratio of **13**/**14** may be determined from the quenching reaction and not the transformation itself. The chemo- and stereoselectivity of the alkylation process were not satisfactory under any of the conditions studied by us.

We were not able to separate the two diastereoisomers of **12** by standard silica gel chromatography.[29] We therefore decided to assign the relative configuration of **12** by chemical correlation (see the Supporting Information). We compared the products obtained by the alkylation of **7** with products obtained by reduction of the corresponding furan **24**. This comparison allowed us to tentatively assign the relative configuration.

Table 2. Alkylation reactions of **7** with KHMDS as base.



Entry	T_1 [°C]/t_1 [h]	Solvent mixture[a]	T_2 [°C]/t_2 [h]	Product (yield [%])
1	–78/1	toluene/THF (40:60)	–78 to –20/1.5	**12** (16) **13** (<4) **14** (44)
2	–78/0.5	toluene/THF (40:60)	–78 to –70/0.5	**12** (33) **13** (4) **14** (20)
3	–87/0.5	toluene/THF/2-Me-THF[b] (40:30:30)	–87 to 20/0.75	**12** (43) **13** (<4) **14** (37)
4	–87/0.5	THF/2-Me-THF (50:50)	–87/0.5	**12** (26) **13** (<4) **14** (<32)
5	–90/0.5	THF/2-Me-THF (50:50)	–90/0.5	**12** (26) **13** (6) **14** (30)
6	–100/0.5	THF/2-Me-THF (50:50)	–100/0.5	**12** (16) **13** (18) **14** (18)

[a] 10% of DMPU unless indicated otherwise. [b] Without DMPU.

Ring-Opening/Ring-Closing Sequence for the Alkylation

Our results are compatible with the mechanistic hypothesis that ring-opening (retro-Michael reaction) occurred under all the conditions tested and that the ring-closed products **11**, **12** and **S-4** (see the Supporting Information) had been formed by a ring-opening/ring-closing sequence. In this context it is worth mentioning that the biosynthesis of nonactin uses Michael addition to a linear α,β-unsaturated ester to form selectively the tetrahydrofuran ring.[36–40] We decided to take advantage of this inherent reactivity and to use the ring-opened products as intermediates in our quest to obtain lipophilically substituted analogues of nonactic acid. We developed a second method that proceeds via ring-opened intermediates to try to ascertain the *syn*/*anti* relative configuration of the two centres at the α- and β-positions of the ester (Figure 3). The strategy involves a three-step sequence: a retro-Michael reaction, a 5-*exo*-iodocyclisation to introduce a halogen atom and a stereospecific radical substitution of the iodine atom by a radical chain reaction (Figure 3).

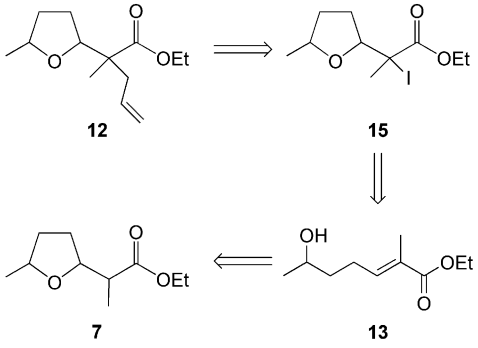
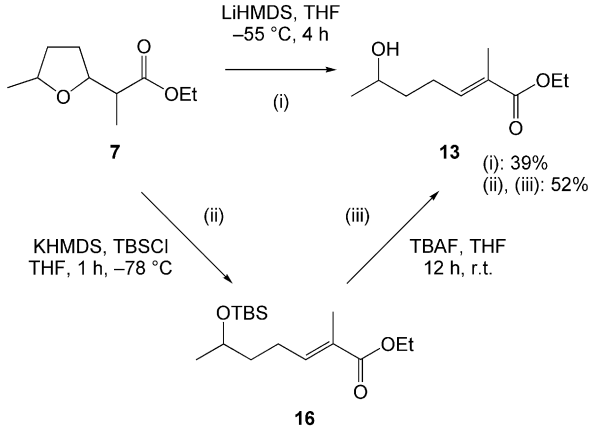


Figure 3. Retrosynthetic analysis for the synthesis of **12** via the α-halogeno ester **15**.

To perform the planned sequence we had to obtain the ring-opened compound **13** selectively by a retro-Michael reaction. By using NaHMDS as base up to 40% of the double bond migrated leading to a loss of conjugation as a result of deprotonation of **13** by the sodium alkoxide. By

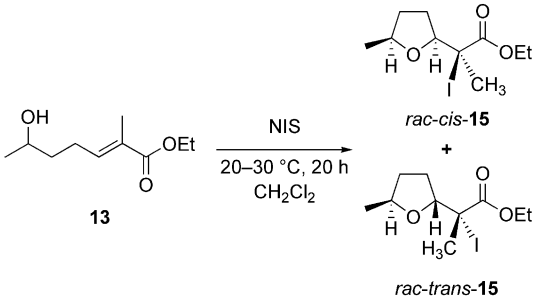
using LiHMDS in THF, the ring-opened product **13** was obtained without detectable double-bond migration.

In our hands, conversion and yield were low [maximum yield 39%; Scheme 5, path (i)]. By using the stronger base KHMDS in THF, total conversion of **7** could be achieved, but double-bond migration could not be avoided. To obtain good yields of the ring-opened product **13** we had to add TBSCl as an internal quenching reagent, which gave the TBS-protected product **16**.[41] Deprotection of the alcohol with TBAF in THF led to a considerable amount of oligomerisation and thereby to a relatively low yield for the total conversion [Scheme 5, total yield of 52% of **13** over the two steps (ii) and (iii)].



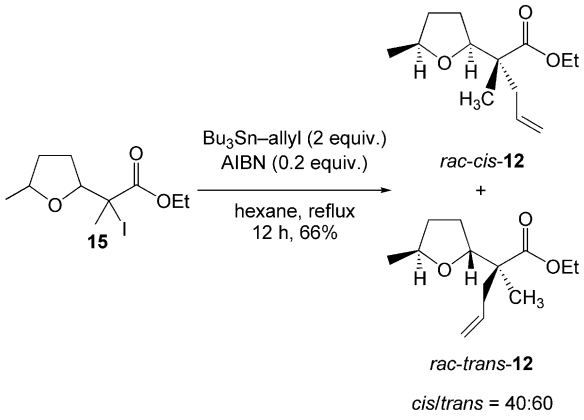
Scheme 5. Selective retro-Michael reaction.

According to the reports of Bartlett and co-workers,[8,42,43] we planned to use oxidative iodocyclisation for the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans.[44] The oxidative 5-*exo*-iodocyclisation[45] of γ,δ-unsaturated alcohols has been reported to afford a mixture of *cis*/*syn* and *trans*/*syn* diastereoisomers. The literature reports indicate that the *trans* diastereoisomers are slightly favoured in the iodocyclisation of δ,γ-unsaturated alcohols (Scheme 6).[43]



Scheme 6. Oxidative iodocyclisation.

To achieve the radical substitution, we applied the excellent work of Guindon and co-workers (Scheme 7)[46,47] who described this reaction for a monosubstituted tetrahydrofuran. According to their report, the *syn* product is favoured in the absence of Lewis acids. By using allyltributyltin in hexane at reflux with AIBN as radical initiator, a moderate but acceptable 66% yield of a mixture of essentially two diastereoisomers of **12** was isolated. The lower yield obtained in our case in comparison with the yields reported in the literature is no surprise because of the diminished reactivity of tertiary iodides.



Scheme 7. Radical substitution with allyltributyltin.

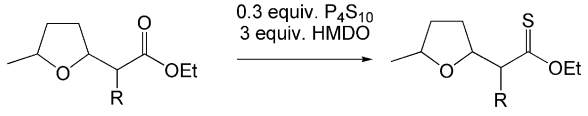
We tentatively assigned the configurations of the diastereoisomers of **12** obtained in this three-step sequence by correlating the products obtained by radical substitution with the products obtained by alkylation of the enolate. The radical substitution reaction has been reported to yield preferentially the *trans*/*syn* and *cis*/*syn* diastereoisomers.[46,47] Assigning the relative configurations of the products obtained by the radical substitution process (Scheme 7) based on the literature report is compatible with the chemical correlation.

Stereoselective Alkylation Using Thione-Enolate Chemistry

As the yields and the diastereoselectivities of the two processes studied so far were not satisfactory, we decided to study the behaviour of thione esters, which should be easier to deprotonate and therefore less prone to the retro-Michael reaction. By using Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide],[48,49] the yields of thione esters **17** and **18** were disappointingly small, less than 10% (see the Supporting Information). The thione esters **17** and **18** were partially degraded during silica gel chromatography. Curphey[50] reported that the reactivity of P_4S_{10} can be increased considerably by using hexamethyldisiloxane (HMDO). The side-products generated by the P_4S_{10}/HMDO system can be easily removed by appropriate workup procedures. We applied the optimal conditions reported by Curphey (0.25–0.33 mol of P_4S_{10} per mol of ester, 3–4 mol of HMDO) using aqueous K_2CO_3 and acetone in the workup (Table 3). The conversion of **7** reached a satisfying 70–75%. Purification by silica gel chromatography was necessary to separate unreacted esters from the corresponding thione esters.

Deprotonating the thione ester **17** with LDA in THF followed by Michael addition to cyclopentenone[51] gave a non-optimised yield of 52% of **19** as a 75:25 mixture of two diastereoisomers (Scheme 8). The product was formed as a

Table 3. Thionation of the model compounds **5** and **7** with P_4S_{10}/HMDO.



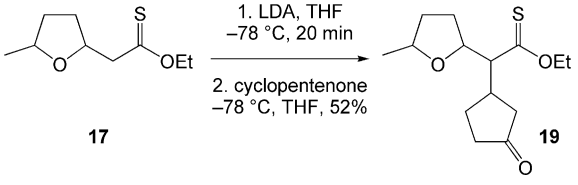
5, R = H
7, R = Me

17, R = H
18, R = Me

Entry	R[a]	Solvent	Time[b] [h]	Conv.[a] [%]	Product/yield [%]
1	H	toluene	16	–[c]	**17**/42[b]
2	Me	toluene	16	70	**18**/30[b]
3	Me	toluene	16	70	**18**/100[d]
4	Me	toluene	20	75	**18**/34[b]
5	Me	*o*-xylene	17	60	**18**/27[b]
6	Me	acetonitrile	20	15	**18**/–[c]

[a] According to ^{1}H NMR spectroscopy. [b] Isolated by chromatography. [c] Not determined. [d] Raw product obtained after workup.

result of a 1,4-addition of the enolate of the thione ester to the α,β-unsaturated ketone. The *cis*/*trans* ratio of the starting material **17** was 90:10. The *cis*/*trans* ratio of the recovered starting material **17** was 70:30 after chromatography. This reduction of the *cis*/*trans* ratio can be attributed to the occurrence of the retro-Michael reaction.

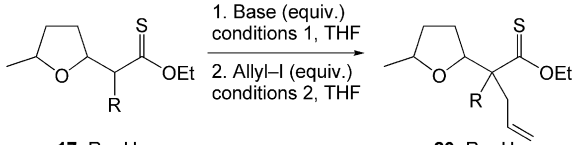


Scheme 8. Alkylation of thione ester with cyclopentenone.

By treating the enolate obtained under the same conditions with allyl iodide, **20** was obtained in 62% yield and 25% of **17** was recovered (Table 4). By using *t*BuOK as base under the reaction conditions reported,[52] total conversion could be achieved. The enolate of the thione ester was generated at –78 °C, warmed to –10 °C and cooled again to –78 °C before the addition of the electrophile. The racemates of two diastereoisomers were isolated by chromatography in 56 and 3% yields, respectively. Applying the same reaction conditions to the α-methylated thione ester **18** gave similar results. The racemates of two diastereoisomers were again isolated by chromatography, this time in 66 and 20% yields, respectively. The chemistry using the enolates of the thione esters proved to be robust giving good yields of the alkylated products.

We modified the reported reaction conditions in the hope of avoiding the retro-Michael elimination. By keeping the enolate of the thione ester at –78 °C we still observed total conversion, and the alkylated products could be isolated in a reproducible 85% yield. Only two diastereoisomers were obtained in a 90:10 ratio according to ^{1}H NMR spectroscopy. The GC ratio was 87:13, which is in good agreement with the NMR result. This observation is compatible with the hypothesis that the retro-Michael elimination can be avoided by keeping the enolate of the thione ester at –78 °C during the whole transformation. The only side-product present in the raw material was the excess allyl io-

Table 4. Alkylation of **17** and **18** with allyl iodide.



17, R = H
18, R = Me

20, R = H
21, R = Me

Entry	R	Base (equiv.) Allyl-I (equiv.)	Conditions 1	Conditions 2[a]	Yield [%]/ratio[b]
1	H	LDA (1.2) allyl-I (1.2)	–78 °C, 0.5 h	–78 °C to –10 °C, 2 h	62/–[c]
2	H	*t*BuOK (1.3) allyl-I (1.3)	–78 °C to –10 °C, 0.5 h	–78 °C to –10 °C, 1.5 h	56/70:30
3	Me	*t*BuOK (1.3) allyl-I (1.3)	–78 °C to 7 °C, 0.5 h	–78 °C to –10 °C, 1.3 h	66/65:35[a]
4	Me	*t*BuOK (1.6) allyl-I (1.6)	–78 °C, 0.5 h	–78 °C to –10 °C, 1.3 h	85/90:10[d]

[a] 20% of an additional fraction containing some impurities was isolated. The ratio between the diastereoisomers was not determined for this fraction. [b] Ratio between the two diastereomeric pairs of enantiomers, according to ^{1}H NMR spectroscopy. [c] *cis*/*trans* ratio of **20** was not determined, and starting material **17** (25%) was recovered. [d] A quantitative yield was recovered before chromatography.

dide. Drying of the crude product after workup removed the volatile allyl iodide and gave the product in quantitative yield without chromatography.

If this methodology is to be applicable to nonactin (**1**) the alkylation reaction has to be selective for the thione ester in the presence of ester functions. We tested the reaction by using a 50:50 mixture of **18/7** (Table 5). The thione ester should be more acidic than the ester, and selective transformation of the thione ester should be feasible.[53] With 1.05 equiv. of *t*BuOK, the formation of acrylate **13** could not be completely avoided: 7.4% of **7** was transformed into the ring-opened product **13**, whereas 12.3% of thione ester **18** remained unreacted. By reducing the amount of *t*BuOK to 0.85 equiv., only 4.6% of acrylate **13** was formed. However, the conversion to thione ester **18** was also lower. The *cis*/*trans* ratios of the products **7**, **18** and **21** were still roughly 90:10. Therefore, selective transformation of thione esters in the presence of "normal" esters is feasible.

Table 5. Allylation from a 50:50 mixture of **18/7**.

Entry	*t*BuOK [equiv.]	**7/18/13/21**[a]
1	1.05	46:12.3:7.4:34.3
2	0.85	32.3:32.6:4.6:30.5

[a] According to GC.

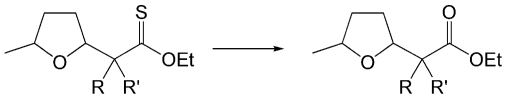
We then studied the conversion of thione ester back to the ester function. Corsaro and Pistara reported in 1998 in their review[54] many different reagents for the conversion of thiocarbonyl groups into carbonyl groups. We tested first the behaviour of thione ester **17** against $P(OMe)_3$ at 105 °C. The ^1H NMR spectrum of the crude reaction mixture showed complete loss of the compound (Table 6). The thione ester was then treated with $[Fe(CO)_5]$ in toluene at reflux.[55] The maximum conversion never exceeded 70%. By using *m*-CPBA total conversion of **17** could be achieved. It has been reported that *m*-CPBA[56] in CH_2Cl_2 allows the conversion of thiocarbonyl groups into carbonyl groups in the presence of double bonds. We therefore tested these conditions with compound **20**. We obtained a drastically reduced yield of only 28% of **11**. By using **21** as the substrate, 22 h were required to obtain total conversion. Elution of the polar fractions from the chromatography column with AcOEt/MeOH showed the presence of uncharacterised polar compounds lacking the double bond. This is circumstantial evidence that *m*-CPBA attacked the double bonds of **20** and **21**. To avoid the problems of overoxidation we tested the reagent trifluoroacetic anhydride (TFAA) in the reaction with **18**.[57] The reaction was exothermic at the beginning. However, the conversion stopped after only 35%. Finally, tin derivatives like $(Bu_3Sn)_2O$ and Bu_2SnO in dioxane at reflux[58] afforded the best results for the transformation of the thione esters into the ester function. Several days were required to obtain total conversion of **21**, as indicated by GC–NMR.[59] The unoptimised yield of **12** was 66% with $(Bu_3Sn)_2O$ and 48% with Bu_2SnO. The excess of Bu_2SnO is easier to remove than the excess of $(Bu_3Sn)_2O$, because the reaction mixture is heterogeneous.

Introduction of Hydrophobic Side-Chains by Organometallic Coupling

Having achieved the functionalisation α to the ester function we decided to apply the Heck and metathesis[60–63] reactions to modify the terminal double bond of **12** and thereby increase the lipophilicity of our model compounds.

For the cross-metathesis reaction we used 1-(hex-5-enyloxy)dodecane (**23**), prepared in one step by treating hex-5-en-1-ol (**22**) with 1-bromododecane under the conditions reported for the alkylation of hex-5-en-1-ol with bromononane.[64] Deprotonation of the alcohol **22** with NaH at room temperature for 2 h followed by alkylation with 1-bromododecane gave the product **23** in moderate yield (Table 7).

Table 6. Conversion of thione esters into their corresponding esters.



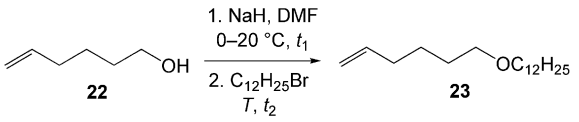
17, R = R' = H
18, R = H, R' = Me
20, R = H, R' = Allyl
21, R = Me, R' = Allyl

5, R = R' = H
7, R = H, R' = Me
11, R = H, R' = Allyl
12, R = Me, R' = Allyl

Entry	R	R′	Reagent	Conditions	Conv.[a] [%]	Yield[b] [%]
1	H	H	$P(OMe)_3$	105 °C	100	0
2	H	H	$[Fe(CO)_5]$	toluene, 105 °C, 16 h	70	–[c]
3	H	H	*m*-CPBA	CH_2Cl_2, 25 °C, 2 h	100	55
4	H	allyl	*m*-CPBA	CH_2Cl_2, 25 °C, 4 h	<90	28
5	Me	allyl	*m*-CPBA	CH_2Cl_2, 20 °C, 22 h	90	29
6	H	Me	TFAA	CH_2Cl_2, 25 °C, 4 h	<30	–[c]
7	H	H	$(Bu_3Sn)_2O$	dioxane, reflux, 15 h	100	43
8	Me	allyl	$(Bu_3Sn)_2O$	dioxane, reflux, 48 h	100	66
9	Me	allyl	Bu_2SnO	dioxane, reflux, 8 d[d]	>95	48

[a] According to ^1H NMR spectroscopy. [b] Isolated by chromatography. [c] Not determined. [d] Overall time for the two reactions required to obtain total conversion.

Table 7. Synthesis of 1-(hex-5-enyloxy)dodecane (**23**).

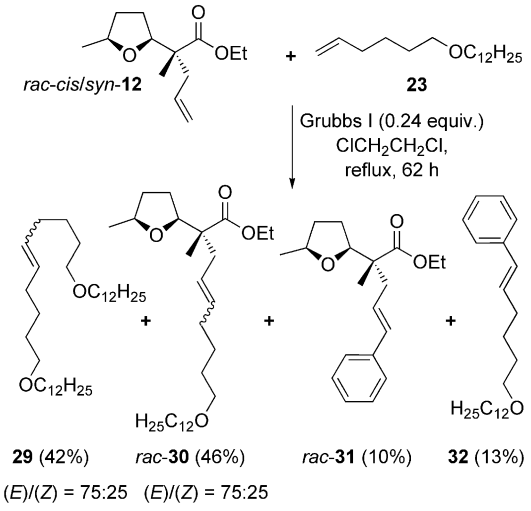


Entry	T [°C]	t_1 [h]	t_2 [h]	Yield [%]
1	20	0.25	20	23
2	20	2	3.5	40
3	50	2	20	47

For our model studies we tested only the Grubbs I catalyst.[63,65,66] Preliminary attempts at the cross-metathesis reaction between the furan **24** and the olefin **22** afforded **25** in 81% yield (Table 8). The side-products formed by self-coupling were isolated in variable yields:[62] side-products **26** and **27** formed in minor quantities were not isolated.

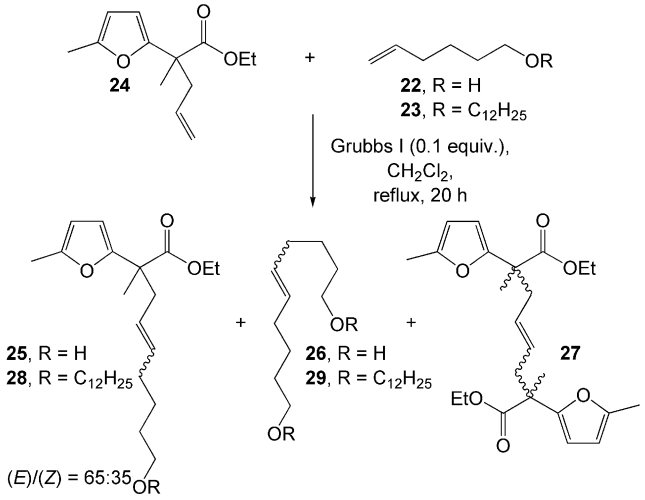
Alkylation of **25** with 1-bromododecane under the conditions developed for the synthesis of **23** gave low yields (not reported). NMR analysis of the crude product obtained by cross-metathesis between **23** and furan **24** indicated a good transformation of the starting materials and the presence of a high amount of the product **29**. On reducing the excess of **23** from 1.6 to 1.2 equiv., the product **28** could still be isolated in an acceptable yield of 54%. The two homodimers **29** (21%) and **27** (8%) were also isolated. Finally, **24** and **23** were allowed to react in equimolar amounts. The homodimers **29** and **27** were isolated in 3 and 6% yields, respectively. Full conversion of **24** could not be achieved under these conditions. The ^{1}H NMR analysis showed that the (*E*)/(*Z*) ratio for both **28** and **25** is 65:35.

Surprisingly, **12** was considerably less reactive than **24**. After 20 h in CH_2Cl_2, only 14% of **30** had undergone the cross-metathesis reaction. We suppose that residual tin derivatives from the previous step could be responsible for the lower reactivity. Use of 1,2-dichloroethane and the addition of further quantities of Grubbs I catalyst during the reaction increased the yield to 46% for **30** and 42% for **29**. The large amount of catalyst needed also led to 10% of **31** and 13% of **32**, products obtained by cross-coupling with the benzylidene coming from the Grubbs catalyst (Scheme 9). According to ^{1}H NMR analysis, the (*E*)/(*Z*) ratio is 75:25 for **30** and **29**, whereas for **32** only the (*E*) diastereoisomer could be detected in the ^{1}H NMR spectrum.



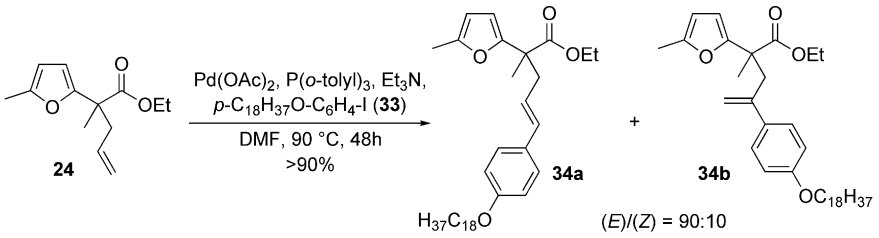
Scheme 9. Cross-metathesis reaction of furan **12** and alkene **23**.

Table 8. Cross-metathesis of furan **24**.

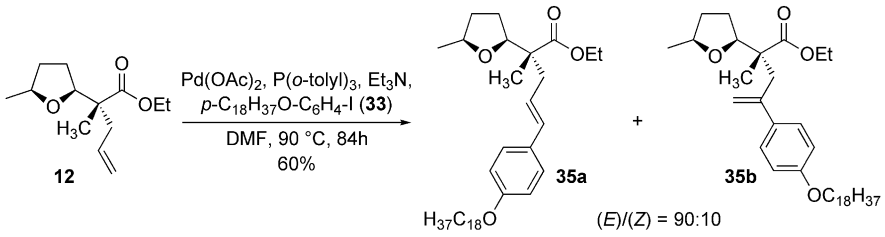


Entry	Olefin [equiv.]	Self-coupling[a] product/yield [%]	Conv. of **24** [%]	Product/ yield [%]
1	**22** [1.6]	–[b]	100	**25**/81
2	**23** [1.2]	**29**/21;[a] **27**/8[c]	100	**28**/54[a]
3	**23** [1.0]	**29**/3;[a] **27**/6[c]	90[a]	**28**/30[c]

[a] According to ^{1}H NMR spectroscopy. [b] Not determined. [c] Isolated by chromatography.



Scheme 10. Heck coupling reaction of compound **24** with **33**.



Scheme 11. Heck coupling reaction of compound **12** with **33**.

We decided to test the Heck reaction as an alternative method for introducing the hydrophilic side-chains. Mizoroki et al. reported the first case of a Heck reaction in 1971[67] using MeOH as solvent at 120 °C. One year later Heck and Nolley reported milder conditions.[68] The so-called Heck coupling reaction has become one of the most efficient synthetic methodologies for coupling between olefins and aromatic halides.[69] We decided to use 1-iodo-4-octadecyloxybenzene (**33**), synthesised from commercially available 4-iodophenol and octadecyl iodide in a moderate 58% yield after 24 h. We used the furan derivative **24** for the optimisation of the conditions.[70,71] Complete transformation could be achieved within 48 h (Scheme 10). The combined overall yield of **34a** and **34b** was more than 90%.

In the case of compound **12**, 84 h were required to achieve total consumption (Scheme 11). The overall combined yield of **35a** and **35b** was only 60%. Small amounts of residual tin derivatives from the previous step might be responsible for the reduced reactivity. A mixture of two regioisomers was isolated in a 90:10 ratio in both reactions. The major isomers **34a** and **35a** have the relative configuration (*E*).

Conclusions

Simple analogues of ethyl nonactate **5** and **7** have been successfully prepared. These model compounds were used to develop reaction conditions suitable for the diastereoselective introduction of hydrophobic side-chains at the α-position of the ester functionality (Schemes 10 and 11). With NaHMDS and KHMDS as bases, direct alkylation was possible by using enolate chemistry. Under these reaction conditions, partial isomerisation of the crucial relative configuration of the side-chains on the tetrahydrofuran ring occurred. The relative configurations of the new compounds were tentatively assigned by chemical correlation. Transformation of the model compounds **5** and **7** into the corresponding thione esters was achieved in moderate yields. Use of the enolate generated from the thione ester has allowed the introduction of activated alkyl substituents at the α-position of the ester, creating a quaternary centre. This procedure avoids to a large extent the *cis*/*trans* isomerisation of the side-chains of the tetrahydrofuran ring. The products of the alkylation reactions were successfully converted into the corresponding esters by using tin oxide derivatives. The relative configurations of the chiral centres were maintained during this process. Cross-metathesis as well as Heck coupling could be successfully applied, introducing lipophilic side-chains in good to excellent yields. The Heck reaction gave slightly better results than the cross-metathesis reaction, forming smaller amounts of side-products.

Experimental Section

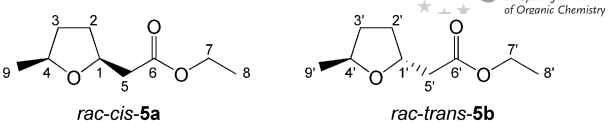
General: All chemicals were used as received unless otherwise noted. Reagent-grade solvents were distilled prior to use. All reported NMR spectra were recorded in $CDCl_3$ (Cambridge Isotope Laboratories) at 298 K either with a Bruker Avance 400 spectrometer at 400 (^{1}H) and 100 MHz (^{13}C) or with a Varian Gemini XL-200 spectrometer at 200 (^{1}H) and 50 MHz (^{13}C). Chemical shifts are reported as δ values relative to TMS, defined as δ = 0.00 ppm (^{1}H) or δ = 0.0 ppm (^{13}C) and are referenced to the residual protonated NMR solvent, defined as δ = 7.264 ppm (^{1}H) or δ = 77.00 ppm (^{13}C). In the case of two isomers, 1,2,3-labelling was applied to the major isomer and 1′,2′,3′-labelling was used to refer to the minor isomer. Infrared spectra were obtained with a Perkin–Elmer Spectrum One version B FT-IR unit by using KBr pressed films or KBr disks. Mass spectra were obtained with a ThermoFinnigan PolarisQ instrument by EI (70 eV) or with a ThermoFinnigan LCQ instrument by ESI or APCI. HRMS were recorded with a Bruker BioAPEX II Daltonics instrument. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh ASTM). TLC analyses were performed on silica gel plates (0.2 mm) 60 F_{254} (Merck). Detection was first achieved by UV light (254 nm) and then by charring with a basic aqueous solution of $KMnO_4$. Prepar-

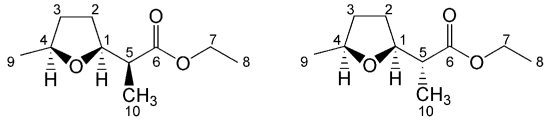
ative thin-layer chromatography was performed on silica gel plates (20 × 20 cm) 60 F_{254} (Merck). Isomeric ratios were determined by gas chromatography (Agilent 6850 Series chromatograph) with a high-resolution gas-chromatograph HP-5 column (30 m × 0.32 mm × 0.25 μm), and the configurations were assigned by comparison of the retention times with reported values. The following temperature programs were employed: (1) 50 °C/3 °C min^{-1}/110 °C (0 min)/20 °C min^{-1}/250 °C; (2) 50 °C/20 °C min^{-1}/140 °C (1 min)/5 °C min^{-1}/250 °C (10 min); (3) 30 °C/20 °C min^{-1}/110 °C (0 min)/10 °C min^{-1}/250 °C. GC–MS analyses were performed with a ThermoFinnigan PolarisQ instrument, equipped with a Trace GC gas chromatograph and a PolarisQ mass spectrometer. The following temperature program was employed: 60 °C (1 min)/10 °C min^{-1}/250 °C (60 min).

General Procedure for Catalytic Hydrogenation

Ethyl 2-(5-Methyltetrahydrofuran-2-yl)acetate (5): Methanol (15 mL) and furan **3** (400 mg, 2.38 mmol) were added to rhodium on activated alumina (50 mg, 0.024 mmol) introduced into a glass hydrogenation bottle under argon. The resulting mixture was hydrogenated in a shaker-type hydrogenation apparatus at room temperature under a pressure of 3.6 atm for 12 h. The reaction mixture was filtered through a mixture of Celite/silica gel (2:1) and washed with Et_2O. Removal of the solvents by rotary evaporation afforded a yellow oil. This product was purified by chromatography on silica gel (hexane/EtOAc, 9:1) to give a colourless oil **5** as a mixture of two isomers in an 85:15 ratio (^{1}H NMR integral estimation, NOESY correlation 1-H,4-H) in 77% overall yield (316 mg, 1.83 mmol). Sometimes traces of ethyl 2-[5-methyldihydrofuran-2(3*H*)-ylidene]acetate (**6**) were observed. Two signal sets were observed in the ^{1}H NMR spectrum (ratio 85:15), which were assigned to the *cis* (major) and *trans* (minor) isomers. The signals of the *trans* isomer are hidden by those of the *cis* isomer in the ^{1}H NMR spectrum; however, they can be assigned in the ^{13}C NMR spectrum. R_f (hexane/EtOAc, 90:10) = 0.40. GC (temp. progr. 1): t_R = 9.08 (*cis*-**5a**, 84%), 9.33 min (*trans*-**5b**, 16%). IR (KBr film): $\tilde{\nu}$ = 2975 (m), 2875 (w), 1736 (vs), 1463 (w), 1447 (w), 1377 (m), 1279 (m), 1300 (m), 1202 (s), 1175 (s), 1086 (s), 1031 (s), 936 (vw), 881 (vw), 853 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.37 (≈quint, $^3J_{H1,H2} = {}^3J_{H1,H5}$ = 6.7 Hz, 1 H, 1′-H), 4.24 (quint, $^3J_{H1,H2} = {}^3J_{H1,H5}$ = 6.7 Hz, 1 H, 1-H), 4.12 (q, $^3J_{H7,H8}$ = 7.1 Hz, 4 H, 7-H, 7′-H), 4.11–4.06 (m, 1 H, 4′-H), 3.93 (≈dquint, $^3J_{H4,H3a\ or}$ 3b-H = 7.5, $^3J_{H4,H3b\ or}$ 3a-H = $^3J_{H4,H9}$ = 6.2 Hz, 1 H, 4-H), 2.62 (dd, $^2J_{H5b,H5a}$ = 15.2, $^3J_{H5b,H1}$ = 6.7 Hz, 1 H, 5b-H), 2.56 (dd, $^2J_{H5b',H5a'}$ = 14.9, $^3J_{H5b',H1'}$ = 7.0 Hz, 1 H, 5a′-H), 2.47 (dd, $^2J_{H5a,H5b}$ = 15.2, $^3J_{H5a,H1}$ = 6.6 Hz, 1 H, 5a-H), 2.41 (dd, $^2J_{H5a',H5b'}$ = 14.9, $^3J_{H5a',H1'}$ = 6.4 Hz, 1 H, 5a′-H), 2.12–1.96 (m, 4 H, 2a-H, 2a′-H, 3a-H, 3a′-H), 1.74–1.55 (m, 2 H, 2b-H, 2b′-H), 1.50–1.38 (m, 2 H, 3b-H, 3b′-H), 1.22 (t, $^3J_{H8,H7} = {}^3J_{H8',H7'}$ = 7.1 Hz, 6 H, 8-H, 8′-H), 1.19 (d, $^3J_{H9,H4}$ = 6.2 Hz, 3 H, 9-H), 1.19 (d, $^3J_{H9',H4'}$ = 6.2 Hz, 3 H, 9′-H) ppm. ***cis*-5a:** ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 171.3 (C-6), 75.6 (C-4), 75.3 (C-1), 60.3 (C-7), 41.2 (C-5), 32.6 (C-3), 31.2 (C-2), 21.4 (C-9), 14.2 (C-8) ppm. ***trans*-5b:** ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 171.3 (C-6′), 74.9 (C-4′), 74.8 (C-1′), 60.3 (C-7′), 41.0 (C-5′), 33.7 (C-3′), 32.0 (C-2′), 21.2 (C-9′), 14.2 (C-8′) ppm. HRMS: calcd. for $[C_9H_{16}O_3Na]^+$ 195.09917; found 195.09973.

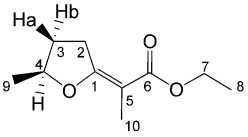
Ethyl 2-(5-Methyltetrahydrofuran-2-yl)propanoate (7): Methanol (30 mL) and furan **4** (1.00 g, 5.49 mmol) were added to rhodium on activated alumina (90 mg, 0.045 mmol) introduced into a glass hydrogenation bottle under argon. The resulting mixture was hydrogenated in a shaker-type hydrogenation apparatus at room temperature under a pressure of 3.9 atm for 16 h. The reaction mixture was filtered through a mixture of Celite/silica gel (2:1) and washed with Et_2O. Removal of the solvents by rotary evaporation afforded colourless oil **7** as a complex mixture of four pairs of enantiomers. The two pairs of *cis*-disubstituted major enantiomers (**7a** and **7b**) were separated in a 60:40 ratio by chromatography in order to be characterised. However, each of them also contained one of two pairs of *trans*-disubstituted minor enantiomers (**7c** and **7d**). When **8** was formed in considerable quantity, a second hydrogenation was carried out. R_f (hexane/EtOAc, 90:10) = 0.14 (*cis* isomer **7a**), 0.21 (*cis* isomer **7b**). GC (temp. progr. 1): t_R = 10.08 (isomer 1, *cis*-**7b**, 37%), 10.33 (isomer 1, *trans*-**7c**, 4%), 10.83 (isomer 2, *cis*-**7a**, 54%), 10.96 min (isomer 2, *trans*-**7d**, 5%). GC (temp. progr. 2): t_R = 5.08 (isomer 1, *cis*-**7b**, 39%), 5.12 (isomer 1, *trans*-**7c**, 4%), 5.24 (isomer 2, *cis*-**7a**, 55%), 5.40 min (isomer 2, *trans*-**7d**, 2%). IR (KBr film): $\tilde{\nu}$ = 2975 (s), 2939 (m), 2875 (m), 1736 (vs), 1631 (vw), 1461 (m), 1377 (s), 1330 (w), 1257 (s), 1179 (s), 1093 (s), 1057 (m), 1024 (w), 950 (w), 906 (w), 862 (vw) cm^{-1}. ***cis*-7a:** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.16 (dq, $^2J_{H7a,H7b}$ = 10.8, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.15 (dq, $^2J_{H7b,H7a}$ = 10.8, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.00 (q, $^3J_{H1,H5} = {}^3J_{H1,H2,obs.}$ ≈ 7.2 Hz, 1 H, 1-H), 3.95 (≈dquint, $^3J_{H4,H3a,obs.}$ = 7.5, $^3J_{H4,H3b,obs.} = {}^3J_{H4,H9}$ ≈ 6.1 Hz, 1 H, 4-H), 2.55 (≈quint, $^3J_{H5,H1} = {}^3J_{H5,H10,obs.}$ ≈ 7.2 Hz, 1 H, 5-H), 2.02–1.86 (m, 2 H, 3a-H, 2a-H), 1.68–1.57 (m, 1 H, 2b-H), 1.45–1.35 (m, 1 H, 3b-H), 1.24 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.18 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.10 (d, $^3J_{H10,H5}$ = 7.2 Hz, 3 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.9 (C-6), 80.3 (C-1), 75.5 (C-4), 60.2 (C-7), 45.2 (C-5), 32.6 (C-3), 28.5 (C-2), 21.2 (C-9), 14.1 (C-8), 13.1 (C-10) ppm. ***cis*-7b:** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.13 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 4.01–3.91 (m, 2 H, 1-H, 4-H), 2.55 (≈quint, $^3J_{H5,H1,obs.} = {}^3J_{H5,H10,obs.}$ ≈ 7.1 Hz, 5-H), 1.99–1.93 (m, 2 H, 3a-H, 2a-H), 1.74–1.65 (m, 1 H, 2b-H), 1.46–1.41 (m, 1 H, 3b-H), 1.24 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.22 (d, $^3J_{H10,H5}$ = 7.0 Hz, 3 H, 10-H), 1.19 (d, $^3J_{H9,H4,obs.}$ = 6.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.7 (C-6), 80.3 (C-1), 75.5 (C-4), 60.2 (C-7), 45.3 (C-5), 32.7 (C-3), 29.3 (C-2), 21.2 (C-9), 14.2 (C-8), 14.0 (C-10) ppm. MS (APCI$^+$): *m*/*z* (%) = 187.0 (100) [M + H]$^+$. HRMS: calcd. for $[C_{10}H_{18}O_3Na]^+$ 209.11481; found 209.11464.





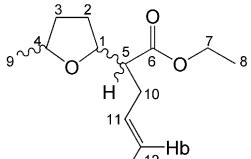
Ethyl (*E*)-2-[5-Methyldihydrofuran-2(3*H*)-ylidene]propanoate (8): The ester **8** was formed as a byproduct according to the procedure given for compound **7**. To isolate this compound, a mixture (470 mg, **7**/**8**, 90:10) of **7** (422 mg, 2.27 mmol) and **8** (48 mg, 0.26 mmol) was dissolved in THF (30 mL) at 20 °C, and then a solution of KOH (472 mg, 8.4 mmol) in distilled water (30 mL) was added portionwise. The reaction mixture was heated at reflux for 16 h with stirring. THF was removed in a rotary evaporator, and the resulting residue was treated with an aqueous 32% solution of HCl (1.17 mL, 10.4 mmol). The reaction mixture was extracted with Et_2O (4 × 30 mL), and the combined organic layers were washed with brine (40 mL), dried with anhydrous $MgSO_4$ and fil-

tered. The solvent was evaporated to give a yellow oil, which was purified by flash chromatography on silica gel (hexane/EtOAc, 90:10 and then EtOAc/MeOH, 95:5) to give the non-saponified ester **8** (29 mg, 0.16 mmol) and the acid **9** (310 mg, 1.96 mmol, 86%). **8:** R_f (hexane/EtOAc, 90:10) = 0.27. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.50 (dquint, $^3J_{H4,H3a}$ = 8.1, $^3J_{H4,H3b}$ = $^3J_{H4,H9}$ = 6.2 Hz, 1 H, 4-H), 4.17 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 3.26 (dddq, $^2J_{H2b,H2a}$ = 18.3, $^3J_{H2b,H3a}$ = 9.0, $^3J_{H2b,H3b}$ = 4.1, $^5J_{H2b,H10}$ = 1.3 Hz, 1 H, 2b-H), 2.94 (≈dtq, $^2J_{H2a,H2b}$ = 18.3, $^3J_{H2a,H3a}$ ≈ $^3J_{H2a,H3b}$ ≈ 9.0, $^5J_{H2a,H10}$ = 1.7 Hz, 1 H, 2a-H), 2.20 (dddd, $^2J_{H3b,H3a}$ = 12.3, $^3J_{H3b,H2a}$ = 9.0, $^3J_{H3b,H4}$ = 8.1, $^3J_{H3b,H2b}$ = 4.1 Hz, 1 H, 3b-H), 1.80 (≈t, $^5J_{H10,H2,obs.}$ = 1.5 Hz, 3 H, 10-H), 1.66 (dtd, $^2J_{H3a,H3b}$ = 12.3, $^3J_{H3a,H2a}$ = $^3J_{H3a,H2b}$ = 9.0, $^3J_{H3a,H4}$ = 8.1 Hz, 1 H, 3a-H), 1.37 (d, $^3J_{H9,H4}$ = 6.2 Hz, 3 H, 9-H), 1.27 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 170.7, 169.9 (C-1, C-6), 97.5 (C-5), 79.9 (C-4), 59.8 (C-7), 32.1 (C-3), 31.9 (C-2), 21.0 (C-9), 14.9 (C-8), 11.7 (C-10) ppm. MS (EI, 70 eV): *m/z* (%) = 185.32 (100) $[M + H]^+$, 84.32 (78) $[M]^+$, 139.30 (58) $[M – H – CO_2]^+$, 138.30 (58) $[M – 46]^+$, 111.30 (27) $[M – H – CO_2Et]^+$, 102.23 (65) $[M – 83]^+$.



rac-**8**

Ethyl 2-(5-Methyltetrahydrofuran-2-yl)pent-4-enoate (11). Method A: At –78 °C, NaHMDS (1 M, 3.8 mL, 3.8 mmol) was added to a cooled mixture of dry THF (7 mL) and DMPU (1 mL) at –75 °C under argon. A solution of **5** (500 mg, 2.9 mmol) in dry THF (5 mL) was added dropwise over a period of 15 min to the resulting mixture at –78 °C. The reaction mixture was stirred for 1.66 h, and then a solution of allyl iodide (2 mL, 21.9 mmol) in dry THF (2 mL) was added dropwise over a period of 10 min. Stirring was continued at –78 °C for 1.5 h, and then the resulting mixture was warmed to –50 °C over a period of 0.5 h and diluted with saturated aqueous NH_4Cl solution (7.5 mL), water (1 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/EtOAc, 90:10) to give compound **11** (340 mg, 1.6 mmol, 55%) as a mixture of two pairs of enantiomers in a ratio of 55:45 ratio. **Method B:** At –115 °C, DMPU (1.2 mL) in dry THF (2 mL) was added to a cooled mixture of dry 2-Me-THF (3 mL) and NaHMDS (1 M, 3.8 mL, 3.8 mmol) at –60 °C under argon. A solution of **5** (500 mg, 2.9 mmol) in a mixture of dry THF (2 mL) and dry 2-Me-THF (1 mL) was added dropwise over a period of 25 min to the resulting mixture at –115 °C. The reaction mixture was stirred for 2 h, and then a solution of allyl iodide (2.65 mL, 29 mmol) was added dropwise over a period of 17 min. Stirring was continued at –115 °C for 1.25 h, and then the resulting mixture was warmed to –40 °C over a period of 0.75 h and diluted with saturated aqueous NH_4Cl solution (7.5 mL), water (1 mL) and Et_2O (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/EtOAc, 90:10) to give compound **11** (227 mg, 1.06 mmol, 38%) as a mixture of two pairs of enantiomers in a ratio of 75:25. R_f (hexane/EtOAc, 90:10) = 0.20. IR (KBr film): $\tilde{\nu}$ = 3079 (vw), 2974 (s), 2935 (m), 2872 (w), 1735 (vs), 1643 (w), 1444 (w), 1376 (m), 1299 (vw), 1268 (w), 1176 (s), 1132 (w), 1093 (s), 1027 (m), 914 (w), 855 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.77 (dddd, $^3J_{H11,H12b}$ = 17.1, $^3J_{H11,H12a}$ = 10.1, $^3J_{H11,H10a,obs.}$ = 7.1, $^3J_{H11,H10b}$ = 6.8 Hz, 1 H, 11-H), 5.76 (m, 1 H, 11′-H), 5.05 (≈dq, $^3J_{H12b,H11}$ = $^3J_{H12b',H11'}$ = 17.1, $^2J_{H12b,H12a}$ = $^2J_{H12b',H12a'}$ = $^3J_{H12b,H10}$ = $^3J_{H12b',H10'}$ = 1.5 Hz, 2 H, 12b-H, 12b′-H), 4.98 (dd, $^3J_{H12a,H11}$ = $^3J_{H12a',H11'}$ = 10.1, $^2J_{H12a,H12b}$ = $^2J_{H12a',H12b',obs.}$ = 1.0 Hz, 2 H, 12a-H, 12a′-H), 4.18 (dq, $^2J_{H7a,H7b}$ = 10.5, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.17 (dq, $^2J_{H7a',H7b'}$ = 10.5, $^3J_{H7a',H8'}$ = 7.1 Hz, 1 H, 7a′-H), 4.15 (m, 1 H, 1′-H), 4.14 (dq, $^2J_{H7b,H7a}$ = 10.5, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.11 (dq, $^2J_{H7b',H7a'}$ = 10.5, $^3J_{H7b',H8'}$ = 7.1 Hz, 1 H, 7b′-H), 4.08 (≈dm, $^3J_{H4',H3a' \text{ or } 3b'\text{-H},obs.}$ = 8.2, $^3J_{H4',H3b' \text{ or } 3a'\text{-H}}$ = $^3J_{H4',H9'}$ = 6.1 Hz, 1 H, 4′-H), 4.01 (≈q, $^3J_{H1,H2a,obs.}$ = $^3J_{H1,H2b,obs.}$ = $^3J_{H1,H5,obs.}$ = 7.3 Hz, 1 H, 1-H), 3.97 (≈dquint, $^3J_{H4,H3a}$ = 7.5, $^3J_{H4,H3b}$ = $^3J_{H4,H9}$ = 6.1 Hz, 1 H, 4-H), 2.49 (ddd, $^3J_{H5,H10a}$ = $^3J_{H5',H10a',obs.}$ = 10.2, $^3J_{H5,H1,obs.}$ = $^3J_{H5',H'1,obs.}$ = 8.0, $^3J_{H5,H10b}$ = $^3J_{H5',H10b',obs.}$ = 4.3 Hz, 2 H, 5-H, 5′-H), 2.38–2.30 (m, 2 H, 10a-H, 10a′-H), 2.28–2.15 (m, 2 H, 10b-H, 10b′-H), 2.08–1.91 (m, 4 H, 2a-H, 2a′-H, 3a-H, 3a′-H), 1.74–1.60 (m, 2 H, 2b-H, 2b′-H), 1.50–1.38 (m, 2 H, 3b-H, 3b′-H), 1.24 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.24 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.19 (d, $^3J_{H9,H4}$ = 6.0 Hz, 3 H, 9-H), 1.18 (d, $^3J_{H9',H4'}$ = 6.1 Hz, 3 H, 9′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 173.6 (C-6, C-6′), 135.1 (C-11, C-11′), 116.6 (C-12, C-12′), 79.7, 79.1 (C-1, C-1′), 75.5, 75.0 (C-4, C-4′), 60.2 (C-7, C-7′), 51.5, 51.3 (C-5, C-5′), 33.6, 33.2 (C-3, C-3′), 33.0, 32.5 (C-10, C-10′), 30.1, 29.1 (C-2, C-2′), 21.3, 21.1 (C-9, C-9′), 14.3 (C-8, C-8′) ppm. MS (ESI$^+$): *m/z* (%) = 213.31 (100) $[M + H]^+$, 171.31 (20) $[M – 41]^+$ = $[M – allyl]^+$, 125.26 (30) $[M – 87]^+$ = $[M – allyl – EtOH]^+$, 85.25 (50) $[M – 125]^+$, 67.23 (42) $[M – 145]^+$. HRMS: calcd. for $[C_{12}H_{22}O_3Na]^+$ 235.13047; found 235.13003.

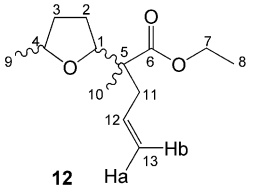


11

Ethyl 2-Methyl-2-(5-methyltetrahydrofuran-2-yl)pent-4-enoate (12). Method A: KHMDS (1.05 g, 5.23 mmol) was added to a cooled mixture of dry THF (7.5 mL), dry 2-Me-THF (7.5 mL) and DMPU (1.5 mL) at –87 °C under argon. A solution of **7** (0.76 g, 4.03 mmol) in a mixture of dry THF (1.5 mL) and dry 2-Me-THF (1.5 mL) was added dropwise to the resulting mixture. The reaction mixture was stirred for 45 min, and then a solution of allyl iodide (1.8 mL, 20.13 mmol) in a mixture of dry THF (1.5 mL) and dry 2-Me-THF (1.5 mL) was added dropwise. Stirring was continued at –87 °C for 45 min, and then the reaction mixture was diluted with a saturated aqueous NH_4Cl solution (15 mL) and Et_2O (30 mL). Water (30 mL) was added at 0 °C to dissolve the salts. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (100 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane and then hexane/Et_2O gradually to 50:50) to give compound **12** (0.19 g, 0.84 mmol, 21%) in the second fraction, compound **14** (0.11 g, 0.49 mmol, 11%) in the third fraction and compound **13** (0.23 g, 1.24 mmol, 30%) in the fourth fraction. Two signal sets were observed in the ^{1}H NMR spectrum (ratio 60:40), which were assigned to the *cis* (major) and *trans* (minor) isomers. The signals of the *trans* isomer are hidden by those of the *cis* isomer in the ^{1}H NMR spectrum.

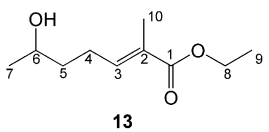
They cannot be unambiguously assigned in the ^{13}C NMR spectrum. R_f (hexane/EtOAc, 90:10) = 0.33. GC (temp. progr. 1): t_R = 17.89 (isomer 2, *cis*-**12**, 62%), 18.09 min (isomer 2, *trans*-**12**, 32%). ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.76–5.65 (m, $^3J_{H12,H11a}$ = $^3J_{H12',H11a',obs.}$ = 7.0, $^3J_{H12,H13b}$ = $^3J_{H12',H13b'}$ = 17.0 Hz, 2 H, 12-H, 12′-H), 5.07–5.01 (m, $^3J_{H13b,H12}$ = $^3J_{H13b',H12'}$ = 17.0 Hz, 4 H, 13b-H, 13b′-H, 13a-H, 13a′-H), 4.25–4.06 (m, $^3J_{H8,H7}$ = $^3J_{H8',H7'}$ = 7.1 Hz, 6 H, 7-H, 7′-H, 1′-H, 4′-H), 4.07 (≈t, $^3J_{H1,H2,obs.}$ ≈ 7.3 Hz, 1 H, 1-H), 3.98 (≈dquint, $^3J_{H4,H9}$ ≈ $^3J_{H4,H3a\ or\ H3b}$ ≈ 6.1, $^3J_{H4,H3b\ or\ H3a,obs.}$ ≈ 7.4 Hz, 1 H, 4-H), 2.53–2.48 (m, $^3J_{H11a,H12,obs.}$ = 7.0 Hz, 1 H, 11a-H), 2.28 (≈dd, $^3J_{H11a',H11b'}$ = 13.4, $^3J_{H11a',H12',obs.}$ = 7.0 Hz, 1 H, 11a′-H), 2.16–2.01 (m, $^3J_{H11b,H11a}$ = 13.4 Hz, 2 H, 11b-H, 11b′-H), 2.00–1.70 (m, 6 H, 3a-H, 3a′-H, 2a-H, 2a′-H, 2b-H, 2b′-H), 1.53–1.41 (m, 1 H, 3b′-H), 1.39–1.33 (m, 1 H, 3b-H), 1.25 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.24 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.19 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.18 (d, $^3J_{H9',H4'}$ = 6.1 Hz, 3 H, 9′-H), 1.11 (s, 3 H, 10-H), 1.10 (s, 3 H, 10′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.4, 175.3 (C-6, C-6′), 133.9 (C-12, C-12′), 117.9 (C-13, C-13′), 83.6, 83.10 (C-1, C-1′), 75.9, 75.3 (C-4, C-4′), 60.4, 60.2 (C-7, C-7′), 50.0, 49.4 (C-5, C-5′), 40.4, 40.1 (C-11, C-11′), 34.0, 32.9 (C-2, C-2′), 27.3, 26.2 (C-3, C-3′), 21.2, 21.0 (C-9, C-9′), 16.4, 16.2 (C-10, C-10′), 14.2 (C-8, C-8′) ppm. GC–MS (EI, 70 eV): t_R = 10.22 min (isomer 2, *cis*-**12**). GC–MS (EI, 70 eV): *m*/*z* (%) = 227.27 (40) $[M + H]^+$, 185.33 (20) $[M - 41]^+$, 139.24 (65) $[M - 87]^+$, 114.24 (20) $[M - 112]^+$, 85.31 (50) $[M - 141]^+$, 67.23 (100) $[M - 159]^+$. GC–MS (EI, 70 eV): t_R = 10.39 min (isomer 2, *trans*-**12**). GC–MS (EI, 70 eV): *m*/*z* (%) = 227.27 (17) $[M + H]^+$, 185.24 (13) $[M - 41]^+$, 139.23 (42) $[M - 87]^+$, 114.23 (20) $[M - 112]^+$, 85.24 (46) $[M - 141]^+$, 67.22 (100) $[M - 159]^+$. HRMS: calcd. for $[C_{13}H_{22}O_3Na]^+$ 249.14611; found 249.14602. HRMS: calcd. for $C_{13}H_{22}O_3$ $[M + H]^+$ 227.16417; found 227.16417. **Method B:** Allyltributyltin (0.39 mL, 1.28 mmol) was added dropwise to a solution of iodo ester **15** (200 mg, 0.64 mmol) in dry hexane (6.5 mL) under argon at 25 °C. After disappearance of a rose colour, AIBN (21 mg, 0.13 mmol) was added, and the reaction mixture was stirred at reflux for 12 h. The resulting mixture was cooled to 25 °C, and a diluted saturated aqueous NaCl solution (30 mL) and Et_2O (30 mL) were added. The layers were separated, the aqueous layer was extracted with Et_2O (30 mL), and the combined organic layers were dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/EtOAc, 90:10) to give the title compound **12** as a mixture of two isomers in a ratio of 55:45 in 66% overall yield (95 mg, 0.42 mmol). Traces of allyltributyltin were observed. R_f (hexane/EtOAc, 90:10) = 0.25. GC (temp. progr. 1): t_R = 17.44 (isomer 1, *cis*-**12a**, 43%), 17.73 min (isomer 1, *trans*-**12c**, 57%). IR (KBr film): $\tilde{\nu}$ = 3077 (w), 2975 (vs), 2932 (s), 2873 (m), 2110 (vw), 1730 (vs), 1641 (w), 1464 (m), 1445 (m), 1383 (m), 1287 (m), 1217 (s), 1144 (s), 1093 (s), 1024 (s), 916 (w), 859 (vw), 668 (vw) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.80–5.70 (m, $^3J_{H12,H13a}$ = $^3J_{H12',H13a'}$ = 10.1, $^3J_{H12,H13b}$ = $^3J_{H12',H13b'}$ = 17.0 Hz, 2 H, 11-H, 11′-H), 5.02 (m, $^3J_{H13b,H12}$ = $^3J_{H13b',H12'}$ = 17.0 Hz, 2 H, 13b-H, 13b′-H), 5.00 (m, $^3J_{H13a,H12}$ = $^3J_{H13a',H12'}$ = 10.0 Hz, 2 H, 13a-H, 13a′-H), 4.13 (≈t, $^3J_{H1',H2'}$ ≈ 6.9 Hz, 1 H, 1′-H), 4.11 (≈q, $^3J_{H7,H8}$ = $^3J_{H7',H8'}$ = 7.1 Hz, 4 H, 7-H, 7′-H), 4.05–3.99 (m, 1 H, 4-H), 4.03 (≈t, $^3J_{H1,H2}$ ≈ 7.2 Hz, 1 H, 1-H), 3.92 (≈dquint, $^3J_{H4',H3a'\ or\ 3b'\text{-}H}$ ≈ 8.0, $^3J_{H4',H9'}$ ≈ $^3J_{H4',H3b'\ or\ 3a'\text{-}H}$ ≈ 6.1 Hz, 1 H, 4′-H), 2.51 (dd, $^3J_{H11b,H12}$ = $^3J_{H11b',H12'}$ = 13.6, $^3J_{H11b,H13a\ or\ H13b}$ = $^3J_{H11b',H13a'\ or\ 13b'\text{-}H}$ = 6.8 Hz, 2 H, 11b-H, 11b′-H), 2.29 (dt, $^3J_{H11a,H12}$ = $^3J_{H11a',H12'}$ = 13.6, $^3J_{H11b,H13}$ = $^3J_{H11b',H13'}$ = 8.3 Hz, 2 H, 11a-H, 11a′-H), 2.00–1.71 (m, 5 H, 3b-H, 3b′-H, 2b-H, 2b′-H, 2a-H), 1.69–1.59 (m, 1 H, 2a′-H), 1.49–1.39 (m, 1 H, 3a-H), 1.38–1.26 (m, 1 H, 3a′-H), 1.23 (t, $^3J_{H8,H7}$ = $^3J_{H8',H7'}$ = 7.1 Hz, 6 H, 8-H, 8′-H), 1.18 (d, $^3J_{H9,H4,obs.}$ = $^3J_{H9',H4'}$ = 6.1 Hz, 6 H, 9-H, 9′-H), 1.08 (s, 6 H, 10-H, 10′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.4, 175.5 (C-6, C-6′), 134.6 (C-12, C-12′), 118.1 (C-13, C-13′), 80.2, 80.3 (C-1, C-1′), 76.5, 75.8 (C-4, C-4′), 60.7 (C-7, C-7′), 50.2 (C-5, C-5′), 42.4, 42.1 (C-11, C-11′), 33.6, 34.4 (C-3, C-3′), 28.1, 27.5 (C-2, C-2′), 21.5, 21.2 (C-9, C-9′), 16.2, 16.1 (C-10, C-10′), 14.7 (C-8, C-8′) ppm. MS (ESI^+): *m*/*z* (%) = 227.32 (100) $[M + H]^+$. **Method C. From Thione Esters. Procedure 1:** *m*-CPBA (70%, 130 mg, 0.76 mmol) was added portionwise to a solution of thione ester **21** (**21a**/**21b**, 87:13, 140.4 mg, 0.58 mmol) in dry CH_2Cl_2 (9 mL) under argon. The resulting mixture was stirred at room temperature for 22 h and then treated with a saturated aqueous $NaHCO_3$ solution (10 mL). Stirring was continued for 15 min, the layers were separated, and the organic layer was washed with brine (10 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane and then hexane/EtOAc, 97:3) to give the title compound **12** as a yellow oil (37.7 mg, 0.167 mmol, 29%). **Procedure 2:** Under argon, a mixture of thione ester **21** (**21a**/**21b**, 87:13, 200 mg, 0.82 mmol) and bis(tri-*n*-butyltin) oxide (566 mg, 0.95 mmol) in dioxane (10 mL) was heated under reflux with stirring for 8.5 h. The progress of the reaction was monitored by TLC. Further bis(tri-*n*-butyltin) oxide (0.43 mL, 0.84 mmol) and dioxane (2 mL) were added, and the resulting mixture was heated at reflux for 16 h. Additional bis(tri-*n*-butyltin) oxide (0.43 mL, 0.84 mmol) and dioxane (2 mL) were then added, and the mixture was heated under reflux for 24 h until total conversion. The crude product was purified by chromatography on silica gel (hexane and then hexane/EtOAc, 95:5) to give the title compound **12** as a yellow oil and as a mixture of two isomers in 66% overall yield (*cis*/*trans*, 90:10, 132 mg, 0.58 mmol). Traces of bis(tri-*n*-butyltin) were observed by NMR spectroscopy. **Procedure 3:** Under argon, a mixture of thione ester **21** (**21a**/**21b**, 87:13, 288 mg, 1.19 mmol) and di-*n*-butyltin oxide (470 mg, 1.9 mmol) in dioxane (6 mL) was heated under reflux with stirring for 29 h. The progress of the reaction was monitored by TLC. Then further di-*n*-butyltin oxide (200 mg, 0.80 mmol) and dioxane (2 mL) were added, and the resulting mixture was heated at reflux for another 27 h. The conversion being about 60% (^1H NMR), the reaction mixture was heated at reflux for a further 92 h (77% conversion). The mixture was filtered through a mixture of Celite/silica gel (30:70) and washed with dioxane. The solvent was removed in vacuo and the residue taken up in dioxane (6 mL) under argon. Di-*n*-butyltin oxide (300 mg, 1.2 mmol) was then added, and the resulting mixture was heated under reflux for 48 h until total conversion. The crude product was purified by chromatography on silica gel (from hexane gradually to hexane/EtOAc, 90:10) to give the title compound **12** as a yellow oil (130 mg, 57 mmol, 48%). R_f (hexane/EtOAc, 90:10) = 0.40 (isomer 1, *cis*-**12a**), 0.30 (isomer 1, *trans*-**12c**). GC (temp. progr. 2): t_R = 7.00 min (isomer 1, *cis*-**12a**, 90%), 7.07 min (isomer 1, *trans*-**12c**, 10%). IR (KBr film): $\tilde{\nu}$ = 3078 (vw), 2975 (vs), 2931 (s), 2873 (m), 1732 (vs), 1641 (w), 1464 (m), 1379 (m), 1291 (m), 1218 (s), 1143 (s), 1093 (vs), 1058 (m), 1022 (s), 916 (m), 859 (vw), 662 (vw) cm^{-1}. ***cis*-12a:** ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.71 (dddd, $^3J_{H12,H13b}$ = 17.0, $^3J_{H12,H13a}$ = 10.1, $^3J_{H12,H11b}$ = 8.0, $^3J_{H12,H11a}$ = 6.8 Hz, 1 H, 12-H), 5.04 (ddt, $^3J_{H13b,H12}$ = 17.0, $^2J_{H13b,H13a}$ = 2.3, $^4J_{H13b,H11b\ and\ H11a,obs.}$ ≈ 1.3 Hz, 1 H, 13b-H), 5.02 (ddt, $^3J_{H13a,H12}$ = 10.1, $^2J_{H13a,H13b}$ = 2.3, $^4J_{H13a,H11b\ and\ H11a}$ = 1.0 Hz, 1 H, 13a-H), 4.13 (dq, $^2J_{H7a,H7b}$ = 10.8, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.10 (dq, $^2J_{H7b,H7a}$ = 10.8, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.04 (≈dd, $^3J_{H1,H2a}$ = 7.1, $^3J_{H1,H2b}$ = 7.5 Hz, 1 H, 1-H), 3.94 (dquint, $^3J_{H4,H3a}$ = 7.8, $^3J_{H4,H9}$ = $^3J_{H4,H3b}$ = 6.0 Hz, 1 H, 4-H),

2.52 (m, $^2J_{H11a,H11b}$ = 13.6, $^3J_{H11a,H12}$ = 6.8 Hz, 1 H, 11a-H), 2.28 (≈ddt, $^2J_{H11b,H11a}$ = 13.6, $^3J_{H11b,H12}$ = 8.0, $^4J_{H11b,H13a\ and\ H13b}$ = 1.0 Hz, 1 H, 11b-H), 1.92 (dddd, $^2J_{H3b,H3a}$ = 11.6, $^3J_{H3b,H2b}$ = 8.4, $^3J_{H3b,H4}$ = 6.0, $^3J_{H3b,H2a}$ = 5.0 Hz, 1 H, 3b-H), 1.83 (≈ddt, $^2J_{H2b,H2a}$ = 12.3, $^3J_{H2b,H3b}$ = 8.4, $^3J_{H2b,H1}$ ≈ $^3J_{H2b,H3a}$ ≈ 7.8 Hz, 1 H, 2b-H), 1.72 (dddd, $^2J_{H2a,H2b}$ = 12.3, $^3J_{H2a,H3a}$ = 9.3, $^3J_{H2a,H1}$ = 7.1 Hz, $^3J_{H2a,H3b}$ = 5.0 Hz, 1 H, 2a-H), 1.33 (≈ddt, $^2J_{H3a,H3b}$ = 11.6, $^3J_{H3a,H2a}$ = 9.3 Hz, $^3J_{H3a,H4}$ ≈ $^3J_{H3a,H2b}$ ≈ 7.8 Hz, 1 H, 3a-H), 1.23 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.20 (d, $^3J_{H9,H4}$ = 6.0 Hz, 3 H, 9-H), 1.09 (s, 3 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.1 (C-6), 134.2 (C-12), 117.7 (C-13), 82.9 (C-1), 75.4 (C-4), 60.3 (C-7), 49.8 (C-5), 41.7 (C-11), 33.2 (C-3), 27.1 (C-2), 20.7 (C-9), 15.8 (C-10), 14.3 (C-8) ppm. MS (APCI$^+$): *m*/*z* (%) = 228.0 (16) [M + 2 H]$^+$, 226.90 (100) [M + H]$^+$, 181.00 (9) [M – OEt]$^+$, 153.10 (10).



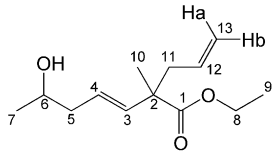
12

Ethyl (*E*)-6-Hydroxy-2-methylhept-2-enoate (13): LiHMDS (2.6 mmol, 2.6 mL) was added to dry THF (2 mL) at –55 °C under argon. A solution of ester **7** (250 mg, 1.34 mmol) in dry THF (2 mL) was then added dropwise over 10 min. Stirring was continued at –55 °C for 4 h, and then the reaction mixture was diluted portionwise with a 2 M aqueous HCl solution (3.35 mL) and then with Et_2O (20 mL). The mixture was allowed to reach room temperature. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (25 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvents were evaporated, and the residue was purified by chromatography on silica gel (hexane/EtOAc gradually from 90:10 and to 75:25) to give the alcohol **13** as a colourless oil (0.96 mg, 5.15 mmol, 39%). R_f (hexane/EtOAc, 75:25) = 0.21. GC (temp. progr. 1): t_R = 18.40 min (100%). IR (KBr film): $\tilde{\nu}$ = 3436 (br), 2969 (m), 2930 (m), 1710 (vs), 1648 (w), 1448 (w), 1369 (m), 1271 (vs), 1193 (m), 1138 (s), 1096 (m), 1030 (w), 974 (vw), 936 (vw), 869 (vw), 746 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 6.75 (tq, $^3J_{H3,H4,obs.}$ = 7.5, $^4J_{H3,H10}$ ≈ 1.2 Hz, 1 H, 3-H), 4.17 (q, $^3J_{H8,H9}$ = 7.1 Hz, 2 H, 8-H), 3.81 (≈sext, $^3J_{H6,H7}$ ≈ $^3J_{H6,H5}$ ≈ 6.1 Hz, 1 H, 6-H), 2.32–2.21 (m, $^3J_{H4,H3}$ = 7.5 Hz, 2 H, 4-H), 1.83 (≈d, $^4J_{H10,H3}$ ≈ 1.2 Hz, 3 H, 10-H), 1.62–1.57 (m, $^3J_{H5,H6}$ = 6.1 Hz, 3 H, 5-H, OH), 1.28 (t, $^3J_{H9,H8}$ = 7.1 Hz, 3 H, 9-H), 1.20 (d, $^3J_{H7,H6}$ = 6.1 Hz, 3 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 167.6 (C-1), 142.0 (C-3), 128.5 (C-2), 67.8 (C-6), 60.0 (C-8), 38.2 (C-5), 25.4 (C-4), 24.0 (C-7), 14.7 (C-9), 12.7 (C-10) ppm. MS (EI, 70 eV): *m*/*z* (%) = 188.22 (11) [M + 2 H]$^+$, 187.19 (100) [M + H]$^+$, 141.34 (15) [M – OEt]$^+$, 95.38 (21). HRMS: calcd. for $[C_{10}H_{18}O_3Na]^+$ 209.11481; found 209.11447.



13

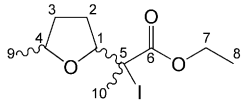
Ethyl (*E*)-2-Allyl-6-hydroxy-2-methylhept-3-enoate (14): The acrylate **14** was obtained as a mixture of two isomers in a ratio of 65:35 in 11% overall yield (0.11 g, 0.49 mmol) according to the procedure given for compound **12** (Method A). R_f (hexane/EtOAc, 75:25) = 0.33. IR (KBr film): $\tilde{\nu}$ = 3427 (br), 3079 (vw), 2978 (s), 2933 (m), 1729 (vs), 1641 (w), 1457 (m), 1378 (m), 1285 (m), 1230 (s), 1180 (m), 1143 (s), 1118 (s), 1077 (m), 1023 (m), 995 (w), 976 (m), 918 (w), 863 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.72–5.68 (m, 2 H, 12-H, 12′-H), 5.69 (≈dt, $^3J_{H3,H4}$ = $^3J_{H3',H4'}$ = 15.8, $^3J_{H3,H5}$ = $^3J_{H3',H5'}$ = 1.2 Hz, 2 H, 3-H, 3′-H), 5.52–5.45 (m, 1 H, 4′-H), 5.49 (dt, $^3J_{H4,H3}$ = 15.8 Hz, 1 H, 4-H), 5.06–5.02 (m, 4 H, 13-H, 13′-H), 4.12 (q, $^3J_{H8,H9}$ = $^3J_{H8',H9'}$ = 7.1 Hz, 4 H, 8-H, 8′-H), 3.79 (≈dquint, $^3J_{H6',H5',obs.}$ = 7.5, $^3J_{H6',H7'}$ = $^3J_{H6',H5'}$ = 6.2 Hz, 1 H, 6′-H), 3.79 (≈dquint, $^3J_{H6,H5,obs.}$ = 7.5, $^3J_{H6,H7}$ = $^3J_{H6,H5}$ = 6.1 Hz, 1 H, 6-H), 2.45 (br. dt, $^2J_{H11b,H11a,obs.}$ = $^2J_{H11b',H11a',obs.}$ = 14.3, $^3J_{H11b,H12,obs.}$ = $^3J_{H11b',H12',obs.}$ = 7.0 Hz, 2 H, 11b-H, 11b′-H), 2.34 (≈ddt, $^2J_{H11a,H11b,obs.}$ = $^2J_{H11a',H11b',obs.}$ = 13.7, $^3J_{H11a,H12,obs.}$ = $^3J_{H11a',H12',obs.}$ = 7.2, $^4J_{H11a,H13,obs.}$ = $^4J_{H11a',H13',obs.}$ = 1.2 Hz, 2 H, 11a-H, 11a′-H), 2.27–2.20 (m, $^2J_{H5b,H5a}$ = $^2J_{H5b',H5a'}$ = 13.6 Hz, 2 H, 5b-H, 5b′-H), 2.13 (dtd, $^2J_{H5a,H5b}$ = $^2J_{H5a',H5b'}$ = 13.6, $^3J_{H5a,H6}$ = $^3J_{H5a',H6'}$ = $^3J_{H5a,H4}$ = $^3J_{H5a',H4'}$ = 7.5, $^4J_{H5a,H3}$ = $^4J_{H5a',H3'}$ = 1.0 Hz, 2 H, 5a-H, 5a′-H), 1.89 (br., 2 H, OH), 1.26 (s, 6 H, 10-H, 10′-H), 1.23 (t, $^3J_{H9,H8}$ = $^3J_{H9',H8'}$ = 7.1 Hz, 6 H, 9-H, 9′-H), 1.17 (d, $^3J_{H7,H6}$ = 6.2 Hz, 3 H, 7-H), 1.16 (d, $^3J_{H7',H6'}$ = 6.20 Hz, 3 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.5 (C-1, C-1′), 136.9 (C-3, C-3′), 133.9, 133.8 (C-12, C-12′), 125.6, 125.5 (C-4, C-4′), 118.2 (C-13, C-13′), 69.9, 66.9 (C-6, C-6′), 60.7 (C-8, C-8′), 47.7 (C-2, C-2′), 43.5, 43.4 (C-11, C-11′), 42.4 (C-5, C-5′), 22.5 (C-7, C-7′), 21.1, 21.0 (C-10, C-10′), 14.1 (C-9, C-9′) ppm. MS (APCI$^+$): *m*/*z* (%) = 228.0 (14) [M + 2]$^+$, 226.9 (100) [M + H]$^+$, 275.0 (32) [M – 1]$^+$, 210.1 (12) [M – 16]$^+$, 209.1 (86) [M – 17]$^+$, 156.9 (12) [M – 69]$^+$. HRMS: calcd. for $[C_{13}H_{22}O_3Na]^+$ 249.1461; found 249.14611.



14

Ethyl 2-Iodo-2-(5-methyltetrahydrofuran-2-yl)propanoate (15): NIS (0.62 g, 2.78 mmol) was added to a solution of acrylate **13** (0.41 g, 2.22 mmol) in dry CH_2Cl_2 (12 mL) under argon. The reaction mixture was stirred at room temperature for 4 h, and then more NIS (0.25 g, 1.11 mmol) was added. The resulting mixture was stirred in the dark at 30 °C for 16 h, and then the reaction mixture was diluted with a saturated aqueous $Na_2S_2O_3$ solution (20 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (50 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane and then hexane/EtOAc, 90:10) to give the title compound **15** as a mixture of two isomers in a ratio of 55:45 and in 74% overall yield (0.51 g, 1.63 mmol). R_f (hexane/EtOAc, 90:10) = 0.42. IR (KBr film): $\tilde{\nu}$ = 2975 (m), 2931 (w), 2871 (w), 2110 (vw), 1730 (vs), 1446 (m), 1377 (w), 1330 (vw), 1297 (w), 1252 (s), 1196 (w), 1128 (m), 1085 (s), 1049 (m), 1024 (m), 970 (vw), 898 (vw), 873 (vw), 862 (vw), 588 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.49 (dd, $^3J_{H1,H2a}$ = 7.1, $^3J_{H1,H2b}$ = 8.0 Hz, 1 H, 1-H), 4.37 (dd, $^3J_{H1',H2a'}$ = 5.8, $^3J_{H1',H2b'}$ = 8.0 Hz, 1 H, 1′-H), 4.28–4.15 (m, $^3J_{H4,H9}$ = 6.1 Hz, 1 H, 4-H), 4.24 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 4.23 (q, $^3J_{H7',H8'}$ = 7.1 Hz, 2 H, 7′-H), 4.11–4.06 (m, $^3J_{H4',H9'}$ = 6.0 Hz, 1 H, 4′-H), 2.36–2.29 (m, $^3J_{H2a,H1}$ = 7.1 Hz, 1 H, 2a-H), 2.24–2.19 (m, $^3J_{H2a',H1'}$ = 5.8 Hz, 1 H, 2a′-H), 2.10–1.92 (m, $^3J_{H2b,H1}$ = $^3J_{H2b',H1'}$ = 8.0 Hz, 4 H, 2b-H, 2b′-H, 3a′-H, 3a-H), 2.03 (s, 1 H, 10-H), 2.01 (s, 1 H, 10′-H), 1.60–1.42 (m, 2 H, 3b-H, 3b′-H), 1.29 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.28 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.20 (d, $^3J_{H9',H4'}$ = 6.0 Hz, 3 H, 9′-H), 1.18 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ =

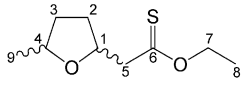
172.1, 172.0 (C-6, C-6′), 83.4, 83.0 (C-1′, C-1), 77.8, 77.7 (C-4, C-4′), 61.9 (C-7, C-7′), 44.8, 44.1 (C-5,C-5′), 34.5, 33.1 (C-3, C-3′), 31.0, 30.4 (C-2, C-2′), 24.5, 24.2 (C-10, C-10′), 21.2, 20.7 (C-9, C-9′), 13.6 (C-8, C-8′) ppm.



15

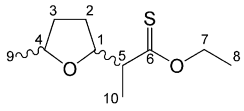
Thionation of Esters

***O*-Ethyl 2-(5-Methyltetrahydrofuran-2-yl)thioacetate (17):** Under argon, P_4S_{10} (3.92 g, 8.8 mmol) and HMDO (19 mL, 88.2 mmol) were dissolved in dry toluene at 100 °C. The reaction mixture was stirred for 10 min and then heated at reflux. Ester **5** (5.0 g, 29 mmol) was added dropwise, and the resulting mixture was heated at reflux for 16 h. After being cooled to 0 °C, the reaction mixture was treated with an aqueous 5% $NaHCO_3$ solution (20 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (200 mL), and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. Toluene was removed by vacuum distillation at 20 Torr, and the residue was purified by chromatography on silica gel (hexane and then hexane/Et_2O, 90:10) to give the thione ester **17** as a mixture of two isomers in a ratio of 85:15 and in 42% overall yield (2.3 g, 12.16 mmol). Two signal sets were observed in the ^1H NMR spectrum, which were assigned to the *cis* (major) and *trans* (minor) isomers. R_f (hexane/EtOAc, 95:5) = 0.31. IR (KBr film): $\tilde{\nu}$ = 2970 (vs), 2871 (s), 2873 (m), 1445 (m), 1372 (m), 1372 (s), 1300 (vs), 1260 (vs), 1201 (vs), 1170 (s), 1091 (vs), 1020 (s), 923 (w), 911 (w), 879 (vw), 810 (vw) cm^{-1}. ***cis*-17**: ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.51 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 4.37 (quint, $^3J_{H1,H2,obs.} = {}^3J_{H1,H5,obs.}$ = 6.6 Hz, 1 H, 1-H), 4.00 (dquint, $^3J_{H4,H3b,obs.}$ = 7.6, $^3J_{H4,H9} = {}^3J_{H4,H3a,obs.}$ = 6.1 Hz, 1 H, 4-H), 3.07 (dd, $^2J_{H5a,H5b}$ = 14.1, $^3J_{H5a,H1}$ = 6.5 Hz, 1 H, 5a-H), 2.85 (dd, $^2J_{H5b,H5a}$ = 14.1, $^3J_{H5b,H1}$ = 6.8 Hz, 1 H, 5b-H), 2.10–1.95 (m, 2 H, 3b-H, 2a-H), 1.73–1.65 (m, 1 H, 2b-H), 1.54–1.45 (m, 1 H, 3a-H), 1.41 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.24 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 220.7 (C-6), 76.1 (C-1), 75.3 (C-4), 68.6 (C-7), 54.0 (C-5), 33.0 (C-3), 31.3 (C-2), 21.9 (C-9), 14.0 (C-8) ppm. MS (APCI$^+$): *m*/*z* (%) = 188.9 (100) [M + H]$^+$. HRMS: calcd. for $[C_9H_{16}O_2SNa]^+$ 211.07687; found 211.07637.



17

***O*-Ethyl 2-(5-Methyltetrahydrofuran-2-yl)propanethioate (18):** According to the procedure reported for compound **17** (Method B), HMDO (1.7 mL, 8.1 mmol), P_4S_{10} (0.36 g, 0.81 mmol), and ester **7** (0.5 g, 2.7 mmol) reacted to give two isomers of **18** in 30% overall yield after chromatography on silica gel (hexane/Et_2O, 90:10). R_f (hexane/EtOAc, 90:10) = 0.30 (*cis* isomer 1, **18b**), 0.25 (*cis* isomer 2, **18a**). Four pairs of enantiomers were observed. GC (temp. progr. 2): t_R = 6.41 (isomer 1, *cis*-**18b**, 36%), 6.48 (isomer 1, *trans*-**18c**, 4%), 6.58 (isomer 2, *cis*-**18a**, 58%), 6.85 (isomer 2, *trans*-**18d**, 2%). ***cis*-18b:** 80 mg, 0.40 mmol, 15%. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.51 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 4.00–3.95 (m, $^3J_{H1,H5}$ = 8.6 Hz, 2 H, H^1, 4-H), 2.90 (dq, $^3J_{H5,H1}$ = 8.6, $^3J_{H5,H10}$ = 6.8 Hz, 1 H, 5-H), 1.99–1.88 (m, 2 H, 3a-H, 2a-H), 1.72–1.65 (m, 1 H, 2b-H), 1.47–1.40 (m, 1 H, 3b-H), 1.39 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.34 (d, $^3J_{H10,H5}$ = 6.8 Hz, 3 H, 10-H), 1.22 (d, $^3J_{H9,H4,obs.}$ = 6.1 Hz, 3 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 225.8 (C-6), 82.3 (C-1), 75.6 (C-4), 67.8 (C-7), 56.7 (C-5), 32.7 (C-3), 29.5 (C-2), 21.4 (C-9), 18.0 (C-10), 13.5 (C-8) ppm. MS (EI, 70 eV): *m*/*z* (%) = 203.11 (7) [M + H]$^+$, 173.14 (4) [M – Et]$^+$, 169.14 (19), 156.02 (51) [M – EtOH]$^+$, 141.08 (14), 117.06 (30), 99.09 (98), 98.09 (82), 85.12 (66), 83.12 (14), 67.11 (100), 57.15 (69). ***cis*-18a:** 80 mg, 0.40 mmol, 15%. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.55 (dq, $^2J_{H7a,H7b}$ = 11.0, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.51 (dq, $^2J_{H7b,H7a}$ = 11.0, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.11 (≈dt, $^3J_{H1,H5}$ = 8.0, $^3J_{H1,H2a/H2b}$ = 6.8 Hz, 1 H, 1-H), 3.98 (≈dquint, $^3J_{H4,H3a\ or\ H3b,obs.}$ = 7.3, $^3J_{H4,H3b\ or\ H3a,obs.} = {}^3J_{H4,H9}$ = 6.1 Hz, 1 H, 4-H), 2.93 (dq, $^3J_{H5,H1}$ = 8.0, $^3J_{H5,H10}$ = 6.9 Hz, 1 H, 5-H), 2.03–1.89 (m, 2 H, 3a-H, 2a-H), 1.73–1.64 (m, $^3J_{H2a,H1}$ = 6.8 Hz, 1 H, 2b-H), 1.47–1.38 (m, 1 H, 3b-H), 1.39 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.19 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.16 (d, $^3J_{H10,H5}$ = 6.9 Hz, 3 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 226.5 (C-6), 82.5 (C-1), 75.5 (C-4), 67.9 (C-7), 55.9 (C-5), 32.6 (C-3), 28.7 (C-2), 21.4 (C-9), 16.6 (C-10), 13.5 (C-8) ppm. MS (EI, 70 eV): *m*/*z* (%) = 204.15 (8) [M + 2 H]$^+$, 203.06 (69) [M + H]$^+$, 202.03 (13) [M]$^+$, 173.14 (6) [M – Et]$^+$, 169.12 (28), 156.02 (76) [M – EtOH]$^+$, 141.13 (16), 117.06 (27), 99.09 (100), 98.09 (60), 85.13 (89), 83.10 (16), 67.12 (94), 57.09 (69). HRMS: calcd. for $[C_{10}H_{18}O_2SNa]^+$ 225.09252; found 225.09254.

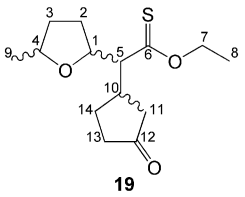


18

Alkylation of Thione Esters

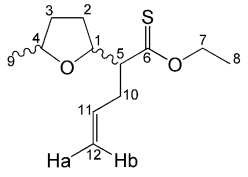
***O*-Ethyl 2-(5-Methyltetrahydrofuran-2-yl)-2-(3-oxocyclopentyl)-thioacetate (19):** *n*BuLi (1.6 M in hexane, 0.8 mL, 1.29 mmol) was added dropwise to a solution of diisopropylamine (0.21 mL, 1.49 mmol) in dry THF (3 mL) under argon at 0 °C. The mixture was stirred for 30 min and then cooled to –78 °C, and a solution of thione ester **17** (200 mg, 1.06 mmol, 2,5-*cis*/2,5-*trans*, 90:10) in dry THF (3 mL) was added dropwise. Stirring was continued at –78 °C for 20 min, and then a solution of cyclopentenone (0.13 mL, 1.59 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was allowed to reach –40 °C, stirred at this temperature for 1 h and then treated with saturated aqueous NH_4Cl solution (10 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/Et_2O, 90:10) to give the title compound **19** as a yellow oil and as a mixture of two enantiomers in a ratio of 75:25 and in 52% overall yield (150 mg, 55 mmol). R_f (hexane/EtOAc, 75:25) = 0.27. IR (KBr film): $\tilde{\nu}$ = 2969 (s), 2934 (w), 2873 (w), 1744 (vs), 1459 (vw), 1402 (vw), 1372 (w), 1314 (m), 1292 (m), 1228 (m), 1192 (m), 1162 (s), 1088 (m), 1017 (w), 894 (vw) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 4.50 (dq, $^2J_{H7a',H7b'}$ = 12.1, $^3J_{H7a',H8'}$ = 7.1 Hz, 1 H, 7a′-H), 4.48 (dq, $^2J_{H7b',H7a'}$ = 12.1, $^3J_{H7b',H8'}$ = 7.1 Hz, 1 H, 7b′-H), 4.47 (dq, $^2J_{H7a,H7b}$ = 12.1, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.47 (dq, $^2J_{H7b,H7a}$ = 12.1, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.29 (ddd, $^3J_{H1',H5'}$ = 9.2, $^3J_{H1',H2a'}$ = 7.4, $^3J_{H1',H2b'}$ = 6.3 Hz, 1 H, 1′-H), 4.13 (≈dt, $^3J_{H1,H5}$ = 9.0, $^3J_{H1,H2} \approx$ 7.8 Hz, 1 H, 1-H), 4.08–3.93 (m, $^3J_{H9,H4} = {}^3J_{H9',H4'}$ = 6.1 Hz, 2 H, 4-H, 4′-H), 2.79–2.58 (m, 2 H, 10-H, 10′-H), 2.38–2.23 (m, 6 H, 14a-H, 13a-H, 11a-H, 14a′-H, 13a′-H, 11a′-H), 2.22–2.18 (m, 4 H, 13b-H, 11b-H, 13b′-H, 11b′-

H), 2.02–1.88 (m, 4 H, 2a-H, 3a-H, 2a′-H, 3a′-H), 1.78–1.67 (m, 4 H, 2b-H, 14b-H, 2b′-H, 14b′-H), 1.48–1.38 (m, 2 H, 3b-H, 3b′-H), 1.37 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.37 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.19 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.17 (d, $^3J_{H9',H4'}$ = 6.1 Hz, 3 H, 9′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 221.9, 218.6 (C-12, C-6), 222.1, 218.6 (C-12′, C-6′), 80.6 (C-1), 80.3 (C-1′), 75.8 (C-4), 75.1 (C-4′), 67.8 (C-7), 66.7 (C-7′), 65.8 (C-5), 65.4 (C-5′), 44.5 (C11′), 42.4 (C-11), 40.2 (C10′), 40.1 (C-10), 38.8 (C-13), 38.0 (C-13′), 33.2 (C-3′), 32.3 (C-3), 29.7 (C-2), 28.3 (C-2′), 28.2 (C-14), 27.2 (C-14′), 21.4 (C-9), 21.1 (C-9′), 13.5 (C-8, C-8′) ppm.



19

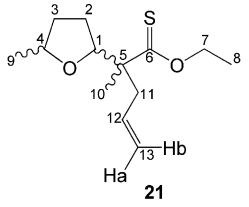
***O*-Ethyl 2-(5-Methyltetrahydrofuran-2-yl)pent-4-enethioate (20):** A solution of *t*BuOK (155 mg, 1.38 mmol) in dry THF (2 mL) was added dropwise to a solution of thione ester **17** (0.2 g, 1.06 mmol) in dry THF (4 mL) under argon at –78 °C. The reaction mixture was stirred at –78 °C for 15 min and then warmed and stirred at –10 °C for 6 min. Stirring was continued at –78 °C for 10 min, and then allyl iodide (0.13 mL, 1.38 mmol) was added dropwise. The resulting mixture was allowed to reach –10 °C and then treated with a saturated aqueous NH_4Cl solution (10 mL) and Et_2O (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/Et_2O gradually) to give the title compound **20** as a yellow oil in two fractions in 56% overall yield (141 mg, 0.62 mmol). The first fraction proved to be a mixture of two pairs of major enantiomers in a ratio of 70:30 (120 mg, 0.53 mmol, 50%). The second fraction was found to be a complex mixture of four pairs of enantiomers and purified once more to afford two pairs of major enantiomers (14 mg, 0.06 mmol, 6%) and two pairs of minor enantiomers in a ratio of 65:35 (7 mg, 0.03 mmol, 3%). Two pairs of major enantiomers (70:30 ratio, 56%): R_f (hexane/EtOAc, 90:10) = 0.47. IR (KBr film): $\tilde{\nu}$ = 3076 (vw), 2974 (vs), 2870 (m), 1639 (v; traces of ester), 1444 (m), 1386 (m), 1292 (m), 1251 (vs), 1193 (s), 1165 (s), 1145 (w), 1092 (vs), 1017 (s), 973 (vw), 915 (m), 860 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.84–5.74 (m, $^3J_{H11,H12b}$ = $^3J_{H11',H12b'}$ = 17.0, $^3J_{H11,H12a}$ = $^3J_{H11',H12a'}$ = 10.2 Hz, 2 H, 11-H, 11′-H), 5.00 (≈dq, $^3J_{H12b,H11}$ = $^3J_{H12b',H11'}$ = 17.0, $^3J_{H12b,H12a}$ = $^3J_{H12b',H12a'}$ ≈ $^3J_{H12b,H10}$ = $^3J_{H12b',H10b',obs.}$ ≈ 1.5 Hz, 2 H, 12b-H, 12b′-H), 4.94 (dd, $^3J_{H12a,H11}$ = $^3J_{H12a',H11'}$ = 10.2, $^2J_{H12a,H12b}$ = $^2J_{H12a',H12b',obs.}$ ≈ 1.0 Hz, 2 H, 12a-H, 12a′-H), 4.50 (q, $^3J_{H7,H8}$ = $^3J_{H7',H8'}$ = 7.1 Hz, 4 H, 7-H, 7′-H), 4.14 (dt, $^3J_{H1',H5'}$ = 9.0, $^3J_{H1',H2',obs.}$ = 6.7 Hz, 1 H, 1′-H), 4.03 (dt, $^3J_{H1,H5}$ = 8.2, $^3J_{H1,H2,obs.}$ = 6.0 Hz, 1 H, 1-H), 4.04–3.94 (m, $J_{obs.}$ = 6.1 Hz, 2 H, 4′-H, 4-H), 2.94–2.86 (m, 2 H, 5-H, 5′-H), 2.72–2.66 (m, 2 H, 3a-H, 3a′-H), 2.54–2.46 (m, 2 H, 3b-H, 3b′-H), 2.04–1.83 (m, 4 H, 2a-H, 2a′-H, 10a-H, 10a′-H), 1.75–1.62 (m, 2 H, 10b-H, 10b′-H), 1.48–1.39 (m, 2 H, 2b-H, 2b′-H), 1.37 (t, $^3J_{H8,H7}$ = $^3J_{H8',H7'}$ = 7.1 Hz, 6 H, 8-H, 8′-H), 1.21 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.20 (d, $^3J_{H9',H4'}$ = 6.1 Hz, 3 H, 9′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 223.5, 223.5 (C-6, C-6′), 135.5 (C-11, C-11′), 116.2, 116.1 (C-12, C-12′), 81.3, 81.1 (C-1, C-1′), 75.7, 75.0 (C-4, C-4′), 67.6 (C-7, C-7′), 62.3, 62.0 (C-5, C-5′), 37.1, 37.0 (C-3, C-3′), 33.4, 32.6 (C-2, C-2′), 30.2, 29.4 (C-10, C-10′), 21.5, 21.1 (C-9, C-9′), 13.6 (C-8, C-8′) ppm. MS (APCI$^+$): *m*/*z* (%) = 229.9 (14) [M + H]$^+$, 228.9 (100) [M]$^+$. HRMS: calcd. for [$C_{12}H_{20}O_2SNa$]$^+$ 251.10817; found 251.10731. Two pairs of minor enantiomers (65:35 ratio, 3%): R_f (hexane/EtOAc, 90:10) = 0.35. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.76–5.65 (m, $^3J_{H11,H12b}$ = $^3J_{H11',H12b'}$ = 17.0, $^3J_{H11,H12a}$ = $^3J_{H11',H12a'}$ = 10.1 Hz, 2 H, 11-H, 11′-H), 5.02 (dm, $^3J_{H12b,H11}$ = $^3J_{H12b',H11'}$ = 17.0 Hz, 2 H, 12b-H, 12b′-H), 4.95 (dm, $^3J_{H12a,H11}$ = $^3J_{H12a',H11'}$ = 10.1 Hz, 2 H, 12a-H, 12a′-H), 4.62–4.49 (m, $^3J_{H7',H8'}$ = 7.1 Hz, 2 H, 7′-H), 4.58 (dq, $^2J_{H7a,H7b}$ = 11.0, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.53 (dq, $^2J_{H7b,H7a}$ = 11.0, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.25 (≈td, $^3J_{H1',H5'}$ = $^3J_{H1',H2a' \text{ or } H2b',obs.}$ ≈ 8.1, $^3J_{H1',H2b' \text{ or } H2a',obs.}$ = 6.5 Hz, 1 H, 1′-H), 4.13–4.05 (m, 2 H, 1-H, 4′-H), 3.97 (≈dquint, $^3J_{H4,H3a \text{ or } H3b,obs.}$ = 7.3, $^3J_{H4,H3b \text{ or } H3a,obs.}$ = $^3J_{H4,H9}$ = 6.1 Hz, 1 H, 4-H), 3.00 (≈ddd, $^3J_{H5',H10a' \text{ or } H10b',obs.}$ = 10.3, $^3J_{H5',H1'}$ = 8.1, $^3J_{H5',H10b' \text{ or } H10a',obs.}$ = 4.0 Hz, 1 H, 5′-H), 2.95 (ddd, $^3J_{H5,H10a \text{ or } H10b,obs.}$ = 10.6, $^3J_{H5,H1,obs.}$ = 8.1, $^3J_{H5,H10b \text{ or } H10a,obs.}$ = 4.0 Hz, 1 H, 5-H), 2.55–2.40 (m, 2 H, 3a-H, 3a′-H), 2.36–2.22 (m, 2 H, 3b-H, 3b′-H), 2.10–2.01 (m, 2 H, 2a′-H, 10a′-H), 2.00–1.90 (m, 2 H, 2a-H, 10a-H), 1.80–1.64 (m, 2 H, 10b-H, 10b′-H), 1.50–1.42 (m, 2 H, 2b-H, 2b′-H), 1.38 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.38 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.20 (d, $^3J_{H9,H4}$ = 6.1 Hz, 3 H, 9-H), 1.19 (d, $^3J_{H9',H4',obs.}$ ≈ 6.4 Hz, 3 H, 9′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 224.2, 224.0 (C-6, C-6′), 135.1 (C-11, C-11′), 116.5 (C-12, C-12′), 81.9, 81.1 (C-1, C-1′), 75.4, 74.8 (C-4, C-4′), 67.8 (C-7, C-7′), 61.7, 61.4 (C-5, C-5′), 35.8, 35.5 (C-3, C-3′), 33.5, 32.5 (C-2, C-2′), 30.0, 29.1 (C-10, C-10′), 21.5, 21.1 (C-9, C-9′), 13.6 (C-8, C-8′) ppm. MS (APCI$^+$): *m*/*z* (%) = 229.9 (12) [M + H]$^+$, 229.0 (100) [M]$^+$, 193.2 (7), 183 (7).



20

***O*-Ethyl 2-Methyl-2-(5-methyltetrahydrofuran-2-yl)pent-4-enethioate (21):** A solution of thione ester **18** (210 mg, 1.04 mmol) in dry THF (2 mL) was added dropwise to a solution of *t*BuOK (185.5 mg, 1.65 mmol) in dry THF (4 mL) under argon at –78 °C over a period of 25 min. The reaction mixture was stirred at –78 °C for 45 min, and then allyl iodide (0.15 mL, 1.66 mmol) was added dropwise. The resulting mixture was allowed to reach –30 °C. The acetone/N_2 cooling bath was removed, and the reaction mixture was treated with a saturated aqueous NH_4Cl solution (13 mL) and then extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (eluting with a gradient solvent system of hexane/EtOAc from 100:0 to 95:5) to give the title compound **21** as a yellow oil as a mixture of two isomers (**21a**/**21b**, 87:13) in 85% overall yield (212 mg, 0.84 mmol). The thione ester **21** was used in the next step without further purification. R_f (hexane/EtOAc, 90:10) = 0.50 (isomer 1, *cis*-**21a**), 0.46 (isomer 1, *trans*-**21b**). GC (temp. progr. 2): t_R = 9.04 (isomer 1, *cis*-**21a**, 87%), 9.12 min (isomer 1, *trans*-**21b**, 13%). IR (KBr film): $\tilde{\nu}$ = 3076 (w), 2975 (vs), 1733 (w; traces of ester), 1639 (w), 1458 (m), 1387 (m), 1291 (m), 1252 (vs), 1193 (s), 1166 (s), 1145 (s), 1092 (vs), 1016 (s), 915 (s), 722 (vw), 620 (vw) cm^{-1}. ***cis*-21a**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.70 (dddd, $^3J_{H12,H13b}$ = 17.0, $^3J_{H12,H13a}$ = 10.1,

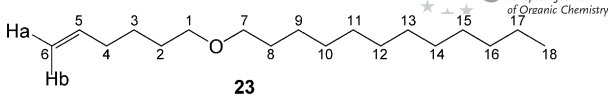
$^3J_{H12,H11b}$ = 8.1, $^3J_{H12,H11a}$ = 6.8 Hz, 1 H, 12-H), 5.03 (ddt, $^3J_{H13b,H12}$ = 17.0, $^2J_{H13b,H13a}$ = 2.3, $^4J_{H13b,H11b\ and\ H11a,obs.}$ ≈ 1.3 Hz, 1 H, 13b-H), 5.00 (ddt, $^3J_{H13a,H12}$ = 10.1, $^2J_{H13a,H13b}$ = 2.3, $^4J_{H13a,H11b\ and\ H11a}$ = 1.0 Hz, 1 H, 13a-H), 4.53 (dq, $^2J_{H7a,H7b}$ = 11.1, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.50 (dq, $^2J_{H7b,H7a}$ = 11.1, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.26 (≈dd, $^3J_{H1,H2a}$ = 6.8, $^3J_{H1,H2b}$ ≈ 8.0 Hz, 1 H, 1-H), 3.97 (dquint, $^3J_{H4,H3a}$ = 8.2, $^3J_{H4,H9}$ = $^3J_{H4,H3b}$ = 6.0 Hz, 1 H, 4-H), 2.72 (m, $^2J_{H11a,H11b}$ = 13.5, $^3J_{H11a,H12}$ = 6.8 Hz, 1 H, 11a-H), 2.45 (≈ddt, $^2J_{H11b,H11a}$ = 13.5, $^3J_{H11b,H12}$ = 8.1, $^4J_{H11b,H13a\ and\ H13b}$ = 1.0 Hz, 1 H, 11b-H), 1.93 (dddd, $^2J_{H3b,H3a}$ = 11.8, $^3J_{H3b,H2b}$ = 8.4, $^3J_{H3b,H4}$ = 6.0, $^3J_{H3b,H2a}$ = 4.7 Hz, 1 H, 3b-H), 1.81 (≈ddt, $^2J_{H2b,H2a}$ = 12.8, $^3J_{H2b,H3b}$ = 8.4, $^3J_{H2b,H1}$ ≈ $^3J_{H2b,H3a}$ ≈ 8.0 Hz, 1 H, 2b-H), 1.69 (dddd, $^2J_{H2a,H2b}$ = 12.8, $^3J_{H2a,H3a}$ = 9.3, $^3J_{H2a,H1}$ = 6.8, $^3J_{H2a,H3b}$ = 4.7 Hz, 1 H, 2a-H), 1.40 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.34 (≈ddt, $^2J_{H3a,H3b}$ = 11.8, $^3J_{H3a,H2a}$ = 9.3, $^3J_{H3a,H4}$ ≈ $^3J_{H3a,H2b}$ ≈ 8.0 Hz, 1 H, 3a-H), 1.24 (d, $^3J_{H9,H4}$ = 6.0 Hz, 3 H, 9-H), 1.21 (s, 3 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 226.3 (C-6), 134.3 (C-12), 117.4 (C-13), 84.3 (C-1), 75.5 (C-4), 68.0 (C-7), 57.6 (C-5), 44.4 (C-11), 33.4 (C-3), 27.0 (C-2), 20.7 (C-9), 17.5 (C-10), 13.5 (C-8) ppm. MS (EI, 70 eV): *m*/*z* (%) = 244.17 (2) [M + 2H]$^+$, 243.13 (17) [M + H]$^+$, 227.09 (32) [M – CH_3]$^+$, 213.14 (60) [M – CH_2–CH_3]$^+$, 169.12 (22), 157.09 (34), 155.10 (100), 153.22 (50), 129.12 (28), 85.18 (42), 67.11 (85). ***trans*-21b:** MS (EI, 70 eV): *m*/*z* (%) = 244.17 (6) [M + 2H]$^+$, 243.07 (34) [M + H]$^+$, 227.12 (32) [M – CH_3]$^+$, 213.08 (55) [M – CH_2–CH_3]$^+$, 169.21 (22), 158.21 (40), 155.09 (81), 153.16 (46), 129.16 (33), 111.12 (26), 85.20 (55), 67.11 (100). HRMS: calcd. for [$C_{13}H_{22}O_2SNa$]$^+$ 265.12382; found 265.12389.



21

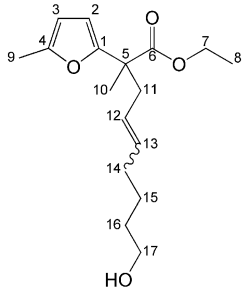
Olefin (Alkene) Metathesis Reactions

1-Hex-5-enyloxydodecane (23): Hex-5-enol (**22**; 0.6 mL, 5.0 mmol) was added dropwise to a suspension of NaH (100%, 180 mg, 7.5 mmol) in DMF (over molecular sieves, 6 mL) under argon at 5 °C over a period of 5 min. The reaction mixture was allowed to reach room temperature, after which time stirring was continued for 2 h. Dodecyl bromide (1.45 mL, 6.0 mmol) was added dropwise, and the resulting mixture was stirred for 3.5 h and then diluted with Et_2O (10 mL). Water (10 mL) was added portionwise, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane/EtOAc, 98:2) to give the title compound **23** as a yellow oil (525 mg, 1.96 mmol, 40%). R_f (hexane/EtOAc, 98:2) = 0.09. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.80 (ddt, $^3J_{H5,H6b}$ = 17.0, $^3J_{H5,H6a}$ = 10.2, $^3J_{H5,H4}$ = 6.7 Hz, 1 H, 5-H), 5.00 (dm, $^3J_{H6b,H5}$ = 17.0 Hz, 1 H, 6b-H), 4.94 (dm, $^3J_{H6a,H5}$ = 10.2 Hz, 1 H, 6a-H), 3.40 and 3.38 (t, *J* = 6.6, 6.7 Hz, 2 × 2 H, 1-H, 7-H), 2.06 (≈qm, $^3J_{H4,H5,obs.}$ ≈ $^3J_{H4,H3,obs.}$ ≈ 7.1 Hz, 2 H, 4-H), 1.61–1.51 (m, 4 H, 2 CH_2), 1.47–1.41 (m, 2 H, 3-H), 1.35–1.20 (m, 18 H, 9 CH_2), 0.88 (t, $^3J_{H18,H17,obs.}$ = 7.2 Hz, 3 H, 18-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 138.8 (C-5), 114.4 (C-6), 71.0, 70.7 (C-1, C-7), 33.6 (C-4), 31.9 to 22.7 (12 C): 31.9, 29.8, 29.7, 29.6 (3 C), 29.5, 29.3, 29.2, 26.1, 25.5, 22.7, 14.1 (C-18) ppm. MS (APCI$^+$): *m*/*z* (%) = 269.1 (100) [M + H]$^+$.



23

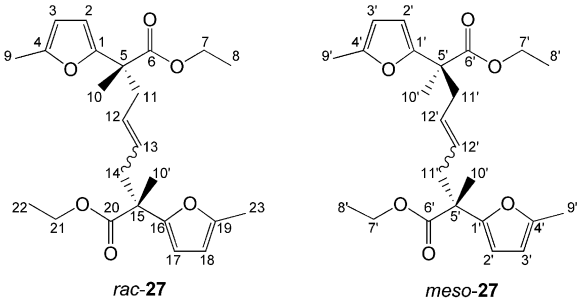
Ethyl 9-Hydroxy-2-methyl-2-(5-methylfuran-2-yl)non-4-enoate (25): Under argon, CH_2Cl_2 was degassed with argon bubbling for 40 min. A solution of Grubbs I catalyst (74 mg, 0.09 mmol) in degassed CH_2Cl_2 (2 mL) was added dropwise to a solution of **24**[72] (200 mg, 0.90 mmol) and **22** (0.17 mL, 1.45 mmol) in degassed CH_2Cl_2 (2 mL) under argon. The reaction mixture was heated at reflux for 5 h, and the progress of the reaction was monitored by TLC. Then further Grubbs I catalyst (20 mg, 0.02 mmol) was added, and the resulting mixture was heated at reflux for another 17 h. Removal of solvent gave an oily residue, which was purified by chromatography on silica gel (from hexane gradually to hexane/EtOAc, 75:25) to afford the title compound **25** as a mixture of two isomers [(*E*)/(*Z*) = 65:35] in 81% overall yield (215 mg, 0.73 mmol). R_f (hexane/EtOAc, 75:25) = 0.10. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 6.02 (d, $^3J_{H2',H3'}$ = 3.1 Hz, 2 H, 2′-H), 6.00 (d, $^3J_{H2,H3}$ = 3.1 Hz, 1 H, 2-H), 5.88 (dq, $^3J_{H3',H2'}$ = 3.1, $^4J_{H3',H9'}$ = 1.0 Hz, 1 H, 3′-H), 5.87 (dq, $^3J_{H3,H2}$ = 3.1, $^4J_{H3,H9}$ = 1.0 Hz, 1 H, 3-H), 5.46 (dtm, $^3J_{H13,H12}$ = 15.1, $^3J_{H13,H14}$ = 6.9 Hz, 1 H, 13-H), 5.49–5.43 (m, 1 H, 13′-H), 5.28–5.18 (m, $^3J_{H12,H13}$ = 15.1 Hz, 2 H, 12-H, 12′-H), 4.09 (dq, $^2J_{H7a,H7b}$ = 11.2, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.10 (m, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.18–4.05 (m, $^3J_{H7a',H8'}$ = $^3J_{H7b',H8'}$ = 7.1 Hz, 2 H, 7a′-H, 7b′-H), 3.62 (t, $^3J_{H17',H16',obs.}$ = 6.5 Hz, 3 H, 17′-H), 3.59 (t, $^3J_{H17,H16,obs.}$ = 6.5 Hz, 3 H, 17-H), 2.76–2.61 (m, 2 H, 11′-H), 2.67 (≈dd, $^2J_{H11a,H11b}$ = 12.8, $^3J_{H11a,H12,obs.}$ ≈ 7.4 Hz, 1 H, 11a-H), 2.55 (ddd, $^2J_{H11b,H11a}$ = 12.8, $^3J_{H11b,H12}$ = 7.0, $^4J_{H11b,H13,obs.}$ = 1.0 Hz, 1 H, 11b-H), 2.24 (d, $^3J_{H9,H3}$ = $^3J_{H9',H3'}$ = 1.0 Hz, 6 H, 9-H, 9′-H), 2.07–1.99 (m, 1 H, 14′-H), 1.98 (≈q, $^3J_{H14,H15,obs.}$ = $^3J_{H14,H13}$ = 6.9 Hz, 14-H), 1.73 (br., 2 H, OH), 1.65–1.34 (m, 8 H, 15-H, 16-H, 15′-H, 16′-H), 1.45 (s, 3 H, 10′-H), 1.43 (s, 3 H, 10-H), 1.20 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.20 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.2, 174.1 (C-6, C-6′), 154.6, 154.4 (C-1, C-1′), 151.1, 151.0 (C-4, C-4′), 134.2, 132.6 (C-13, C-13′), 125.0, 124.3 (C-12, C-12′), 106.3, 106.1 (C-2, C-2′), 105.8, 105.7 (C-3, C-3′), 62.6 (C-17, C-17′), 60.9, 60.8 (C-7, C-7′), 47.1, 47.0 (C-5, C-5′), 40.3 (C-11), 34.7 (C-11′), 34.6, 26.9 (C-14, C-14′), 32.2, 32.1 (C-16, C-16′), 25.6, 25.4 (C-15, C-15′), 20.9, 20.8 (C-10, C-10′), 14.1, 14.0 (C-8, C-8′), 13.5 (C-9, C-9′) ppm. MS (APCI$^+$): *m*/*z* (%) = 295.9 (17) [M + 2 H]$^+$, 295.0 (100) [M + H]$^+$, 221.10 (13).

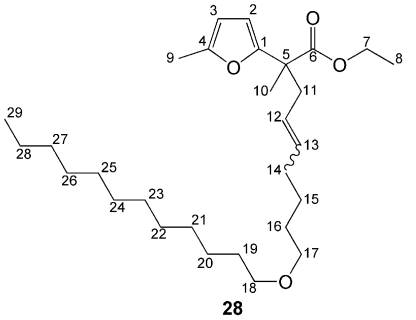


25

Ethyl 9-Dodecyloxy-2-methyl-2-(5-methylfuran-2-yl)non-4-enoate (28) and Diethyl 2,7-Dimethyl-2,7-bis(5-methylfuran-2-yl)oct-4-enedioate (27): According to the procedure reported for the synthesis of compound **25**, ester **24** (135 mg, 0.61 mmol), olefin **23** (0.36 g, 0.81 mmol) and Grubbs I catalyst (69 mg, 0.08 mmol) reacted to give compounds **28** in 54% overall yield and **29** in 21% overall

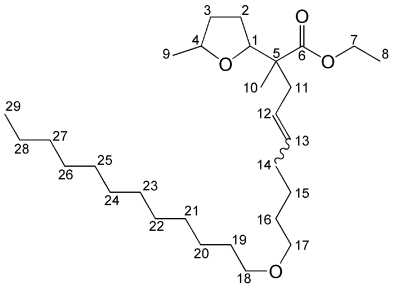
yield as an inseparable mixture in the first and second fractions and the self-coupling product **27** (21 mg, 0.05 mmol, 8%) in the third fraction after chromatography on silica gel (from hexane gradually to hexane/EtOAc, 90:10). The first fraction (155 mg, **28/29**, 64:36) corresponds to **28** (0.20 mmol, 33%) and **29** (0.11 mmol, 18%). The second fraction (74 mg, **28/29**, 84:66) corresponds to **28** (0.13 mmol, 21%) and **29** (0.02 mmol, 3%). **27:** R_f (hexane/EtOAc, 95:5) = 0.19. IR (KBr film): $\tilde{\nu}$ = 2982 (m), 2937 (m), 1732 (vs), 1610 (vw), 1561 (w), 1452 (w), 3063 (vw), 1376 (vw), 1235 (s), 1144 (m), 1098 (s), 1023 (s), 964 (vw), 964 (vw), 942 (w), 859 (vw), 783 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 6.01 (d, $^3J_{H2',H3'}$ = 3.1 Hz, 2 H, 2′-H), 5.97, 5.96 (2 d, $^3J_{H2,H3}$ = 3.1, $^3J_{H17,H18}$ = 3.1 Hz, 2 H, 2-H, 17-H), 5.87, 5.86 (2 dq, $^3J_{H3',H2'}$ = 3.1, $^4J_{H3',H9'}$ = 1.1, $^3J_{H3,H2}$ = $^3J_{H18,H17}$ = 3.1, $^4J_{H3,H9}$ = $^4J_{H18,H23}$ = 1.1 Hz, 2×2 H, 3′-H, 3-H, 18-H), 5.33–5.28 (m, 4 H, 12-H, 13-H, 12′-H), 4.11, 4.13 (2 q, $^3J_{H7',H8'}$ = 7.1, $^3J_{H7,H8}$ = $^3J_{H21,H22}$ = 7.1 Hz, 2×4 H, 7′-H, 7-H, 21-H), 5.75–5.55 (m, 8 H, 11-H, 14-H, 11′-H), 2.25, 2.24 (2 d, $^3J_{H9',H3'}$ = 1.1, $^3J_{H9,H3}$ = $^3J_{H23,H18}$ = 1.1 Hz, 2×6 H, 9′-H, 9-H, 23-H), 1.44 (s, 6 H, 10′-H), 1.39, 1.40 (s, 6 H, 10-H, 24-H), 1.21, 1.20 (2 t, $^3J_{H8',H7'}$ = 7.1, $^3J_{H8,H7}$ = $^3J_{H22,H21}$ = 7.1 Hz, 2×6 H, 8′-H, 8-H, 22-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.1, 174.0, 173.9 (C-6, C-20, C-6′), 154.5, 154.4, 154.3 (C-1, C-16, C-1′), 151.2, 1551.1 (C-4, C-19, C-4′), 129.0, 127.3 (C-12, C-13, C-12′), 106.4, 106.3, 106.2 (C-2, C-17, C-2′), 105.9, 105.8 (C-3, C-18, C-3′), 61.0, 60.9 (C-7, C-21, C-7′), 47.0 (C-5, C-15, C-5′), 40.3, 34.8 (C-11, C-14, C-11′), 20.9, 20.8 (C-10, C-24, C-10′), 14.1 (C-8, C-22, C-8′), 13.6 (C-9, C-23, C-9′) ppm. MS (APCI$^+$): *m*/*z* (%) = 418.0 (25) [M + 2 H]$^+$, 417.0 (100) [M + H]$^+$, 359.1 (13) [M – 57]$^+$, 343.1 (16) [M – 73 (CO_2Et)]$^+$. HRMS: calcd. for $[C_{24}H_{32}O_6Na]^+$ 439.20966; found 439.20900. **28:** (*E*)/(*Z*) = 65:35. R_f (hexane/EtOAc, 95:5) = 0.30. IR (KBr film): $\tilde{\nu}$ = 2926 (vs), 2854 (vs), 1735 (vs), 1562 (vw), 1460 (w), 1376 (w), 1234 (m), 1115 (s), 1023 (m), 970 (w), 780 (w), 722 (vw) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 6.02 (d, $^3J_{H2',H3'}$ = 3.1 Hz, 1 H, 2′-H), 6.00 (d, $^3J_{H2,H3}$ = 3.1 Hz, 1 H, 2-H), 5.88–5.86 (m, 1 H, 3′-H), 5.86 (dq, $^3J_{H3,H2}$ = 3.1, $^4J_{H3,H9}$ = 1.0 Hz, 1 H, 3-H), 5.48 (≈dtm, $^2J_{H13,H12}$ ≈ 15.0, $^3J_{H13,H14}$ ≈ 7.0 Hz, 1 H, 12-H), 5.50–5.43 (m, 2 H, 13-H, 13′-H), 5.26 (≈dtm, $^2J_{H12,H13}$ ≈ 15.0, $^3J_{H12,H11a\ and\ H11b,obs.}$ = 7.0 Hz, 1 H, 12-H), 5.24–5.19 (m, 1 H, 12′-H), 4.14 (q, $^3J_{H7',H8'}$ = 7.1 Hz, 2 H, 7′-H), 4.13 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 3.39 (t, $^3J_{H17',H18'}$ or $^3J_{H18',H17'}$ = 6.8 Hz, 2 H, 17′-H or 18′-H), 3.38 (t, $^3J_{H17',H18'}$ or $^3J_{H18',H17'}$ = 6.7 Hz, 2 H, 17′-H or 18′-H), 3.37 (t, $^3J_{H17,H18}$ or $^3J_{H18,H17}$ = 6.8 Hz, 2 H, 17-H or 18-H), 2.76 (≈ddd, $^2J_{H11a',H11b'}$ ≈ 14.5, $^3J_{H11a',H12',obs.}$ ≈ 7.6, $^4J_{H11a',H13',obs.}$ = 1.4 Hz, 1 H, 11a′-H), 2.70 (≈ddd, $^2J_{H11a,H11b}$ ≈ 13.7, $^3J_{H11a,H12,obs.}$ ≈ 7.6, $^4J_{H11a,H13,obs.}$ = 0.8 Hz, 1 H, 11b-H), 2.70–2.64 (m, $^2J_{H11b',H11a'}$ ≈ 14.5 Hz, 1 H, 11b′-H), 2.58 (ddd, $^2J_{H11b,H11a}$ = 13.7, $^3J_{H11b,H12}$ = 7.0, $^4J_{H11b,H13,obs.}$ = 1.0 Hz, 1 H, 11b-H), 2.25 (d, $^4J_{H9,H3}$ = $^4J_{H9',H3'}$ = 1.0 Hz, 6 H, 9-H, 9′-H), 2.07 (≈q, $^3J_{H14',H13',obs.}$ ≈ $^3J_{H14',H15',obs.}$ ≈ 7.3 Hz, 2 H, 14′-H), 2.00 (≈q, $^3J_{H14,H13,obs.}$ ≈ $^3J_{H14,H15,obs.}$ ≈ 7.0 Hz, 2 H, 14-H), 1.64–1.51 (m, $^3J_{obs.}$ = 6.8 Hz, 8 H, 16′-H, 19′-H, 16-H, 19-H), 1.44–1.24 (m, 40 H, 15-H, 15′-H, 20-H to 28-H, 20′-H to 28′-H), 1.46 (s, 3 H, 10′-H), 1.44 (s, 3 H, 10-H), 1.21 (t, $^3J_{H8',H7'}$ = 7.1 Hz, 3 H, 8′-H), 1.21 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 0.88 (t, $^3J_{H29,H28}$ = $^3J_{H29',H28',obs.}$ ≈ 6.8 Hz, 6 H, 29-H, 29′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.1 (C-6, C-6′), 154.7, 154.5 (C-1, C-1′), 151.1, 151.0 (C-4, C-4′), 134.4, 134.8 (C-13, C-13′), 124.9, 124.2 (C-12, C-12′), 106.3, 106.1 (C-2, C-2′), 105.9, 105.8 (C-3, C-3′), 71.0, 70.9, 70.7 (C-17, C-17′, C-18, C-18′), 60.9, 60.8 (C-8, C-8′), 47.2, 47.1 (C-5, C-5′), 40.4 (C-11, C-11′), 31.9, 26.2 (C-14, C-14′), 32.4, 29.8, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.2, 26.0, 22.7 (C-15, C-15′, C-16, C-16′, C-19 to C-28, C-19′ to C-28′), 21.0, 20.9 (C-10, C-10′), 14.1 (C-8, C-8′, C-29, C-29′), 13.6 (C-9, C-9′) ppm. MS (APCI$^+$): *m*/*z* (%) = 464.1 (29) [M + 2 H]$^+$, 463.2 (100) [M + H]$^+$, 389.3 (8) [M – 73 (CO_2Et)]$^+$. HRMS: calcd. for $[C_{29}H_{50}O_4Na]^+$ 485.36068; found 485.35940.





Ethyl 9-Dodecyloxy-2-methyl-2-(5-methyltetrahydrofuran-2-yl)non-4-enoate (30) and Ethyl (*E*)-2-Methyl-2-(5-methyltetrahydrofuran-2-yl)-5-phenylpent-4-enoate (31): Under argon, $ClCH_2CH_2Cl$ (7 mL) was degassed with argon bubbling for 40 min. A solution of Grubbs I catalyst (42 mg, 0.05 mmol) in degassed $ClCH_2CH_2Cl$ (1.5 mL) was added dropwise to a solution of **12** (*cis*-**12a**/*trans*-**12c**, 90:10, 116 mg, 0.51 mmol) and **23** (165 mg, 0.62 mmol) in degassed $ClCH_2CH_2Cl$ (1.5 mL) under argon at 20 °C. The reaction mixture was heated at reflux for 5 h, and the progress of the reaction was monitored by TLC. Then, further Grubbs I catalyst (17 mg, 0.02 mmol) was added, and the resulting mixture was heated at reflux for another 15 h. The presence of starting materials was observed by TLC. Thus, more **23** (20 mg, 0.08 mmol) and Grubbs I catalyst (20 mg, 0.02 mmol) were added. The reaction mixture was heated at reflux again for another 21 h, and the presence of starting materials was detected by TLC. Again, even more **23** (20 mg, 0.08 mmol) and Grubbs I catalyst (20 mg, 0.02 mmol) were added, and the resulting solution was heated at reflux for a further 21 h. Removal of the solvent gave an oily residue, which was purified by chromatography on silica gel (from hexane gradually to hexane/Et_2O, 95:5) to give four fractions. The first fraction proved to be a complex mixture (45 mg, **12/29/32**, 10:40:50) corresponding to **23** (4.5 mg, 0.02 mmol, 3%), **29** (18 mg, 0.04 mmol, 7%) and **32** (22.5 mg, 0.07 mmol, 13%). The second fraction contained **29** (90 mg, 0.18 mmol, 35%). The third fraction was found to be a complex mixture (47 mg, **12/30**, 60:40) corresponding to **12** (28.2 mg, 0.13 mmol, 24%) and **30** (18.8 mg, 0.04 mmol, 8%). The fourth fraction showed a complex mixture (106.1 mg, **30/31**, 85:15) corresponding to **30** (90.2 mg, 0.193 mmol, 38%) and **31** (15.9 mg, 0.053 mmol, 10%). Fourth fraction (**30/31**, 85:15): R_f (hexane/Et_2O, 90:10) = 0.18. IR (KBr film): $\tilde{\nu}$ = 2927 (vs), 2854 (s), 1732 (s), 1465 (m), 1378 (w), 1292 (w), 1179 (m), 1116 (s), 1095 (s), 1024 (m), 970 (w), 835 (s), 859 (vw), 722 (vw) cm^{-1}. **30 [(*E*)/(*Z*) = 75:25]. (*E*)-30:** ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.44 (dt, $^3J_{H13,H12}$ = 15.0, $^3J_{H13,H14,obs.}$ = 6.6 Hz, 1 H, 13-H), 5.31 (ddd, $^3J_{H12,H13}$ = 15.0, $^3J_{H12,H11b}$ = 7.9, $^3J_{H12,H11a}$ = 6.8 Hz, 1 H, 12-H), 4.12 (dq, $^2J_{H7a,H7b}$

= 11.4, $^3J_{H7a,H8}$ = 7.1 Hz, 1 H, 7a-H), 4.11 (dq, $^2J_{H7b,H7a}$ = 11.4, $^3J_{H7b,H8}$ = 7.1 Hz, 1 H, 7b-H), 4.02 (≈dd, $^3J_{H1,H2a}$ = 7.1, $^3J_{H1,H2b,obs.}$ ≈ 7.5 Hz, 1 H, 1-H), 3.94 (dquint, $^3J_{H4,H3a}$ = 7.8, $^3J_{H4,H9}$ = $^3J_{H4,H3b}$ = 6.0 Hz, 1 H, 4-H), 3.40–3.35 (m, $^3J_{H17,H16,obs.}$ = $^3J_{H18,H19,obs.}$ = 6.7 Hz, 4 H, 17-H, 18-H), 2.51–2.41 (m, $^2J_{H11a,H11b}$ = 13.6, $^3J_{H11a,H12}$ = 6.8 Hz, 1 H, 11a-H), 2.25–2.17 (m, $^2J_{H11b,H11a}$ = 13.6, $^3J_{H11b,H12}$ = 7.9 Hz, 1 H, 11b-H), 2.10–1.88 (m, $^3J_{H3b,H4}$ = 6.0, $^3J_{H3b,H2a}$ = 5.0 Hz, 3 H, 3b-H, 14-H), 1.83 (≈ddt, $^2J_{H2b,H2a}$ = 12.3, $^3J_{H2b,H3b,obs.}$ = 8.5, $^3J_{H2b,H1}$ ≈ $^3J_{H2b,H3a}$ ≈ 7.8 Hz, 1 H, 2b-H), 1.72 (dddd, $^2J_{H2a,H2b}$ = 12.3, $^3J_{H2a,H3a}$ = 9.3, $^3J_{H2a,H1}$ = 7.1, $^3J_{H2a,H3b}$ = 5.0 Hz, 1 H, 2a-H), 1.64–1.51 (m, 4 H, 16-H, 19-H), 1.41–0.91 (m, $^3J_{H3a,H2a}$ = 9.3, $^3J_{H3a,H4}$ ≈ $^3J_{H3a,H2b}$ ≈ 7.8 Hz, 21 H, 3a-H, 15-H, 20-H to 28-H), 1.23 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.20 (d, $^3J_{H9,H4}$ = 6.0 Hz, 3 H, 9-H), 1.07 (s, 3 H, 10-H), 0.87 (≈t, $^3J_{H29,H28}$ = 6.8 Hz, 3 H, 29-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.2 (C-6), 133.7 (C-13), 125.5 (C-12), 82.9 (C-1), 75.4 (C-4), 70.9 (C-17), 70.7 (C-18), 60.1 (C-7), 50.1 (C-5), 40.5 (C-11), 33.2 (C-3), 32.4 (C-14), 31.9 (C-27), 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2 (C-16, C-19, C-21 to C-26), 27.1 (C-2), 26.2 (C-20), 26.0 (C-15), 22.7 (C-28), 20.8 (C-9), 15.8 (C-10), 14.3 (C-8), 14.1 (C-29) ppm. MS (EI, 70 eV): *m*/*z* (%) = 466.40 (2) $[M]^+$, 341.87 (3), 319.60 (4), 262.29 (13), 251.28 (22), 239.30 (35), 186.17 (100), 138.16 (60), 126.16 (85), 67.18 (87). **31 (Partial Data):** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.33–7.29 (m, $^3J_{H16,H17}$ = $^3J_{H16',H17}$ = 6.8 Hz, $^3J_{H16,H15}$ = $^3J_{H16',H15'}$ = 6.3 Hz, 2 H, 16-H, 16′-H), 7.27–7.25 (m, $^3J_{H15,H16}$ = $^3J_{H15',H16'}$ = 6.3 Hz, 2 H, 15-H, 15′-H), 7.21–7.17 (m, $^3J_{H17,H16}$ = $^3J_{H17,H16'}$ = 6.8 Hz, 1 H, 17-H), 6.40 (d, $^3J_{H13,H12}$ = 15.7 Hz, 1 H, 13-H), 6.14 (ddd, $^3J_{H12,H13}$ = 15.7 Hz, $^3J_{H12,H11b,obs.}$ = 8.1 Hz, $^3J_{H12,H11a}$ = 7.0 Hz, 1 H, 12-H), 1.15 (s, 3 H, 10-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 133.2 (C-13), 128.4 (C-16, C-16′), 127.0 (C-17), 126.1 (C-15, C-15′), 124.8 (C-12) ppm. MS (EI, 70 eV): *m*/*z* (%) = 302.29 (10) $[M]^+$, 228.23 (10), 202.23 (15), 201.19 (100) $[M - CH_2CHCHC_6H_5]^+$, 187.19 (80), 171.19 (37), 155.19 (25), 129.18 (35), 117.17 (45), 115.16 (65), 95.18 (15), 91.17 (35), 85.16 (23).



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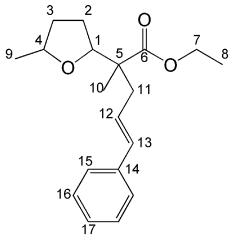
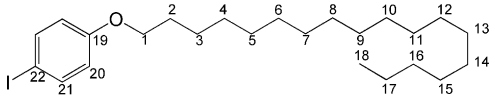


31

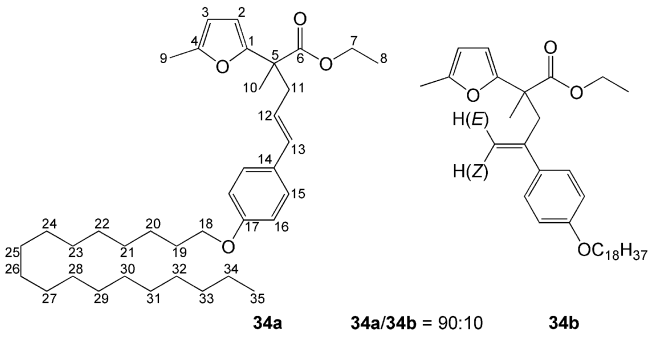
1-Iodo-4-octadecyloxybenzene (33): KOH (842 mg, 15.00 mmol) was added to a solution of 4-iodophenol (3 g, 13.63 mmol) in EtOH (95%, 35 mL). The reaction mixture was heated at 60 °C for 10 min, and octadecyl iodide (5.7 g, 15.00 mmol) was added. Heating was then continued for 6 h. TLC showed the reaction was not yet completed. KOH (200 mg, 3.56 mmol) was added, and the resulting mixture was heated again at 60 °C for another 18 h. After filtration through cotton cloth to remove excess octadecyl iodide, the reaction mixture was concentrated in vacuo. The oily residue was purified twice by chromatography on silica gel (hexane/EtOAc, 90:10) to give the title compound **33** as a white solid (3.33 g, 7.88 mmol, 58%). R_f (hexane/EtOAc, 95:5) = 0.66. IR (KBr film): $\tilde{\nu}$ = 3433 (w) (H_2O), 2955 (m), 2920 (vs), 2849 (vs), 1641 (vw), 1589 (w), 1571 (w), 1489 (m), 1473 (m), 1463 (m), 1397 (vw), 1384 (w), 1285 (m), 1249 (m), 1175 (w), 1101 (vw), 1034 (vw), 1022 (vw), 1010 (vw), 1001 (w), 828 (vw), 814 (m), 729 (vw), 719 (w), 512 (vw) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.54 (AA′BB′ system, partially resolved, $^3J_{H21,H20}$ = 9.0 Hz, 2 H, 21-H), 6.67 (AA′BB′ system, partially resolved, $^3J_{H20,H21}$ = 9.0 Hz, 2 H, 20-H), 3.91 (t, $^3J_{H1,H2}$ = 6.6 Hz, 2 H, 1-H), 1.80–1.73 (m, 2 H, 2-H), 1.46–1.20 (m, 30 H, 3-H to 17-H), 0.89 (≈t, $^3J_{H18,H17,obs.}$ = 6.8 Hz, 2 H, 18-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 159.0 (C-19), 138.1 (2 C, C-21), 116.9 (2 C, C-20), 82.4 (C-22), 68.1 (C-1), 31.9 (C-16), 29.7–29.1 (13 C, C-2, C-4 to C-15), 26.0 (C-3), 22.7 (C-17), 14.1 (C-18) ppm. MS (ESI$^+$): *m*/*z* (%) = 473.1. (100) $[M + H]^+$.



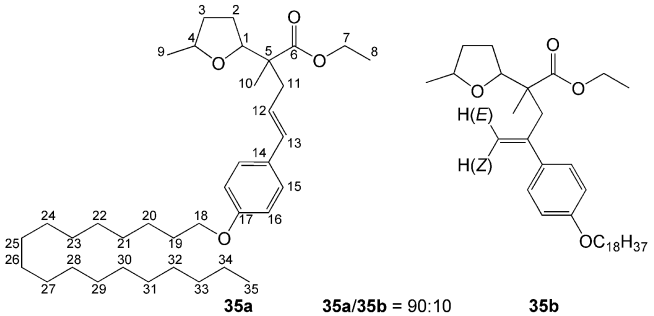
33

Ethyl (*E*)-2-Methyl-2-(5-methylfuran-2-yl)-5-(4-octadecyloxyphenyl)pent-4-enoate (34a): Triethylamine (3.1 mL, 22.3 mmol) was added to a solution of palladium diacetate (43 mg, 0.19 mmol) and tri-*o*-tolylphosphane (128 mg, 0.42 mmol) in dry DMF (35 mL) under argon at 25 °C. The reaction mixture was stirred for a few minutes, and a solution of ester **24** (300 mg, 1.35 mmol) in dry DMF (10 mL) was added. Stirring was continued for 15 min, and then 1-iodo-4-(octadecyloxy)benzene (**33**; 1.59 g, 3.37 mmol), dissolved by heating in dry DMF (10 mL), was added. The resulting mixture was heated at 90 °C for 44 h and then cooled to room temperature and diluted with EtOAc (180 mL) and water (80 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (70 mL). The combined organic layers were washed with brine (70 mL) and dried with anhydrous $MgSO_4$. After filtration, the solvent was removed in vacuo, and the residue was purified twice by chromatography on silica gel (hexane/EtOAc gradually) to give compound **34** as a mixture of two regioisomers (**34a/34b**, 90:10) in a quantitative overall yield (780 mg, 1.38 mmol). R_f (hexane/EtOAc, 90:10) = 0.37. **34a:** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.24 (≈d, $^3J_{H15,H16}$ = 7.7 Hz, 2 H, 15-H), 6.84 (≈d, $^3J_{H16,H15}$ = 7.7 Hz, 2 H, 16-H), 6.39 (d, $^2J_{H13,H12}$ = 15.7 Hz, 1 H, 13-H), 6.08 (d, $^3J_{H2,H3}$ = 3.1 Hz, 1 H, 2-H), 5.87–5.94 (m, $^3J_{H3,H2}$ = 3.1, $^2J_{H12,H13}$ = 15.7 Hz, 2 H, 3-H, 12-H), 4.15–4.22 (m, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 3.96 (t, $^3J_{H18,H19}$ = 6.6 Hz, 2 H, 18-H), 2.91 (ddd, $^2J_{H11a,H11b}$ = 13.8, $^3J_{H11a,H12}$ = 7.7, $^4J_{H11a,H13}$ = 1.1 Hz, 1 H, 11a-H), 2.81 (ddd, $^2J_{H11b,H11a}$ = 13.8, $^3J_{H11b,H12}$ = 7.1, $^4J_{H11b,H13}$ = 1.3 Hz, 1 H, 11b-H), 2.30 (d, $^2J_{H9,H3,obs.}$ = 0.7 Hz, 3 H, 9-H), 1.83–1.73 (m, $^3J_{H19,H18}$ = 6.6 Hz, 2 H, 19-H), 1.51 (s, 3 H, 10-H), 1.46–1.23 (m, 30 H, 20-H to 34-H), 1.22 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 0.90 (≈t, $^3J_{H35,H34,obs.}$ ≈ 6.8 Hz, 3 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 174.0 (C-6), 158.5 (C-17), 154.5 (C-1), 151.2 (C-4), 132.8 (C-13), 130.0 (C-14), 127.2 (C-15), 122.9 (C-12), 114.4 (C-16), 106.3 (C-2), 105.9 (C-3), 68.0 (C-18), 61.0 (C-7), 47.4 (C-5), 40.9 (C-11), 31.9, 29.7, 29.4, 29.4, 29.3, 26.0 (C-20 to C-33), 29.6 (C-19), 22.7 (C-34), 22.6, 21.1 (C-10), 14.2, 14.1 (C-35, C-8), 13.6 (C-9) ppm. HRMS: calcd. for $[C_{37}H_{58}O_4Na]^+$ 589.42328; found 589.42292. **34b (Partial Data):** ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.17 [d, $^2J_{H(Z),H(E)}$ = 1.8 Hz, 1 H, (*Z*)-H], 4.92 [d, ^2JH(*E*),H(*Z*) = 1.8 Hz, 1 H, (*E*)-H] ppm.

Ethyl (*E*)-2-Methyl-2-(5-methyltetrahydrofuran-2-yl)-5-(4-octadecyloxyphenyl)pent-4-enoate (35a): According to the procedure reported for the synthesis of compound **34a**, palladium diacetate (15.5 mg, 0.07 mmol), tri-*o*-tolylphosphane (45 mg, 0.15 mmol), triethylamine (1.1 mL, 7.89 mmol), ester **12** (*cis*-**12a**/*trans*-**12c**, 90:10, 120 mg, 0.48 mmol) and 1-iodo-4-(octadecyloxy)benzene (**33**; 565 mg, 1.20 mmol) reacted to give the title compound **35** (1.13 g, 5.1 mmol, 93%) after purification by chromatography on silica gel (from hexane gradually to hexane/EtOAc, 97:3) as a mix-



ture of two regioisomers (**35a/35b**, 90:10). Ester **35a** was obtained after a second purification in 54% overall yield (148 mg, 0.26 mmol). R_f (hexane/EtOAc, 90:10) = 0.34. IR (KBr film): $\tilde{\nu}$ = 3031 (m), 2922 (vs), 2853 (vs), 2317 (vw), 2029 (w), 1880 (w), 1732 (vs), 1608 (vs), 1576 (m), 1511 (vs), 1468 (vs), 1386 (s), 1340 (m), 1294 (s), 1246 (vs), 1175 (vs), 1122 (vs), 1094 (vs), 1025 (vs), 967 (s), 938 (m), 900 (m), 835 (s), 802 (m), 744 (w), 722 (m), 640 (vw), 605 (vw), 516 (w) cm^{-1}. **35a:** ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.27–7.22 (m, $^3J_{H15,H16} \approx 11.6$ Hz, 2 H, 15-H), 6.83–6.79 (m, $^3J_{H16,H15} \approx 11.6$ Hz, 2 H, 16-H), 6.35 (≈d, $^3J_{H13,H12}$ = 15.7 Hz, 1 H, 13-H), 5.98 (ddd, $^3J_{H12,H13}$ = 15.7, $^3J_{H12,H11b}$ = 8.1, $^3J_{H12,H11a}$ = 7.0 Hz, 1 H, 12-H), 4.14 (q, $^3J_{H7,H8}$ = 7.1 Hz, 2 H, 7-H), 4.09–4.06 (m, $^3J_{H1,H2a,obs.}$ = 7.2 Hz, 1 H, 1-H), 3.97 (dquint, $^3J_{H4,H3a}$ = 7.9, $^3J_{H4,H9} = {}^3J_{H4,H3b}$ = 6.0 Hz, 1 H, 4-H), 3.93 (t, $^3J_{H18,H19,obs.}$ = 6.7 Hz, 3 H, 18-H), 2.67 (ddd, $^2J_{H11a,H11b}$ = 13.7, $^3J_{H11a,H12}$ = 7.0, $^4J_{H11a,H13,obs.}$ = 0.9 Hz, 1 H, 11a-H), 2.42 (ddd, $^2J_{H11b,H11a}$ = 13.7, $^3J_{H11b,H12}$ = 8.1, $^4J_{H11b,H13,obs.}$ = 0.9 Hz, 1 H, 11b-H), 1.95 (dddd, $^2J_{H3b,H3a,obs.}$ = 11.4, $^3J_{H3b,H2b,obs.}$ = 8.4, $^3J_{H3b,H4}$ = 6.0, $^3J_{H3b,H2a,obs.}$ = 5.0 Hz, 1 H, 3b-H), 1.90–1.81 (m, 1 H, 2b-H), 1.80–1.72 (m, 3 H, 2a-H, 19-H), 1.63–1.16 (m, 31 H, 3a-H, 20-Hto 34-H), 1.24 (t, $^3J_{H8,H7}$ = 7.1 Hz, 3 H, 8-H), 1.22 (d, $^3J_{H9,H4}$ = 6.0 Hz, 3 H, 9-H), 1.15 (s, 3 H, 10-H), 0.88 (≈t, $^3J_{H35,H34,obs.}$ = 6.8 Hz, 3 H, 35-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 175.2 (C-6), 158.4 (C-17), 132.2 (C-13), 130.2 (C-14), 127.1 (C-15, C-15′), 123.6 (C-12), 114.4 (C-16, C-16′), 82.8 (C-1), 75.5 (C-4), 67.9 (C-18), 60.3 (C-7), 50.3 (C-5), 40.9 (C-11), 33.2 (C-3), 31.9 (C-33), 29.7, 29.6, 29.5, 29.4, 29.3, 29.2 (C-19, C-21 to C-32), 27.2 (C-2), 26.0 (C-20), 22.7 (C-34), 20.8 (C-9), 16.1 (C-10), 14.3 (C-8), 14.1 (C-35) ppm. MS (APCI$^+$): *m/z* (%) = 572.30 (40) $[M + 2H]^+$, 571.30 (100) $[M + H]^+$. HRMS: calcd. for $[C_{37}H_{62}O_4SNa]^+$ 593.45458; found 593.45350. **35b (Partial Data):** ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.15 [d, $^2J_{H(Z),H(E)}$ = 1.8 Hz, 1 H, (*Z*)-H], 5.00 [d, $^2J_{H(E),H(Z)}$ = 1.8 Hz, 1 H, (*E*)-H] ppm.



Supporting Information (see footnote on the first page of this article): Experimental procedures and full spectroscopical and analytical data for previously unreported compounds not included in the Exp. Sect.; nomenclature used for the diastereoisomers of **7**; tentative assignement of the relative configuaration of **12** by chemical correlation.

Acknowledgments

This research was supported by the Swiss National Science Foundation (funding numbers 200020-104007 and 200020-112205) and the University of Neuchatel. NMR and mass spectra were measured with instruments at the Universities of Neuchatel and Fribourg acquired with the assistance of grants from the Swiss National Science Foundation.

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[72] For the preparation of this compound see the Supporting Information.

Received: December 29, 2009
Published Online: July 7, 2010

