Inter- and Intramolecular Hetero Diels-Alder Reactions, XXV[1]

The Tandem Knoevenagel Hetero Diels-Alder Reaction with a Formylacetic Acid Equivalent. Synthesis of Dihydropyrancarboxylates

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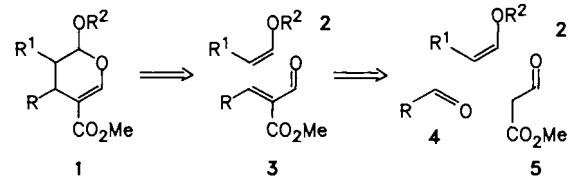
The tandem Knoevenagel hetero Diels-Alder reaction of 4,4,4-trichloro-3-oxobutanal (**9**) with the aldehydes **10** as well as **16**–**21** and the enol ethers **6** as well as **28**–**32** followed by base-catalyzed methanolysis yields the methyl dihydro-2*H*-pyran-5-carboxylates **15**, **22**–**27**, and **33**–**37**. In this reaction **9** is used as an equivalent of the non-stable formylacetic acid, since the trichloromethylcarbonyl moiety can be transformed into an alkoxycarbonyl group by solvolysis with an alcohol. As an example, in a three-component reaction **9** was condensed with propanal (**10**) in the presence of potassium fluoride to give the activated oxadiene **11** as an intermediate. This reacts with ethyl vinyl ether (**6**), which is present as one component in the reaction mixture, to afford the cycloadduct **13** after acidic workup. Methanolysis of **13** in the presence of DBU yields the methyl dihydro-2*H*-pyran-5-carboxylate **15** in 50% overall yield.

Tandem-Knoevenagel-Hetero-Diels-Alder-Reaktionen mit einem Fomylessigsäure-Äquivalent. Synthese von Dihydropyrancarbonsäureestern

Die Tandem-Knoevenagel-Hetero-Diels-Alder-Reaktion von 4,4,4-Trichlor-3-oxobutanal (**9**) mit den Aldehyden **10** sowie **16**–**21** und den Enolethern **6** sowie **28**–**32** mit nachfolgender basenkatalysierter Methanolyse führt zu den Dihydropyrancarbonsäure-methylestern **15**, **22**–**27** und **33**–**37**. Hierbei wird **9** als Äquivalent für die nicht stabilen Formylessigsäureester eingesetzt, da die Trichlormethylcarbonyl-Gruppe durch basenkatalysierte Solvolyse mit Alkoholen in eine Alkoxycarbonyl-Gruppe umgewandelt werden kann. Zum Beispiel wird in einer Dreikomponenten-Reaktion **9** mit Propanal (**10**) unter Katalyse von wasserfreiem Kaliumfluorid zu einem reaktiven Oxadien **11** umgesetzt, das mit in der Reaktionsmischung vorhandenem Ethylvinylether (**6**) bei saurer Aufarbeitung die Cycloaddukte **13** ergibt. Methanolyse von **13** in Gegenwart von DBU führt zu den Dihydropyrancarbonsäure-methylestern **15** in einer Gesamtausbeute von 50%.

The hetero Diels-Alder reaction of α,β-unsaturated aldehydes or ketones with enol ethers is a well known and widely used method for the synthesis of dihydropyrans[2]. These cycloadditions belong to the Diels-Alder reaction with inverse electron demand, in which the correlation of the HOMO of the dienophile and the LUMO of the diene is most important[3]. Based on this consideration, we[4] and others[5] have recently shown that the reactivity of this type of heterodiene can be improved by the introduction of an electron-withdrawing group at position 2 or 3. The main advantage in our version of this reaction is the possibility to form the oxadiene, e.g. **3**, in situ only by a simple condensation of a 1,3-dicarbonyl compound and an aldehyde followed by the cycloaddition with an electron-rich dienophile. Thus, the transformation can be carried out as a three-component transformation by mixing an aldehyde, a 1,3-dicarbonyl compound, and an enol ether. In the reaction a broad variety of 1,3-dicarbonyl compounds such as 1,3-dimethylbarbituric acid, meldrum's acid, and malonaldehyde can be used. However, a large group of natural products such as the iridoids, secoiridoids, and some indole alkaloids contain a 2-alkoxydihyrdropyrancarboxylate moiety as in **1**[6]. For the synthesis of this heterocyclic system, according to the proposed scheme, methyl formylacetate (**5**) would have to be used, which could undergo condensation with an aldehyde **4** to give the activated oxadiene **3**. Hetero Diels-Alder reaction of **3** with an enol ether **2** should give **1**.

Scheme 1



Unfortunately, methyl formylacetate (**5**) cannot be applied in the sequence because of its instability, since it di- and trimerizes easily to dimethyl formylglutaconate and trimethyl 1,3,5-benzenetricarboxylate[7].

In this paper we show that 4,4,4-trichloro-3-oxobutanal (**9**)[8] may be used as a formylacetic acid equivalent, as a trichloromethylcarbonyl moiety can easily be transformed into an alkoxycarbonyl group by a base-catalyzed solvolysis with an alcohol.

4,4,4-Trichloro-3-oxobutanal (**9**) was obtained in 66% yield by acylation of ethyl vinyl ether (**6**) with trichloroacetyl chloride (**7**) according to the method of Effenberger[9] followed by solvolysis of the primarily formed enol ether **8** in

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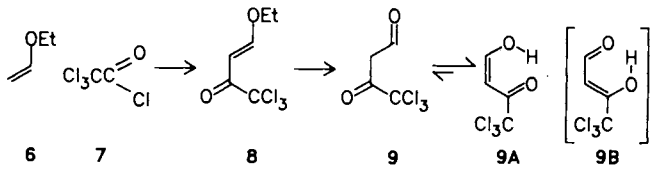
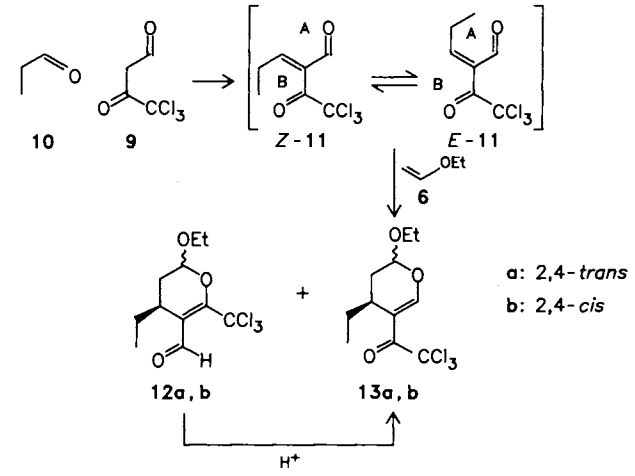
Scheme 2



6 7 8 9 9A 9B

formic acid. **9** is nearly completely enolized; thus the degree of enolization at 25°C in deuteriochloroform was estimated to about 96% by ^{1}H-NMR spectroscopy. For **9** the two enolic tautomers **9A** and **9B** have to be considered. The ^{1}H-NMR data for **9** with doublets at δ = 7.63 (4-H) and δ = 6.14 (3-H) and J = 5.5 Hz suggest that only the tautomer **9A** is present at room temperature. **9** crystallizes at about −25°C and can be stored at this temperature for several months. On exposure to air and with aqueous base, even with sodium hydrogen carbonate, decomposition occurs.

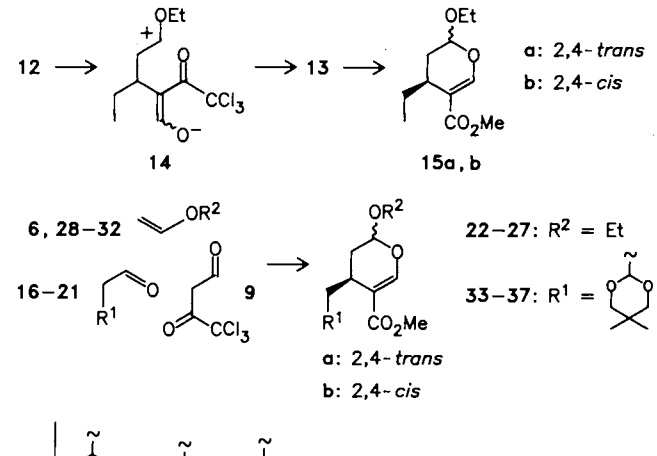
Scheme 3



For the tandem Knoevenagel hetero Diels-Alder reaction **9** can be condensed with a wide variety of aldehydes; in none of the cases we were able to isolate the Knoevenagel products, rather the reaction proceeds directly to the cycloadduct in the presence of an enol ether. Thus, a mixture of **9** and propanal (**10**) with potassium fluoride as condensating agent in dichloromethane was stirred with ethyl vinyl ether (**6**) for 45 h to give the cycloadducts **13a** and **13b** in a ratio of ca. 1:2 in 59% yield after acidic workup, as specified in the experimental part. Although the action of potassium fluoride in the Knoevenagel condensation is regarded as catalytic, it is appropriate to use more than one equivalent, since potassium fluoride is believed to act as a water scavenger in this reaction. Other catalysts for the Knoevenagel condensation such as sodium acetate, tetrabutylammonium fluoride, aluminum oxide, potassium hydrogen carbonate/18-crown-6, and ion exchange resin were less useful. In particular, more typical condensation catalysts such as primary and secondary amines or their salts could not be applied because **9** easily and irreversibly forms enamines[10].

The alkylidene-1,3-dicarbonyl compound **11** contains two different heterodiene moieties B and A, which both react to give **12** and **13**, respectively, in a ratio of ca. 1:1.3. Surprisingly, the *endo/exo* selectivity is quite different in the two cycloadditions, thus, **12a/12b** was obtained in a ca. 1:1 ratio and **13a/13b** in a ca. 1:2.2 ratio. So far we have not been able to improve the low site selectivity in the cycloaddition. This is of no concern, however, since **12a, b** can easily be isomerized to **13a,b** by traces of acid such as *p*-toluenesulfonic acid. As expected for a rearrangement by ring opening/recyclization (**12** → **14** → **13**) the stereochemical integrity at C-2 is lost during this reaction. The transformation of the trichloromethylcarbonyl to an alkoxycarbonyl group to give the desired dihydro-2*H*-pyran-5-carboxylates can be accomplished by base-catalyzed solvolysis with an alcohol; the best results were obtained with 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) as base; thus, in methanol at 20°C **13a** and **13b** were almost instantaneously transformed to **15a** and **15b**, respectively, without change of stereochemistry in about 85% yield.

Scheme 4



R^1						
				PhSCH$_2$	MeOCH$_2$	BzlOCH$_2$
	16/22	**17/23**	**18/24**	**19/25**	**20/26**	**21/27**

R^2	Et	Bzl	CH_2CH_2Cl	CH_2CH_2SPh	$(CH_2)_3OR^{3a)}$	Ph
	6/22	**28/33**	**29/34**	**30/35**	**31/36**	**32/37**

a) **31**: R^3 = 3,5-dinitrobenzoyl; **36**: R^3 = H

In the tandem Knoevenagel hetero Diels-Alder reaction the aldehyde can be varied over a wide range; even monoprotected malonaldehydes and other 3-substituted propanals **16**–**21** may be used. In these transformations (**9** with **6** and **16**–**21** in the presence of potassium fluoride) the primary cycloadducts were not isolated but after acidic workup with DBU in methanol converted to the dihydro-2*H*-pyran-5-carboxylates **22**–**27** (Table 1). As already mentioned, *cis/trans* ratios observed cannot be correlated with the *exo/endo* selectivity in the cycloadditions. Because of the intermediately performed isomerisation of the regioisomeric cycloadducts the stereochemistry at C-2 is scrambled.

In the reactions described so far only ethyl vinyl ether (**6**) was used as heterodienophile; the enol ether, however, can

also be varied over a wide range. Thus, we investigated the reactivity of vinyl ethers **28**–**31** and **32** with alkyl and phenyl substituents (Table 2). One of the reasons for these variations was to introduce a protecting group at C-2 in the final product which can be removed under mild and specific conditions.

With ethyl vinyl ether it is appropriate to perform the reaction at room temperature. With less volatile dienophiles as **28**–**32**, on the other hand, it has been proved useful to apply higher temperatures, thus shortening reaction times.

Performing the tandem Knoevenagel hetero Diels-Alder reactions at 110–120°C in toluene, the transformation of **9** with **16** and the alkyl vinyl ethers **28**–**31**, eventually yielding the dihydropyran-5-carboxylates **33**–**37**, was complete within one hour, whereas with phenyl vinyl ether (**32**) a reaction time of two hours and a higher excess of **9** and **16** was necessary; the latter result can be explained with the lower energy of the HOMO and thus decreased reactivity of phenyl vinyl ethers as compared to alkyl vinyl ethers.

Table 1. Reaction of **9** with **6** and the aldehydes **16**–**21**

Aldehyde	Product[a]	Yield [%][b]	Ratio **a**/**b**[c]
16	**22**	72	1:1.74
17	**23**	57	1:1.39
18	**24**	58	1:1.34
19	**25**	63	1:1.12
20	**26**	62	1:1.22
21	**27**	62	1:1.73

[a] All products were obtained as racemic mixtures. – [b] Yields are based on ethyl vinyl ether (**6**). – [c] Determined from the ^{13}C-NMR spectra of isolated products, standard deviation less than 0.14.

Table 2. Reaction of **9** with **16** and the enol ethers **6**, **28**–**32**

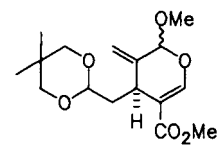
Enol ether	Product[a]	Yield [%][b]	Ratio **a**/**b**[c]
6	**22**	72	1:1.74
28	**33**	60	1:1.38
29	**34**	55	1:1.17
30	**35**	65	1:1.30
31	**36**	65	1:1.36
32	**37**	42	1:1.93

[a] All products were obtained as racemic mixtures. – [b] Yields are based on the vinyl ethers. – [c] Determined from the ^{13}C-NMR spectra of isolated products, standard deviation less than 0.14.

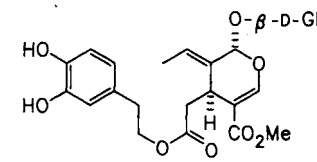
Instead of alkyl vinyl ethers also alkyl allenyl ethers can be applied. Reaction of **9** with methoxyallene and the aldehyde **16** gave after acidic workup and treatment with DBU in methanol the cycloadduct **38** in 45% yield. **38** shows a remarkable similarity with the monoterpene glycoside oleuropein (**39**)[11].

Discussion of the transition structure for the cycloaddition is difficult, as the configuration of the intermediary formed heterodiene cannot be determined. However, it is known that an *E*-heterodiene moiety reacts preferentially[2b,4d], thus **12** may be formed via *E*-**11** and **13** via *Z*-**11**. Under this assumption the 2,4-*trans*-substituted dihydropyrans, e.g. **13a**, should be obtained by an *exo*- and the 2,4-*cis*-diastereomers, e.g. **13b**, by an *endo*-orientation of the enol ether in the transition state.

Scheme 5



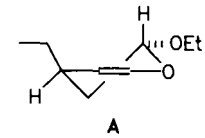
38a, b



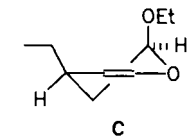
39

The structure of the dihydropyrans **3**, **15**, **22**–**27**, and **33**–**37** was established by NMR spectroscopy. For the 2,4-*trans* and 2,4-*cis* adducts the half chair conformations **A**/**B** and **C**/**D**, respectively, may be drawn. In **B** and **D** the substituent at C-4 displays a pseudo equatorial orientation, which is, as has been shown in many closely related examples[4b,5a,c], unfavorable; thus conformations **A** and **C** should predominate, even though in **A** an equatorial orientation is adopted by the OR group, which should be disfavored by an anomeric effect.

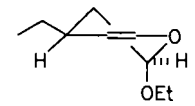
Scheme 6



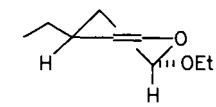
A



C



B



D

This assumption is in agreement with the coupling constants of the 2-H signal for the 2,4-*trans*-substituted dihydropyrans, e.g. **13a** at δ = 5.14 with J = 9.5 and 2.5 Hz. This clearly proves the axial orientation of 2-H in **13b**.

2-H in the 2,4-*cis*-dihydropyrans typically absorbs as a doublet of a triplet, e.g. for **13b** at δ = 5.20 with J = 1.0 and 3.5 Hz. The smaller coupling constant can be attributed to a W-coupling between 2-H and 4-H. Such a coupling is only possible for the 2,4-*cis* products in conformation **C**.

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Experimental

IR: Perkin-Elmer 297 or Bruker IFS 25. – UV: Varian Cary 219. – ^{1}H NMR: Varian XL-200. – ^{13}C NMR: Varian XL-200 (the assignment of the signals for the 2,4-*trans*- and 2,4-*cis*-isomers is indicated by **a** and **b**, respectively. The ratio of the isomers is determined from the ^{13}C-NMR signals with standard deviation in brackets). – MS (70 eV): Varian MAT 311A and MAT 731, (RDA stands for retro Diels-Alder fragments). – Elemental analyses: Microanalytical Laboratory of the University. – Solvents were dis-

tilled prior to use. All reactions were monitored by TLC (Macherey-Nagel & Co., SIL G/UV_{254}). Preparative column chromatography on silica gel (Woelm Pharma, Silica Woelm 32–63, aktiv). Solvents used for TLC and column chromatography: A, *tert*-butyl methyl ether/petroleum ether (1:25); B (1:12); C (1:10); D (1:8); E (1:6.5); F (1:6); G (1:5); H (1:4); I (1:3); K (1:1); L, dichloromethane/petroleum ether (1:6); M, diethyl ether/petroleum ether (1:1); N, acetone/petroleum ether (1:1.5). – All chiral products are obtained as racemic mixtures, since achiral compounds are used as substrates.

Tandem Knoevenagel Hetero Diels-Alder Reaction with 4,4,4-Trichloro-3-oxobutanal (**9**)

General Procedure 1 (GP 1): All experiments were scaled with respect to the amount of vinyl ether used (typically 1 mmol). To a solution of **9** (2.0 eq.) and the aldehydes **10** and **16**–**21**, respectively (2.2 eq.) in anhydrous dichloromethane (5.0 ml/mmol enol ether) was added without delay dried potassium fluoride (50 mg/mmol vinyl ether) and then dropwise the vinyl ethers **6** and **28**–**32**, respectively (1.00 eq.), neat or as solution in dichloromethane. The reaction mixture quickly changed color from yellow to dark brown. An intermediary precipitate was sometimes observed. After stirring for 24 h additional **9** (1 eq.), aldehyde (1.1 eq.), potassium fluoride (30 mg), and occasionally a few ml of the solvent were added. Stirring was continued for ca. 24 h (TLC control), and the reaction was quenched by dilution with ether and filtration through aluminum oxide (neutral, deactivated by addition of 10 g of water to 100 g of adsorbens) with ether as eluent. The solvent was evaporated in vacuo to give a crude mixture of the cycloadducts. In a few cases stirring had to be continued for 72 h and more of **9** (0.50 eq.) as well as potassium fluoride (30 mg) had to be added to complete the reaction.

General Procedure 2 (GP 2): The transformation was performed as in GP1 but with toluene as solvent and at 110–120°C. The reaction was usually complete within 1 h.

Isomerization of 2-Alkoxy-3,4-dihydro-6-(trichloromethyl)-2H-pyran-5-carbaldehydes. – General Procedure 3 (GP 3): To a solution of the crude products, obtained according to GP 1 or 2, in chloroform (ethanol-free) was added a few crystals of *p*-toluenesulfonic acid monohydrate, and the mixture was left standing for about 12 h (TLC control). Rapid filtration through silica gel and removal of the solvent in vacuo yielded an oil of the trichloromethyl ketones.

Transformation of Trichloromethyl Ketones into Methyl Carboxylates. – General Procedure 4 (GP 4), (1-mmol Scale): To a stirred solution of trichloromethyl ketones, obtained according to GP 1, 2, or 3, in anhydrous methanol (10 ml) was added dropwise 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 300 mg). The reaction was usually complete within less than 5 min (TLC control). After concentration in vacuo the residue was dissolved in ether and the solution filtered through silica gel to give the crude *methyl 2-alkoxy-3,4-dihydro-2H-pyran-5-carboxylates* **15**, **22**–**27**, and **33**–**38**, respectively.

(2RS,4RS)- and (2SR,4RS)-2-Ethoxy-4-ethyl-3,4-dihydro-2H-pyran-5-yl Trichloromethyl Ketone (**13a** *and* **13b**): Reaction of **9**, **10**, and 96 µl (1.00 mmol) of **6** according to GP 1 (45 h) and GP 2 afforded 177 mg (59%) of **13a** and **13b** as a ca. 1:2 mixture after chromatography on silica gel with solvent A. Separation of the diastereomeres was accomplished by chromatography on silica gel with solvent L. R_f = 0.10 (**13a**) and 0.16 (**13b**).

13a: IR (film): $\tilde{\nu}$ = 1685 cm^{-1} (C=O), 1610 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 280 nm (3.99). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.95 (t, *J* = 7 Hz, 3H, 4-CH_2CH_3), 1.28 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.15–1.40 (m, 1H, 4-*H*$CHCH_3$), 1.55–1.90 (m, 2H, 4-HC*H*CH_3 and 3-H_{ax}), 2.10 (dt, *J* = 14; 3 Hz, 1H, 3-H_{eq}), 2.63 (ddt, *J* = 9; 6; 3 Hz, 1H, 4-H), 3.69 (dq, *J* = 9.5; 7 Hz, 1H, O*H*$CHCH_3$), 4.02 (dq, *J* = 9.5; 7 Hz, 1H, OHC*H*CH_3), 5.14 (dd, *J* = 9.5; 2.5 Hz, 1H, 2-H), 8.21 (s, 1H, 6-H). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 11.59 (4-CH_2CH_3), 15.14 (OCH_2CH_3), 26.91 (4-CH_2CH_3), 29.92 (C-3), 31.54 (C-4), 65.68 (OCH_2CH_3), 96.01 (CCl_3), 98.89 (C-2), 110.7 (C-5), 159.0 (C-6), 180.4 (C=O). – MS (70 eV): *m/z* (%) = 300 (1) [M^+], 183 (48) [M – CCl_3], 155 (13) [M – $COCCl_3$], 72 (100) [RDA].

$C_{11}H_{15}Cl_3O_3$: 300.0087 found as calcd. (MS)

13b: IR (film) $\tilde{\nu}$ = 1680 cm^{-1} (C=O), 1615 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 279 nm (3.99). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.91 (t, *J* = 7 Hz, 3H, 4-CH_2CH_3), 1.23 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.55–1.8 (m, 2H, 4-CH_2CH_3), 1.88 (ddd, *J* = 14; 6.5; 3.5 Hz, 1H, 3-H_{ax}), 2.13 (dt, *J* = 14; 3.5 Hz, 1H, 3-H_{eq}), 2.62 (m_c, 1H, 4-H), 3.61 (dq, *J* = 9.5; 7 Hz, 1H, O*H*$CHCH_3$), 3.91 (dq, *J* = 9.5; 7 Hz, 1H, OHC*H*CH_3), 5.20 (td, *J* = 3.5; 1 Hz, 1H, 2-H), 8.19 (s, 1H, 6-H). – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 11.33 (4-CH_2CH_3), 15.15 (OCH_2CH_3), 25.10 (4-CH_2CH_3), 28.72 (C-3), 30.11 (C-4), 65.08 (OCH_2CH_3), 96.04 (CCl_3), 99.26 (C-2), 111.6 (C-5), 158.1 (C-6), 180.7 (C=O). – MS (70 eV): *m/z* (%) = 300 (0.6) [M^+], 183 (61) [M – CCl_3], 155 (13) [M – $COCCl_3$], 72 (100) [RDA].

$C_{11}H_{15}Cl_3O_3$: 300.0087 found as calcd. (MS)

Diastereomeric mixture:

$C_{11}H_{15}Cl_3O_3$ (301.6) Calcd. C 43.81 H 5.01 Cl 35.26
Found C 43.70 H 4.84 Cl 35.38

Methyl (2RS,4SR)-2-Ethoxy-4-ethyl-3,4-dihydro-2H-pyran-5-carboxylate (**15a**): 49 mg **13a** (0.16 mmol) in 8 ml of anhydrous methanol was treated with DBU according to GP 3. Flash chromatography on silica gel with solvent C gave 29 mg (82%) of **15a** as a colorless oil. – IR (KBr): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1630 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 235 nm (4.09). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.94 (t, *J* = 7 Hz, 3H, 4-CH_2CH_3), 1.1–1.4 (m, 1H, 4-*H*$CHCH_3$), 1.27 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.65–1.9 (m, 2H, 4-HC*H*CH_3, 3-H_{ax}), 1.96 (ddd, *J* = 13.5; 3.5; 2.5 Hz, 1H, 3-H_{eq}), 2.54 (m_c, 1H, 4-H), 3.64 (dq, *J* = 9.5, *J* = 7 Hz, 1H, O*H*$CHCH_3$), 3.73 (s, 3H, OCH_3), 4.00 (dq, *J* = 9.5; 7 Hz, 1H, OHC*H*CH_3), 5.00 (dd, *J* = 9; 2.5 Hz, 1H, 2-H), 7.50 (d, *J* = 0.5 Hz, 1H, 6-H). – MS (70 eV): *m/z* (%) = 214 (29) [M^+], 185 (100) [M – C_2H_5], 153 (92), 72 (86) [RDA].

$C_{11}H_{18}O_4$ (214.3) Calcd. C 61.66 H 8.47
Found C 61.79 H 8.31

Methyl (2SR,4SR)-2-Ethoxy-4-ethyl-3,4-dihydro-2H-pyran-5-carboxylate (**15b**): 89 mg (0.29 mmol) of **13b** in 8 ml of anhydrous methanol was treated with DBU according to GP 3. Filtration of the crude product through silica gel with ether and evaporation of the solvent gave 56 mg (88%) of **15b** as an oil, solidifying at −25°C. – IR (KBr): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1634 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 226 nm (4.10). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.90 (t, *J* = 7 Hz, 3H, 4-CH_2CH_3), 1.21 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 1.5–1.9 (m, 2H, OCH_2CH_3), 1.83 (ddd, *J* = 14; 7; 3 Hz, 1H, 3-H_{ax}), 2.01 (dt, *J* = 14; 4 Hz, 1H, 3-H_{eq}), 2.45 (m_c, 1H, 4-H), 3.55 (dq, *J* = 9.5; 7 Hz, 1H, O*H*$CHCH_3$), 3.73 (s, 3H, OCH_3), 3.87 (dq, *J* = 9.5; 7 Hz, 1H, OHC*H*CH_3), 5.11 (ddd, *J* = 4; 3; 0.5 Hz, 1H, 2-H), 7.47 (d, *J* = 1 Hz, 1H, 6-H). – MS (70 eV): *m/z* (%) = 214 (7) [M^+], 185 (26) [M – C_2H_5], 153 (37), 72 (81) [RDA], 44 (100).

$C_{11}H_{18}O_4$ (214.3) Calcd. C 61.66 H 8.47
Found C 61.51 H 8.33

Methyl (2RS,4SR)- and (2SR,4SR)-4-[(5,5-Dimethyl-1,3-dioxan-2-yl)methyl]-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**22a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **16**. Scale: 96 µl (72 mg, 1.00 mmol) of ethyl vinyl cther (**6**). Reaction time (GP1): 48 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent D. Flash chromatography of the methyl esters on silica gel with solvent E, repeated with solvent E, gradually changing to G. Yield 226 mg (72%) of **22a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1630 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 233 nm (4.06). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.71 (s, 5′-$CH_{3,eq}$ **a,b**), 1.19 (s, br, 5′-$CH_{3,ax}$ **a,b**), 1.20 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.26 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.60 (ddd, *J* = 14; 9; 5 Hz, 4-*H*CH **a**), 1.70–2.20 (m, 4-*H*CH **b**, 4-HC*H* **a,b**, 3-H_2 **a,b**), 2.73–2.96 (m, 4-H **a,b**), 3.34–4.06 (m, OCH_2CH_3 **a,b**, 4′-H_2 **a,b**, 6′-H_2 **a,b**), 3.71 (s, OCH_3 **a**), 3.72 (s, OCH_3 **b**), 4.55 (t, *J* = 5 Hz, 2′-H **a**), 4.56 (dd, *J* = 5.5; 5 Hz, 2′-H **b**), 5.03 (dd, *J* = 9.5; 2.5 Hz, 2-H **a**), 5.14 (td, *J* = 3; 0.5 Hz, 2-H **b**), 7.48 (s, br, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.12 (OCH_2CH_3 **a,b**), 21.90, 23.12, 23.86 (2 × 5′-CH_3, **a,b**, C-4 **b**) 25.80 (C-4 **a**), 30.04 (C-5′ **a**), 30.12, 30.34 (C-5′ **b**, C-3 **b**), 31.77 (C-3 **a**), 38.46 (4-CH_2 **b**), 39.83 (4-CH_2 **a**), 51.03 (OCH_3 **a,b**), 64.47 (OCH_2CH_3 **b**), 64.90 (OCH_2CH_3 **a**), 77.05–77.21 (C-4′ **a,b**, C-6′ **a,b**), 98.17 (C-2 **b**), 98.21 (C-2 **a**), 101.4 (C-2′ **a**), 101.7 (C-2′ **b**), 109.6 (C-5 **a**), 110.5 (C-5 **b**), 151.9 (C-6 **b**), 153.1 (C-6 **a**), 167.5 (C=O **a**), 167.7 (C=O **b**). Ratio of **22a**/**22b** (Evaluation of 9 signal pairs) = 1:1.74 (0.14). – MS (70 eV): *m/z* (%) = 314 (9) [M^+], 213 (23), 128 (79), 115 (99), 72 (41) [RDA], 69 (100).

$C_{16}H_{26}O_6$ (314.4) Calcd. C 61.13 H 8.34
Found C 60.99 H 8.32

Methyl (2RS,4SR)- and (2SR,4SR)-4-[(1,3-Dioxolan-2-yl)methyl]-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**23a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **17**. Scale: 96 µl (72 mg, 1.00 mmol) of **6**. Reaction time (GP1): 48 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel, starting with solvent D, gradually changing to E. Flash chromatography of the methyl esters on silica gel, starting with solvent G, gradually changing to I. Yield 155 mg (57%) of **23a,b**. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1635 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 234 nm (4.09). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.18 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.24 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.54–2.16 (m, 3-H_2 **a,b**, 4-CH_2 **a,b**), 2.71–2.94 (m, 4-H **a,b**), 3.4–4.06 (m, 3 × OCH_2 **a,b**), 3.71 (s, OCH_3 **a**), 3.72 (s, OCH_3 **b**), 4.96 (t, *J* = 5 Hz, 2′-H **a** or **b**), 5.02 (dd, *J* = 5.5; 5 Hz, 2′-H **a** or **b**), 5.04 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.16 (td, *J* = 3; 0.5 Hz, 2-H **b**), 7.51 (s, br, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.12 (OCH_2CH_3 **a**), 15.16 (OCH_2CH_3 **b**), 24.28 (C-4 **b**), 25.91 (C-4 **a**), 29.62 (C-3 **b**), 31.41 (C-3 **a**), 36.79 (4-CH_2 **b**), 38.40 (4-CH_2 **a**), 51.11 (OCH_3 **a,b**), 64.48–64.98 (3 × OCH_2 **a,b**), 98.19 (C-2 **a,b**), 103.6 (C-2′ **a**), 103.9 (C-2′ **b**), 109.5 (C-5 **a**), 110.3 (C-5 **b**), 152.1 (C-6 **b**), 153.3 (C-6 **a**), 167.5 (C=O **a**) 167.6 (C=O **b**). Ratio of **23a**/**23b** (Evaluation of 6 signal pairs) 1:1.39 (0.14). – MS (70 eV): *m/z* (%) = 272 (3) [M^+], 139 (22), 86 (69), 73 (100), 72 (63) [RDA].

$C_{13}H_{20}O_6$ (272.3) Calcd. C 57.34 H 7.40
Found C 57.55 H 7.34

Methyl(2RS,4RS)-and(2SR,4RS)-4-[(1,3-Dithian-2-yl)methyl]-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**24a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **18**. Scale: 96 µl (72 mg, 1.00 mmol) of **6**. Reaction time (GP1): 48 h. Purification: Repeated flash chromatography on silica gel with solvent E. Yield 183 mg (58%) of **24a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1630 (br, C=C). – UV (CH_3CN): λ_{max} (lg ε) = 235 nm (4.06). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.20 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.26 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.53–2.33 (m, 3-H_2 **a,b**, 4-CH_2 **a,b**, 5′-CH_2 **a,b**), 2.72–3.07 (m, 4′-H_2 **a,b**, 6′-H_2 **a,b**, 4-H **a,b**), 3.54 (dq, *J* = 9.5; 7 Hz, *OH*CHCH$_3$ **b**), 3.64 (dq, *J* = 9.5; 7 Hz, *OH*CHCH$_3$ **a**), 3.73 (s, OCH_3 **a**), 3.74 (s, OCH_3 **b**), 3.84 (dq, *J* = 9.5; 7 Hz, OHC*H*CH$_3$ **b**), 3.98 (dq, *J* = 9.5; 7 Hz, OHC*H*CH$_3$ **a**), 4.10 (dd, *J* = 10.5; 4.5 Hz, 2′-H **a**), 4.12 (dd, *J* = 8; 7 Hz, 2′-H **b**), 4.98 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.17 (t, *J* = 2.5 Hz, 2-H **b**), 7.51 (s, br, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.00 (OCH_2CH_3 **a,b**), 25.19 (C-4 **b**), 25.76 (C-5′ **a**), 25.96 (C-5′ **b**), 27.09 (C-4 **a**), 28.59 (C-3 **b**), 29.14, 29.43, 29.71, 29.95 (C-4′ **a,b**, C-6′ **a,b**), 30.73 (C-3 **a**), 37.87 (4-CH_2 **b**), 40.03 (4-CH_2 **a**), 44.47 (C-2′ **a**), 44.77 (C-2′ **b**), 51.07 (OCH_3 **a,b**), 64.41 (OCH_2CH_3 **b**), 65.01 (OCH_2CH_3 **a**), 97.79 (C-2 **b**), 97.87 (C-2 **b**), 109.1 (C-5 **a**), 109.9 (C-5 **b**), 152.2 (C-6 **b**), 153.3 (C-6 **a**), 167.3 (C=O **a**), 167.4 (C=O **b**). Ratio of **24a**/**24b** (Evaluation of 7 signal pairs) = 1:1.34 (0.07). – MS (70 eV): *m/z* (%) = 318 (82) [M^+], 119 (100), 72 (13) [RDA].

$C_{14}H_{22}O_4S_2$ (318.5) Calcd. C 52.80 H 6.96 S 20.14
Found C 52.70 H 7.03 S 20.33

Methyl (2RS,4RS)- and (2SR,4RS)-2-Ethoxy-3,4-dihydro-4-[2-(phenylthio)ethyl]-2H-pyran-5-carboxylate (**25a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **19**. Scale: 96 µl (72 mg, 1.00 mmol) of **6**. Reaction time (GP1): 48 h. Purification: Twofold flash chromatography of the trichloromethyl ketones on silica gel with solvent D. Repeated flash chromatography of the methyl esters on silica gel with solvents C and D. Yield 198 mg (63%) of **25a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1630 (br, C=C), 1585 (ar-C–C). – UV (CH_3CN): λ_{max} (lg ε) = 238 nm (4.16), 246 (sh). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.16 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.25 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.47–2.16 (m, 4-CH_2 **a,b**, 3-H_2 **a,b**), 2.65–3.18 (m, 2 × SCH_2 **a,b**, 4-H **a,b**), 3.45–4.05 (m, OCH_2CH_3 **a,b**), 3.68 (s, OCH_3 **a,b**), 4.95 (dd, *J* = 8.5; 2.5 Hz, 2-H **a**), 5.15 (t, *J* = 3 Hz, 2-H **b**), 7.10–7.40 (m, Ph **a,b**), 7.48 (s, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.12 (OCH_2CH_3 **a,b**), 27.24 (C-4 **b**), 28.61 (C-3 **b**), 28.89 (C-4 **a**), 30.84, 31.02, 31.19 (C-3 **a**, 2 × SCH_2 **a,b**), 32.44 (4-CH_2 **b**), 34.29 (4-CH_2 **a**), 51.07, 51.11 (OCH_3 **a,b**), 64.54 (OCH_2CH_3 **b**), 65.02 (OCH_2CH_3 **a**), 97.97 (C-2 **a,b**), 109.3 (C-5 **a**), 110.1 (C-5 **b**), 125.4 (Ph-C-4 **b**), 125.8 (Ph-C-4 **a**), 128.6, 128.7, 128.8, 128.9 (Ph-C-2 **a,b**, Ph-C-6 **a,b**, Ph-C-3 **a,b**, Ph-C-5 **a,b**), 136.5 (Ph-C-1 **b**), 137.0 (Ph-C-1 **a**), 152.1 (C-6 **b**), 153.2 (C-6 **a**), 167.5 (C=O **b**), 167.6 (C=O **a**). Ratio of **25a**/**25b** (Evaluation of 5 signal pairs) = 1:1.12 (0.08). – MS (70 eV): *m/z* (%) = 322 (18) [M^+], 166 (100), 123 (52) [$PhSCH_2$], 109 (41) [PhS].

$C_{17}H_{22}O_4S$ (322.4) Calcd. C 63.33 H 6.88 S 9.94
Found C 63.40 H 6.93 S 10.08

Methyl (2RS,4SR)- and (2SR,4SR)-2-Ethoxy-3,4-dihydro-4-{2-[(2-methoxyethoxy)methoxy]ethyl}-2H-pyran-5-carboxylate (**26a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **20**. Scale: 50 µl (37 mg, 0.52 mmol) of **6**. Reaction time (GP1): 48 h. Purification: Flash chromatography on silica gel with solvent M. Yield 103 mg (62%) of **26a,b**. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1635 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 234 nm (4.02). – ^1H-NMR ($CDCl_3$, 200 MHz): δ = 1.18 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.26 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.4–2.12 (m, 4-CH_2 **a,b**, 3-H_2 **a,b**), 2.62–2.84 (m, 4-H **a,b**), 3.41 (s, CH_2OCH_3 **a,b**), 3.44–4.10 (m, 3 × OCH_2CH_2R **a,b**), 3.71 (s, CO_2CH_3 **a**), 3.72 (s, CO_2CH_3 **b**), 4.68–4.80 (m, OCH_2O **a,b**), 5.03 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.14 (t, *J* = 3 Hz, 2-H **b**), 7.51 (s, 6-H **a,b**). The integration

is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.14 (OCH_2CH_3 **a,b**), 25.21 (C-4 **b**), 27.11 (C-4 **a**), 29.02 (C-3 **b**), 31.11 (C-3 **a**), 32.60 (4-CH_2 **b**), 34.48 (4-CH_2 **a**), 51.10 (CO_2CH_3 **a,b**), 58.98 (CH_2OCH_3 **a,b**), 64.55 (OCH_2CH_3 **b**), 65.00 (OCH_2CH_3 **a**), 65.70, 66.66, 66.79, 71.83 (3 × OCH_2CH_2R **a,b**, not well resolved), 95.19 (OCH_2O **a**), 95.38 (OCH_2O **b**), 98.11 (C-2 **a**), 98.27 (C-2 **b**), 109.8 (C-5 **a**), 110.6 (C-5 **b**), 152.0 (C-6 **b**), 153.1 (C-6 **a**), 167.6 (C=O **a**), 167.8 (C=O **b**). Ratio of **26a/26b** (Evaluation of 8 signal pairs) = 1:2.22 (0.13). – MS (70 eV): *m/z* (%) = 287 (2) [M – OCH_3], 243 (4) [M – $CH_2CH_2OCH_3$], 72 (66) [RDA], 59 (100) [$CH_3OCH_2CH_2$].

$C_{15}H_{26}O_7$ (318.4) Calcd. C 56.59 H 8.23
Found C 56.42 H 8.19

Methyl (2RS,4SR)- and (2SR,4SR)-4-[2-(Benzyloxy)ethyl]-2-ethoxy-3,4-dihydro-2H-pyran-5-carboxylate (**27a,b**): Preparation according to GP1, GP3, and GP4 from **6**, **9**, and **21**. Scale: 96 µl (72 mg, 1.00 mmol) of **6**. Reaction time (GP1): 50 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent D, repeated for impure fractions. Flash chromatography of the methyl esters on silica gel with solvent E. Yield 199 mg (62%) of **27a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1630 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 209 nm (4.04), 235 (4.09). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.18 (t, *J* = 7 Hz, OCH_2CH_3 **b**), 1.24 (t, *J* = 7 Hz, OCH_2CH_3 **a**), 1.5–2.2 (m, 3-H_2, 4-CH_2 **a,b**), 2.67–2.85 (m, 4-H **a,b**), 3.46–4.06 (m, OCH_2CH_3 **a,b**, Bzl-OCH_2 **a,b**), 3.73 (s, OCH_3 **a**), 3.74 (s, OCH_3 **b**), 4.49, 4.55 (AB system, *J* = 10 Hz, $PhCH_2$ **a**), 4.50, 4.58 (AB system, *J* = 12 Hz, $PhCH_2$ **b**), 5.04 (dd, *J* = 9, *J* = 2.5 Hz, 2-H **a**), 5.14 (td, *J* = 3; 0.5 Hz, 2-H **b**), 7.24 to 7.45 (m, Ph **a,b**), 7.52 (s, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.14 (OCH_2CH_3 **a,b**), 25.26 (C-4 **b**), 27.43 (C-4 **a**), 29.16 (C-3 **b**), 31.26 (C-3 **a**), 32.51 (4-CH_2 **b**), 34.59 (4-CH_2 **a**), 51.05 (OCH_3 **a,b**), 64.51 (OCH_2CH_3 **b**), 65.00 (OCH_2CH_3 **a**), 68.34 ($PhCH_2$ **b**), 68.52 ($PhCH_2$ **a**), 72.33 (BzlOCH_2 **b**), 72.78 (BzlOCH_2 **a**), 98.28 (C-2 **a,b**), 109.8 (C-5 **a**), 110.7 (C-5 **b**), 127.3, 127.5, 127.5, 128.3, 128.3 (Ph-C-2, -6, -3, -5, -4 **a,b**), 138.4 (Ph-C-1 **a**), 138.7 (Ph-C-1 **b**), 152.0 (C-6 **b**), 153.2 (C-6 **a**), 167.6 (C=O **a**), 167.8 (C=O **b**). Ratio of **27a/27b** (Evaluation of 10 signal pairs) = 1:1.73 (0.09). – MS (70 eV): *m/z* (%) = 320 (18) [M^+], 183 (31), 91 (100) [C_7H_7], 72 (22) [RDA].

$C_{18}H_{24}O_5$ (320.4) Calcd. C 67.48 H 7.55
Found C 67.28 H 7.23

Methyl (2RS,4SR)- and (2SR,4SR)-2-(Benzyloxy)-4-[(5,5-dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2H-pyran-5-carboxylate (**33a,b**): Preparation according to GP2, GP3, and GP4 from **9**, **16**, and **28**. Scale: 124 mg (0.93 mmol) of benzyl vinyl ether (**28**). Reaction time (GP2): 1 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent D. Flash chromatography of the methyl esters on silica gel starting with solvent F gradually changing to H. Yield: 210 mg (60%) of **33a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1635, 1630 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 210 nm (4.00), 217 (3.99), 233 (4.17). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.69 (s, 5′-$CH_{3,eq}$ **a,b**), 1.13 (s, 5′-$CH_{3,ax}$ **a**), 1.17 (s, 5′-$CH_{3,ax}$ **b**), 1.47 (ddd, *J* = 14; 9; 5 Hz, 4-*H*CH **a**), 1.76–2.25 (m, 4-*H*CH **b**, 4-HC*H* **a,b**, 3-H **a,b**), 2.74–2.97 (m, 4-H **a,b**), 3.30–3.48, 3.50–3.66 (m, 4′-H_2 **a,b**, 6′-H_2 **a,b**), 3.71 (s, OCH_3 **a**), 3.72 (s, OCH_3 **b**), 4.51 (t, *J* = 5 Hz, 2′-H **a** or **b**), 4.58 (t, *J* = 5.5 Hz, 2′-H **a** or **b**), 4.60, 4.85 (AB system, *J* = 12.5 Hz, $PhCH_2$ **b**), 4.66, 4.94 (AB system, *J* = 12 Hz, $PhCH_2$ **a**), 5.12 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.22 (t, *J* = 3 Hz, 2-H **b**), 7.28–7.45 (m, Ph **a,b**), 7.50 (d, *J* = 0.5 Hz, 6-H **b**), 7.51 (s, br, 6-H **a**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.86, 23.08 (2 × 5′-CH_3 **a,b**), 23.70 (C-4 **b**), 25.65 (C-4 **a**), 29.91, 29.98, 30.07 (C-5′ **a,b**, C-3 **b**), 31.73 (C-3 **a**), 38.82 (4-CH_2 **b**), 39.69 (4-CH_2 **a**), 51.09 (OCH_3 **a,b**), 70.36 ($PhCH_2$ **b**), 70.63 ($PhCH_2$ **a**), 77.00–77.14 (C-4′ **a,b**, C-6′ **a,b**), 97.28 (C-2 **b**), 97.38 (C-2 **a**), 101.3 (C-2′ **a**), 101.7 (C-2′ **b**), 109.9 (C-5 **a**), 110.7 (C-5 **b**), 127.3–128.4 (Ph-C-2, -3, -4, -5, -6 **a,b**), 137.0 (Ph-C-1 **a**), 137.4 (Ph-C-1 **b**), 151.7 (C-6 **b**), 152.9 (C-6 **a**), 167.4 (C=O **a**), 167.6 (C=O **b**). Ratio of **33a/33b** (Evaluation of 7 signal pairs) = 1:1.38 (0.08). – MS (70 eV): *m/z* (%) = 376 (7) [M^+], 139 (50), 115 (100), 91 (35) [C_7H_7].

$C_{21}H_{28}O_6$ (376.45) Calcd. C 67.00 H 7.50
Found C 66.95 H 7.47

Methyl (2RS,4SR)- and (2SR,4SR)-2-(2-Chloroethoxy)-4-[(5,5-dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2H-pyran-5-carboxylate (**34a,b**): Preparation according to GP2, GP3, and GP4 from **9**, **16**, and **29**. Scale: 105 mg (0.99 mmol) of 2-chloroethyl vinyl ether (**29**). Reaction time (GP2): 1 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent E. Flash chromatography of the methyl esters on silica gel with solvent H and with solvent N. Yield 189 mg (55%) of **34a,b**. – IR (film): $\tilde{\nu}$ = 1705 cm^{-1} (C=O), 1635 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 232 nm (4.05). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.71 (s, 5′-$CH_{3,eq}$ **a,b**), 1.18 (s, 5′-$CH_{3,ax}$ **a,b**), 1.50–2.25 (4-CH_2, 3-H **a,b**), 2.73–2.98 (m, 4H **a,b**), 3.35–4.20 (m, 3 × OCH_2, $ClCH_2$ **a,b**), 4.55 (t, *J* = 5 Hz, 2′-H **a** or **b**), 4.58 (t, *J* = 5 Hz, 2′-H **a** or **b**), 5.08 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.21 (t, *J* = 3 Hz, 2-H **b**), 7.47 (s, br, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C-NMR ($CDCl_3$, 50.3 MHz): δ = 21.87 (5′-CH_3 **a,b**), 23.09 (5′-CH_3 **a,b**), 23.52 (C-4 **b**), 25.57 (C-4 **a**), 29.72, 30.02, 30.10 (C-3 **b**, C-5′ **a,b**), 31.43 (C-3 **a**), 38.30 (4-CH_2 **b**), 39.59 (4-CH_2 **a**), 42.56 ($ClCH_2$ **a,b**), 51.12 (OCH_3 **a,b**), 68.95 (2-OCH_2 **b**), 69.32 (2-OCH_2 **a**), 77.01–77.16 (C-4′ **a,b**, C-6′ **a,b**), 98.38 (C-2 **b**), 98.54 (C-2 **a**), 101.3 (C-2′ **a**), 101.6 (C-2′ **b**), 110.0 (C-5 **a**), 110.9 (C-5 **b**), 151.3 (C-6 **b**), 152.6 (C-6 **a**), 167.3 (C=O **a**), 167.5 (C=O **b**). Ratio of **34a/34b** (Evaluation of 5 signal pairs) = 1:1.17 (0.05). – MS (70 eV): *m/z* (%) = 348 (6) [M^+], 139 (69), 128 (100), 106 (10) [RDA].

$C_{16}H_{25}ClO_6$ (348.8) Calcd. C 55.09 H 7.22 Cl 10.16
Found C 55.10 H 7.27 Cl 10.00

Methyl (2RS,4SR)- and (2SR,4SR)-4-[(5,5-Dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2-[2-(phenylthio)ethoxy]-2H-pyran-5-carboxylate (**35a,b**): Preparation according to GP2, GP3, and GP4 from **9**, **16**, and **30**. Scale: 174 mg (0.97 mmol) of 2-(phenylthio)ethyl vinyl ether (**30**). Reaction time (GP2): 1 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent D. Flash chromatography of the methyl esters on silica gel with solvent H, repeated twice for impure fractions. Yield 266 mg (65%) of **35a,b**. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1635 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 234 nm (4.20), 250 (sh). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.70 (s, 5′-$CH_{3,eq}$ **a,b**), 1.16, 1.18 (2 × s, 5′-$CH_{3,ax}$ **a,b**), 1.48–2.19 (m, 4-CH_2 **a,b**, 3-H_2 **a,b**), 2.72–2.82 (m, 4-H **a,b**), 3.05–3.20 (m, SCH_2 **a,b**), 3.32–4.11 (m, 3 × OCH_3 **a,b**), 3.71, 3.73 (2 × s, OCH_3 **a,b**), 4.53 (t, *J* = 5 Hz, 2′-H **a** or **b**), 4.56 (dd, *J* = 5.5; 5 Hz, 2′-H **a** or **b**), 5.01 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.16 (t, *J* = 3 Hz, 2-H **b**), 7.16–7.5 (m, Ph **a,b**), 7.45 (s, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.81, 21.86 (5′-CH_3 **a,b**), 23.09 (5′-CH_3 **a,b**), 23.57 (C-4 **b**), 25.59 (C-4 **a**), 29.90, 29.98, 30.07 (C-3 **b**, C-5′ **a,b**), 31.48 (C-3 **a**), 33.13 (S-CH_2 **a,b**), 38.39 (4-CH_2 **b**), 39.61 (4-CH_2 **a**), 51.07 (OCH_3 **a,b**), 67.65 (2-OCH_2 **b**), 68.07 (2-OCH_2 **a**), 76.98, 77.07 (C-4′ **a,b**, C-6′ **a,b**), 98.32 (C-2 **b**), 98.48 (C-2 **a**), 101.3 (C-2′ **a**), 101.6 (C-2′ **b**), 109.8 (C-5 **a**), 110.7 (C-5 **b**), 126.2 (Ph-C-4 **b**), 126.3 (Ph-C-4 **a**), 128.9 (Ph-C-2 **a,b**, Ph-C-6 **a,b**), 129.5 (Ph-C-3 **a,b**, Ph-C-5 **a,b**), 135.5 (Ph-C-1 **a**), 135.6 (Ph-C-1 **b**), 151.4 (C-6 **b**), 152.7 (C-6 **a**), 167.3 (C=O **a**), 167.6 (C=O **b**). Ratio of **35a/35b** (Evaluation of 7 signal

pairs) = 1:1.30 (0.09). – MS (70 eV): *m/z* (%) = 422 (31) [M^+], 137 (100) [$PhSCH_2CH_2$], 109 (19) [PhS].

$C_{22}H_{30}O_6S$ (422.5) Calcd. C 62.54 H 7.16 S 7.59
Found C 62.67 H 7.32 S 7.42

Methyl (2RS,4SR)- and (2SR,4SR)-4-[(5,5-Dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2-(3-hydroxypropoxy)-2H-pyran-5-carboxylate (**36a,b**): Preparation according to GP2, GP3, and GP4 from **9**, **16** and **31**. During the haloform cleavage, methanolysis of the dinitrobenzoate occurs, accompanied by a color change to deep red. Scale: 292 mg (0.99 mmol) of **31**. Reaction time (GP2): 1 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent K, repeated for impure fractions. Flash chromatography of the methyl esters on silica gel with solvent N, repeated for impure fractions in ether. Yield 220 mg (65%) of **36a,b**. – IR (film): $\tilde{\nu}$ = 3470 cm^{-1} (OH), 1705 (C=O), 1635 (C=C). – UV (CH_3CN): λ_{max} (lg ε) = 233 nm (4.07). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.71 (s, 5′-$CH_{3,eq}$ **a,b**), 1.18 (s, 5′-$CH_{3,ax}$ **a,b**), 1.55 (ddd, *J* = 14; 9.5; 5 Hz, 4-*H*CH **a**), 1.70–2.10 [m, 4-*H*CH **b**, 4-HC*H* **a,b**, 3-H_{ax} **a,b**, *H*OCH_2 (OH exchangeable with D_2O) **a,b**], 2.14 (dt, *J* = 14; 2.8 Hz, 3-H_{eq} **a**), 2.27 (dt, *J* = 14.5; 2.5 Hz, 3-H_{eq} **b**), 2.75–2.95 (m, 4-H **a,b**), 3.33–3.50, 3.52–3.68 (m, 4′-H_2 **a,b**, 6′-H_2 **a,b**), 3.52–3.84, 3.90–4.16 (m, $OCH_2CH_2CH_2OH$ **a,b**), 3.71 (s,OCH_3 **a**), 3.72 (s, OCH_3 **b**), 4.54 (t, *J* = 5 Hz, 2′-H **a**), 4.56 (t, *J* = 5 Hz, 2′-H **b**), 5.02 (dd, *J* = 9.5; 2.5 Hz, 2-H **a**), 5.17 (t, *J* = 2.5 Hz, 2-H **b**), 7.47 (s, 6-H **a**), 7.48 (d, *J* = 1 Hz, 6-H **b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.86 (5′-CH_3 **a,b**), 23.09 (5′-CH_3 **a,b**), 23.61 (C-4 **b**), 25.73 (C-4 **a**), 29.63, 30.07, 30.10 (C-3 **b**, C-5′ **a,b**), 31.59 (C-3 **a**), 32.22 ($HOCH_2CH_2$ **a,b**), 38.04 (4-CH_2 **b**), 39.70 (4-CH_2 **a**), 51.21 (OCH_3 **a,b**), 60.00 ($HOCH_2$ **b**), 60.22 ($HOCH_2$ **a**), 66.85 (2-OCH_2 **b**), 67.13 (2-OCH_2 **a**), 77.06, 77.16 (C-4′ **a,b**, C-6′ **a,b**), 98.40 (C-2 **b**), 98.46 (C-2 **a**), 101.4 (C-2′ **a**), 101.8 (C-2′ **b**), 109.7 (C-5 **a**), 110.5 (C-5 **b**), 151.9 (C-6 **b**), 153.0 (C-6 **a**), 167.6 (C=O **a**), 167.8 (C=O **b**). Ratio of **36a**/**36b** (Evaluation of 7 signal pairs) = 1:1.36 (0.09). – MS (70 eV): *m/z* (%) = 344 (12) [M^+], 128 (100).

$C_{17}H_{28}O_7$ (344.4) Calcd. C 59.29 H 8.19
Found C 59.19 H 8.15

Methyl (2SR,4SR)- and (2RS,4SR)-4-[(5,5-Dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2-phenoxy-2H-pyran-5-carboxylate (**37a,b**): Preparation according to GP2, GP3, and GP4 from **9**, **16**, and **32**. Scale: 122 mg (1.02 mmol) of phenyl vinyl ether (**32**). Reaction time (GP2): 2 h. Purification: Flash chromatography of the trichloromethyl ketones on silica gel with solvent B. Flash chromatography of the methyl esters on silica gel with solvent H. Yield 156 mg (42%) of **37a,b**. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (br, C=O), 1635 (br, C=C). – UV (CH_3CN): λ_{max} (lg ε) = 227 nm (4.19), 257 (3.07), 264 (2.98). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.71 (s, 5′-$CH_{3,eq}$ **a**), 0.73 (s, 5′-$CH_{a,eq}$ **b**), 1.18 (s, 5′-$CH_{3,ax}$ **a**), 1.21 (s, 5′-$CH_{3,ax}$ **b**), 1.67 (ddd, *J* = 14; 9.5; 5 Hz, 4-*H*CH **a**), 1.94–2.4 (m, 4-*H*CH **b**, 4-HC*H* **a,b**, 3-H_{ax} **a,b**, 3-H_{eq} **a**), 2.41 (dt, *J* = 14.5; 2.5 Hz, 3-H_{eq} **b**), 2.85–3.07 (m, 4-H **a,b**), 3.35–3.68 (m, 4′-H_2 **a,b**, 6′-H_2 **a,b**), 3.73 (s, OCH_3 **a,b**), 4.56 (t, *J* = 5.0 Hz, 2′-H **a**), 4.65 (t, *J* = 5.5 Hz, 2′-H **b**), 5.69 (dd, *J* = 9; 2.5 Hz, 2-H **a**), 5.84 (t, *J* = 2.5 Hz, 2-H **b**), 6.98–7.11 (m, Ph **a,b**), 7.46 (d, *J* = 0.5 Hz, 6-H **b**), 7.48 (d, *J* = 0.5 Hz, 6-H **a**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.89, 23.13 (2 × 5′-CH_3 **a,b**), 23.55 (C-4 **b**), 25.42 (C-4 **a**), 29.74, 30.02, 30.13 (C-3 **b**, C-5′ **a,b**), 31.61 (C-3 **a**), 38.33 (4-CH_2 **b**), 39.37 (4-CH_2 **a**), 51.20 (OCH_3 **a,b**), 77.08–77.24 (C-4′ **a,b**, C-6′ **a,b**), 95.37 (C-2 **b**), 95.69 (C-2 **a**), 101.3 (C-2′ **a**), 101.7 (C-2′ **b**), 110.3 (C-5 **a**), 111.0 (C-5 **b**), 116.3, 116.5 (Ph-C-2 **a,b**, Ph-C-6 **a,b**), 122.5 (Ph-C-4 **b**), 122.7 (Ph-C-4 **a**), 129.4, 129.5 (Ph-C-3 **a,b**, Ph-C-5 **a,b**), 151.2 (C-6 **b**), 152.4 (C-6 **a**), 156.4 (Ph-C-1 **b**), 156.5 (Ph-C-1 **a**), 167.2 (C=O **a**), 167.5 (C–O **b**). Ratio of **37a**/**37b** (Evaluation of 5 signal pairs) = 1:1.93 (0.08). – MS (70 eV): *m/z* (%) = 362 (0.2) [M^+], 139 (100), 120 (3) [RDA].

$C_{20}H_{26}O_6$ (362.4) Calcd. C 66.28 H 7.23
Found C 66.11 H 7.08

Methyl (2RS,4SR)- and (2SR,4SR)-4-[(5,5-Dimethyl-1,3-dioxan-2-yl)methyl]-3,4-dihydro-2-methoxy-3-methylen-2H-pyran-5-carboxylate (**38a,b**): Preparation according to GP1, GP3, and GP4 from **9**, **16**, and methoxyallene. Scale: 80 mg (1.14 mmol) of methoxyallene. Reaction time (GP1): 75 h. Purification: Filtration of the trichloromethyl ketones through silica gel in solvent D. Filtration of the methyl esters through deactivated alumina (neutral, 10% H_2O) with ether and flash chromatography on silica gel with solvent E. Yield 161 mg (45%) of **38a,b**. – IR (film): $\tilde{\nu}$ = 1710 cm^{-1} (C=O), 1660 (C=C), 1630 (C=C, conj.). – UV (CH_3CN): λ_{max} (lg ε) = 234 nm (3.97). – ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.70 (s, 5′-$CH_{3,eq}$ **a,b**), 1.18 (s, 5′-$CH_{3,ax}$ **a**), 1.20 (s, 5′-$CH_{3,ax}$ **b**), 1.60 (ddd, *J* = 14; 10.5; 3.5 Hz, 4-*H*CH **a**), 1.70–2.22 (m, 4-*H*CH **b**, 4-HC*H* **a,b**), 3.3–3.7 (m, 4′-H_2 **a,b**, 6′-H_2 **a,b**), 3.46 (s, 2-OCH_3 **b**), 3.66 (s, 2-OCH_3 **a**), 3.73 (s, CO_2CH_3 **a**), 3.74 (s, CO_2CH_3 **b**), 4.43 [dd, *J* = 7.5; 3 Hz, 2′-H **a** and (hidden) 2′-H **b**], 5.1–5.45 (m, 2′-H **a,b** =CH_2 **a,b**), 7.48 (s, br, 6-H **a,b**). The integration is in accordance with the given assignments. – ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 21.91 (5′-CH_3 **a,b**), 23.14 (5′-CH_3 **a,b**), 30.15 (C-5′ **a**), 30.23 (C-5′ **b**), 33.00 (C-4 **b**), 35.27 (C-4 **a**), 37.25 (4-CH_2 **b**), 39.71 (4-CH_2 **a**), 51.31 (CO_2CH_3 **a,b**), 56.06 (2-OCH_3 **b**), 57.19 (2-OCH_3 **a**), 77.02, 77.10, 77.24, 77.31 (C-4′ **a,b**, C-6′ **a,b**), 98.48, 100.4 (C-2, -2′ **a**), 100.9, 102.4 (C-2, -2′ **b**), 109.4 (C-5 **a**), 110.1 (C-5 **b**), 112.9 (=CH_2 **a**), 117.0 (=CH_2 **b**), 138.8 (C-3 **a**), 139.3 (C-3 **b**), 151.3 (C-6 **b**), 152.8 (C-6 **a**), 167.0 (C=O **a**), 167.2 (C=O **b**). Ratio of **38a**/**38b** (Evaluation of 7 signal pairs) = 2.51:1 (0.12). – MS (70 eV): *m/z* (%) = 312 (2) [M^+], 128 (36), 115 (74), 69 (100).

$C_{16}H_{24}O_6$ (312.4) Calcd. C 61.52 H 7.74
Found C 61.62 H 7.66

CAS Registry Numbers

6: 109-92-2 / **7**: 76-02-8 / **8**: 83124-74-7 / **9A**: 34648-10-7 / **10**: 123-38-6 / (±)-**13a**: 117960-82-4 / (±)-**13b**: 117960-83-5 / (±)-**15a**: 117960-84-6 / (±)-**15b**: 117960-85-7 / **16**: 82995-27-5 / **17**: 90711-96-9 / **18**: 57688-55-8 / **19**: 27098-65-3 / **20**: 91106-33-1 / **21**: 19790-60-4 / (±)-**22a**: 117960-86-8 / (±)-**22b**: 117960-99-3 / (±)-**23a**: 117960-87-9 / (±)-**23b**: 117961-00-9 / (±)-**24a**: 117960-88-0 / (±)-**24b**: 117961-01-0 / (±)-**25a**: 117960-89-1 / (±)-**25b**: 117961-02-1 / (±)-**26a**: 117960-90-4 / (±)-**26b**: 117961-03-2 / (±)-**27a**: 117960-91-5 / (±)-**27b**: 117961-04-3 / **28**: 935-04-6 / **29**: 110-75-8 / **30**: 6613-39-4 / **31**: 117960-92-6 / **32**: 766-94-9 / (±)-**33a**: 117960-93-7 / (±)-**33b**: 117961-06-5 / (±)-**34a**: 117960-94-8 / (±)-**34b**: 117961-07-6 / (±)-**35a**: 117960-95-9 / (±)-**35b**: 117961-08-7 / (±)-**36a**: 117960-96-0 / (±)-**36b**: 117961-09-8 / (±)-**37a**: 117960-97-1 / (±)-**37b**: 117982-92-0 / (±)-**38a**: 117960-98-2 / (±)-**38b**: 117961-05-4 / methoxyallene: 13169-00-1

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