On the Scope of a *Prins*-Type Cyclization of Oxonium Ions

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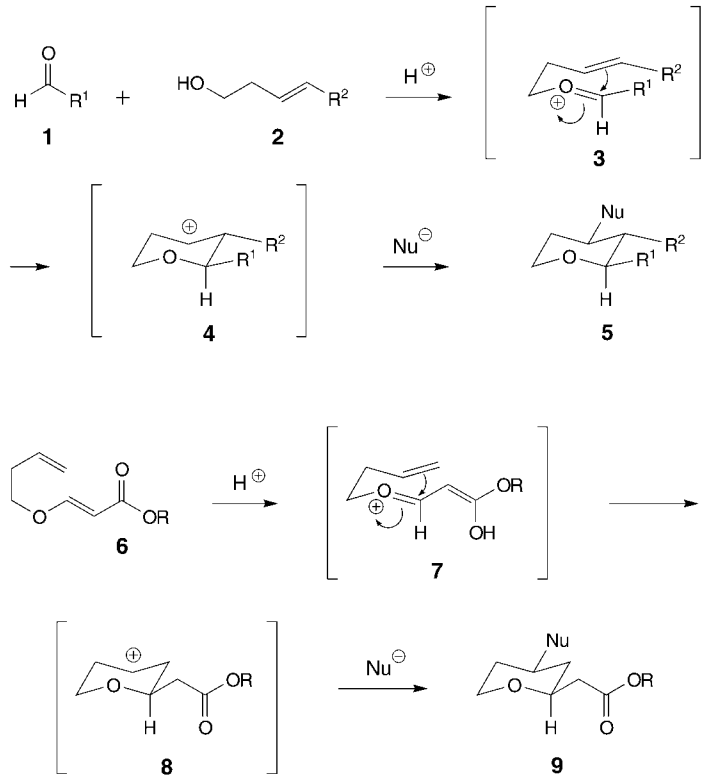
The *Prins* cyclization of an aldehyde **1** with a homoallylic alcohol **2**, affording tetrahydro-2*H*-pyrans **4** *via* the oxonium ion **3** as central intermediate, was conceptually transferred to (alk-3-enyloxy)acrylates **6**, which form a related oxonium ion **7** upon treatment with acids (*Scheme 1*). The scope and utility of this modification of the *Prins*-type cyclization of oxonium ions is discussed exemplarily by means of the syntheses of ten tetrahydro-2*H*-pyran and tetrahydrofuran derivatives, featuring diverse substitution patterns as well as different degrees of molecular complexity. These target structures include (±)-ethyl (2*RS*)-2-[(2*RS*,4*SR*,6*RS*)- and (2*SR*,4*RS*,6*SR*)-2-tetahydro-4-hydroxy-6-methylpyran-2-yl]propanoate (**23**), (±)-ethyl [(2*RS*, 3*RS*)-tetrahydro-3-isopropenylfuran-2-yl]acetate (**32**), (±)-ethyl (2*Z*)-3-(tetrahydro-2,2-dimethylfuran-3-yl)acrylate (**37**), (±)-(3a*RS*,6*RS*,7a*RS*)-octahydro-7a-methylbenzofuran-6-yl formate (**42**), (±)-ethyl (2*RS*,3*RS*,4a*RS*,8*SR*,8a*RS*)-hexahydro-2,5,5,8-tetramethyl-7-oxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-carboxylate (**48**), and (±)-ethyl (2*RS*,3*RS*,6*SR*)-tetrahydro-6-(2-methoxy-2-oxoethyl)-3-methyl-2*H*-pyran-2-carboxylate (**53**) (see *Schemes 3* and *5–8*). Besides the stereochemistry and mechanistic details of this versatile oxonium-ion cyclization, the synthesis of suitable starting materials is also described.

Introduction. – While tetrahydro-2*H*-pyran derivatives are formed only as by-products in the general *Prins* reaction of aldehydes with olefins [1], the acid-catalyzed reaction of an aldehyde **1** with a homoallylic alcohol **2** affords tetrahydro-2*H*-pyrans **4** usually in good yields [2]. This so-called *Prins* cyclization has actually become a quite well-established method for the synthesis of tetrahydro-2*H*-pyrans, with applications even in complex syntheses of natural products [3][4]. A chair conformation of the intermediate oxonium ion **3** accounts for the observed *trans*-configuration of the product **4** (*Scheme 1*).

The related oxonium ion **7** is formed upon treatment of (alk-3-enyloxy)acrylates **6** with acids by protonation of the carbonyl O-atom. Direct protonation of the enol-ether C=C bond is also possible but energetically less favorable. The oxonium ion **7** cyclizes to the carbenium ion **8**, which is either trapped by a nucleophile Nu^- to afford **9** or eliminates a proton under formation of a 3,6-dihydro-2*H*-pyran system. This modification of the *Prins* cyclization was first employed in a stereoselective synthesis of the orris odorant (±)-*cis*-α-irone (**13**) [5], and in a synthesis of (±)-(*cis*-tetrahydro-6-methyl-2*H*-pyran-2-yl)acetic acid (**17**), a constituent of the glandular secretion of the civet cat *Viverra civetta* (*Scheme 2*) [6]. The starting materials **10** and **14** were prepared according to a procedure of *Winterfeld* and *Preuss* [7] by addition of methyl propiolate (= methyl prop-2-ynoate) to the corresponding alcohols in the presence of *N*-methylmorpholine, and the 3-(alkyloxy)acrylate cyclizations were effected by catalytic amounts of methanesulfonic acid (MsOH) in CH_2Cl_2 with the stereochemistry being controlled by the chair-like transition states **11** and **15**, respectively, in which the

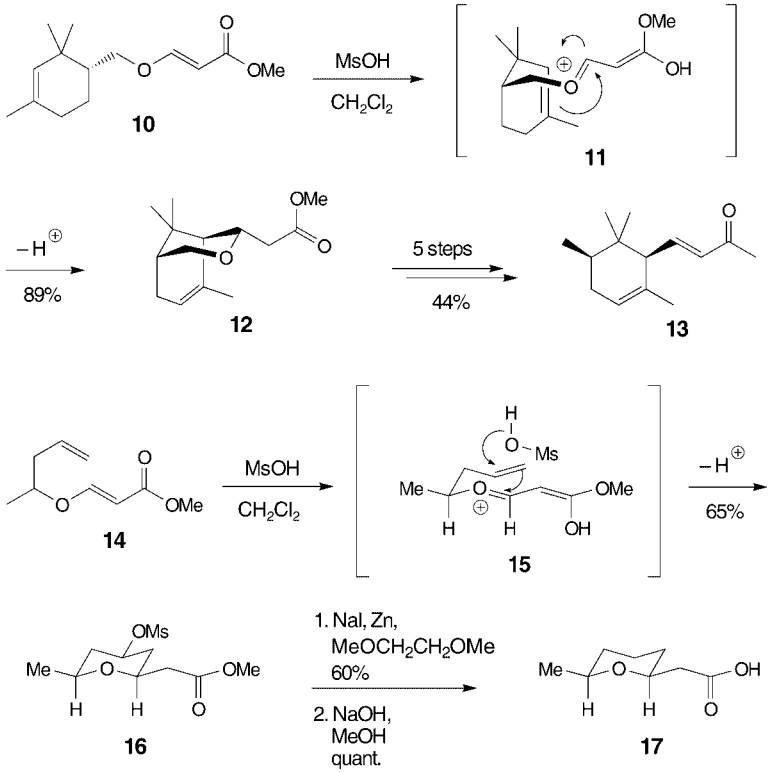
Scheme 1. *The Original* Prins *Cyclization and the Modified Version Discussed Here*



(methoxycarbonyl)methyl group is in quasi-equatorial position. Notably, the cyclohexenyl C=C bond in transition state **11** is in the quasi-axial position.

This modification of the *Prins* cyclization has since been employed successfully in several syntheses of pyran systems, *e.g.*, in the stereocontrolled construction of the C(1)-to-C(15) fragment of the marine macrolide leucascandrolide A by *Kozmin* [8]. *Hart* and *Bennett* recently studied the cyclization of differently (1-substituted alk-3-enyloxy)acrylates [9]. If vinyl enol ethers are used instead of acrylates **6** and treated with a powerful *Lewis* acid such as $TiCl_4$ or $TiBr_4$ in the presence of an aldehyde, *Mukaiyama*-type addition of the enol ether C=C bond to the aldehyde–*Lewis* acid electrophile generates a (but-3-enyl)(3-oxidoalkylidene)oxonium ion, which then cyclizes to a 4-halotetrahydro-2*H*-pyran [10][11]. This so-called *Mukaiyama* aldol–*Prins* cascade reaction, for which the abbreviation MAP cyclization was coined, once more illustrates the usefulness and versatility of the *Prins*-type cyclization of oxonium ions. In the following, we will discuss the scope of the *Prins* cyclization of (alk-3-enyl)(alkylidene)oxonium ions by means of the example of some simple structures, some of which were interesting for their sensory properties or as intermediates in the synthesis of new odorants.

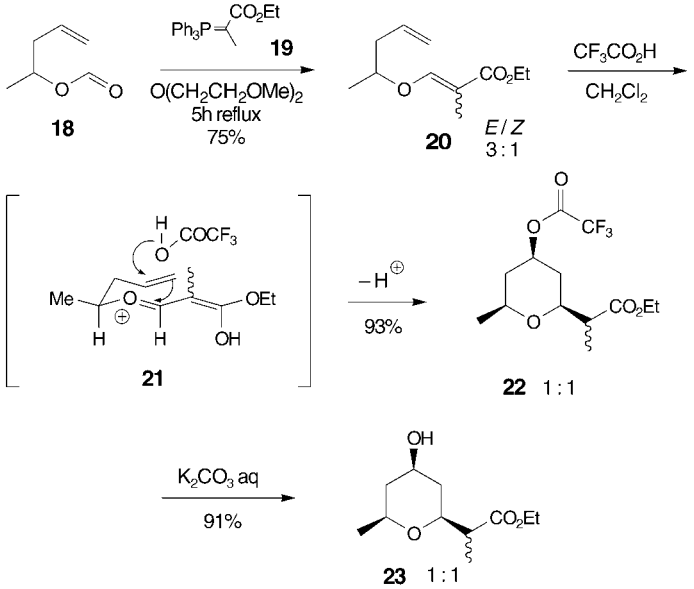
Scheme 2. *The First Examples of the 3-(Alkenyloxy)acrylate Cyclization*



Results and Discussion. – In our investigation on the scope of this *Prins*-type cyclization of oxonium ions, we first revisited the synthesis of the constituent of the glandular secretion of civet cat **17** and introduced an additional substituent, a methyl group, in the butenyl side chain. The corresponding 2-methylacrylate **20** (*Scheme 3*) was prepared from 1-methylbut-3-enyl formate (**18**) according to the efficient protocol of *Suda* [12]. *Wittig* reaction of the homoallyl formate **18** with the (ethoxycarbonyl)-ethylidene ylid **19** in refluxing diglyme ($O(CH_2CH_2OMe)_2$) provided the 2-methyl-3-(1-methylbut-3-enyloxy)acrylate **20** in 75% yield with an (2*E*)/(2*Z*) ratio of 3:1. The three stereogenic ring centers created in the course of the cyclization are controlled by the chair-like transition state **21** to be *all-cis*-configured. Cyclization of acrylate **20** in the presence of a fivefold excess of CF_3COOH in CH_2Cl_2 provided in 93% yield, indeed, a 1:1 mixture of the diastereoisomeric trifluoroacetates **22**, which were subsequently hydrolyzed with 5% aqueous K_2CO_3 solution to afford the two (tetrahydrohydroxypyran-2*H*-yl)propanoate diastereoisomers **23** in 91% yield. These were separated by flash chromatography (FC), and as expected, the substituents at the three stereogenic ring centers of both were *all-cis* configured as was apparent from the vicinal coupling constants of the ring protons $H_{ax}-C(2')$, $H_{ax}-C(4')$, and $H_{ax}-C(6')$ ($J = 11-13.5$ Hz). An additional Me group at C(2) of the ester chain in **20**, therefore,

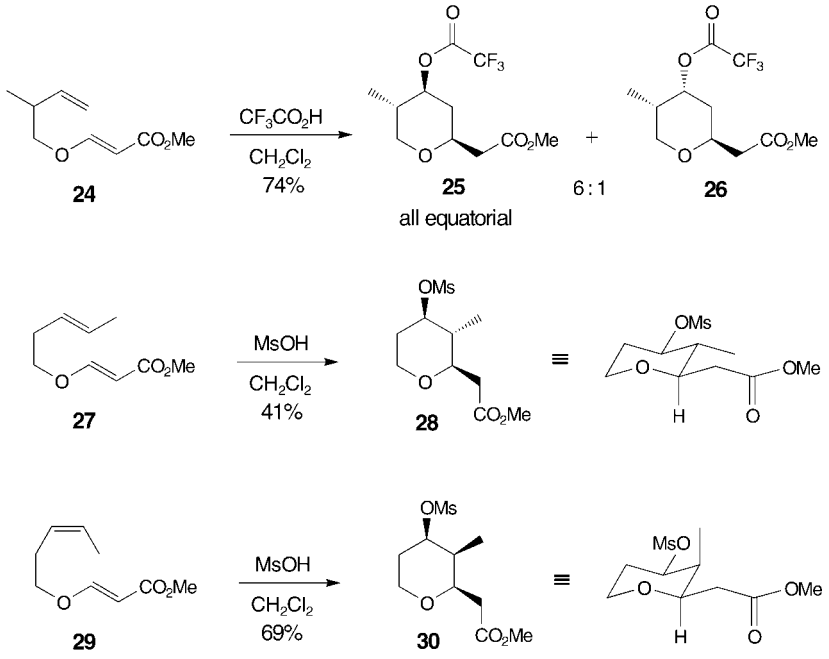
does not hinder the cyclization, and the (*E*/*Z*)-geometry of the α,β-unsaturated ester has no influence on the course of the reaction and the configuration of C(2) in the cyclization product **22**, which is in accord with the proposed mechanism proceeding *via* oxonium ion **21** (*Scheme 3*).

Scheme 3. *Synthesis of (±)-Ethyl (2*RS*)-2-[(2*RS,*4*SR,*6*RS*)- and (2*SR,*4*RS,*6*SR*)*-Tetrahydro-4-hydroxy-6-methyl-2*H*-pyran-2-yl)propanoate* (**23**)



Next, we studied the influence of additional substituents in the alk-3-enyloxy moiety. The methyl 3-(2-methylbut-3-enyloxy)acrylate (**24**) cyclized in the presence of a fivefold excess of CF_3COOH in CH_2Cl_2 in 74% yield to afford a 6:1 mixture of **25** and **26** (*Scheme 4*). The all-equatorial configuration of the ring substituents of **25** was apparent from the vicinal coupling constant for the ring protons $H_{ax}-C(3')$, $H_{ax}-C(4')$ and $H_{ax}-C(6')$ ($J = 11$ Hz). The diastereoisomer **26** only differed in the configuration of C(4′) as a result of a pseudoaxial attack of the nucleophile. Contrary to the configuration of the α,β-unsaturated ester moiety, the (3*E*/3*Z*)-geometry of the alk-3-enyloxy C=C bond should be of crucial importance for the relative configuration of the cyclization products if the postulated mechanism is effective. Indeed, [(3*E*)-pent-3-enyloxy]acrylate **27** provided, in the presence of an excess of MsOH, in 41% yield, the all-equatorial product **28** as the only cyclization product which could be isolated. The configuration of **28** is apparent from the coupling constant for the ring proton $H_{ax}-C(3')$ (δ 1.67) with both vicinal H-atoms ($J = 10$ Hz). Under similar reaction conditions, [(3*Z*)-pent-3-enyloxy]acrylate **29** afforded the (2*RS*,3*SR*,4*RS*)-diastereoisomer **30** in 96% yield. Thus, it is easily possible to control the configuration of C(3′) of the tetrahydro-2*H*-pyran system formed by this *Prins*-type cyclizations of (alk-3-enyloxy)acrylates.

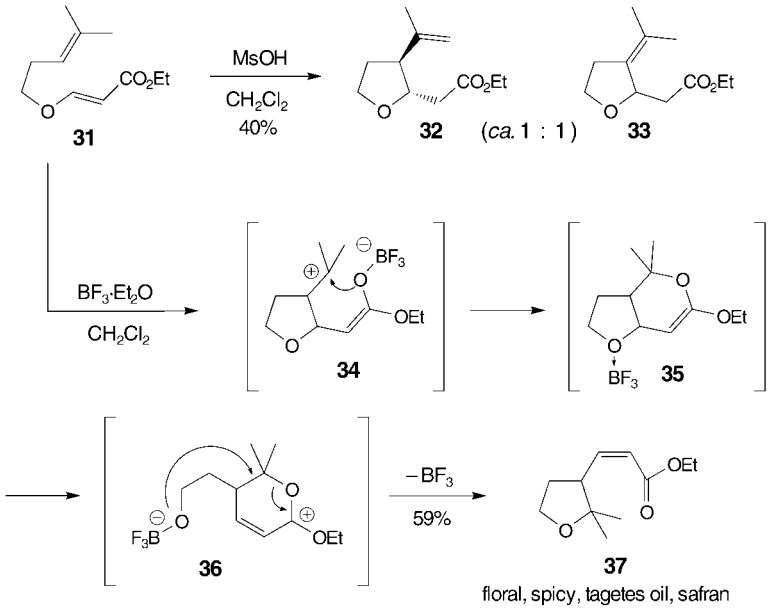
Scheme 4. *Studies on the Stereochemical Course of the Cyclization*



All substitution patterns of the alk-3-enyloxy moiety investigated so far afforded dihydro- or tetrahydro-2*H*-pyrans; yet, if the alkenyloxy C=C bond is geminally dimethyl-substituted, the tertiary carbocation at C(4′) should be favored over a secondary cation at C(3′). Therefore, the cyclization of the 3-(4-methylpent-3-enyloxy)acrylate **31** should lead to tetrahydrofurans. Indeed, upon treatment of a solution of **31** in CH_2Cl_2 with a catalytic amount of MsOH at room temperature, a *ca.* 1:1 mixture of **32** and **33** was isolated in 40% yield, which was separated by prep. GC for spectroscopic characterization (*Scheme 5*).

Interestingly, the acid used for the formation of the oxonium ion can also severely influence the course of the reaction, as it can induce further reactions and rearrangements of initially formed products. Employing an excess of boron trifluoride etherate instead of MsOH in the *Prins*-type cyclization of **31** led to the formation of the (tetrahydrofuranyl)acrylate **37**, which was isolated in 59% yield (*Scheme 5*). We propose that the zwitterionic boron ester enolate **34** is formed by reaction of boron trifluoride with **32** and **33**. This then is supposed to cyclize to the tetrahydro-4*H*-furo[3,2-*c*]pyran **35**, and cleavage of the allylic tetrahydrofuranyl ether bond then would lead to **36**. The boron trifluoride alcoholate nucleophile is then supposed to intramolecularly attack the geminally dimethyl-substituted C-atom resulting finally in the formation of the (tetrahydrofuranyl)acrylate **37** with extrusion of boron trifluoride. The α,β-unsaturated tetrahydrofuranyl-substituted ester **37** is not only mechanistically interesting, but also in terms of its olfactory properties: it emanates a floral, spicy odor reminiscent of tagetes oil and safran.

Scheme 5. *Synthesis of the Tetrahydrofurans* **32**/**33** *and* **37**

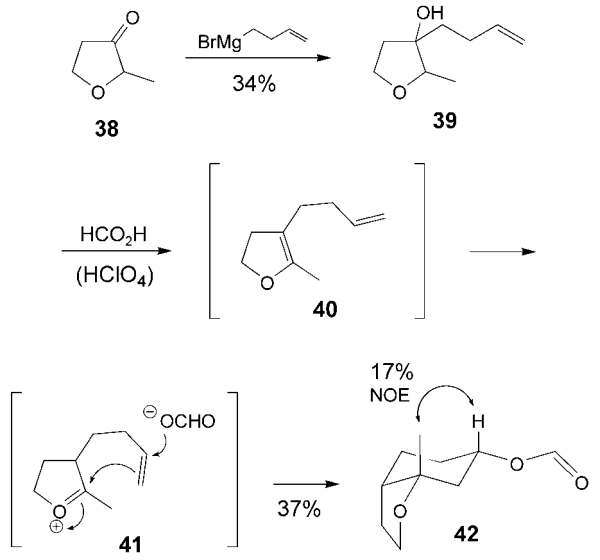


Employing the alkenyltetrahydrofuran-3-ol **39** as a precursor for the *in situ* generation of the oxonium ion **41**, we could further extend the scope of the *Prins*-type cyclization. The tetrahydrofuranol **39** was synthesized in a straightforward approach by *Grignard* reaction of (but-3-enyl)magnesium bromide with dihydro-2-methyl-4,5-furan-3(2*H*)-one (**38**) (*Scheme 6*). Dissolving **39** in formic acid with a catalytic amount of perchloric acid furnished, after 15 h of stirring at room temperature, diastereoselectively the (3a*RS*,6*RS*,7a*RS*)-octahydro-7a-methylbenzofuran-6-yl formate (**42**) in 37% yield. Mechanistically, it is supposed that the reaction proceeds *via* the oxonium ion **41**, which is formed by protonation of the dehydration product **40**. Nucleophilic attack of a formate anion at C(3′) of the side chain of **41** then initiates the cyclization to **42** *via* a six-membered chair-type transition state. Noteworthy, and contrary to the previous examples, the oxonium O-atom is not part of the chair-type transition state.

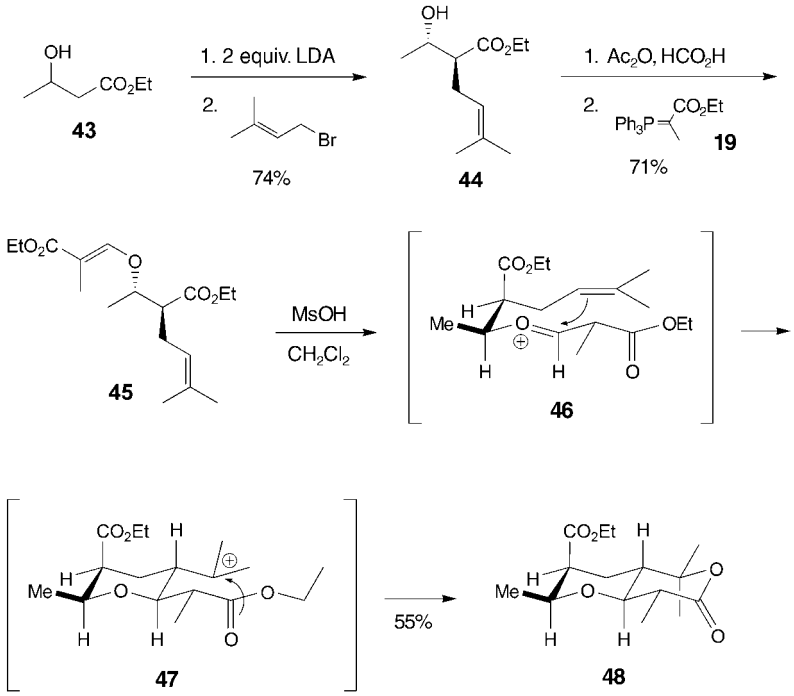
The configuration of **42** was deduced by a simple NOE-DIFF experiment: Irradiation of Me–C(7a) at δ 1.31 resulted in a 17% enhancement of the signal of H–C(6) at δ 4.80–4.87, establishing the 1,3-diaxial relationship of these two substituents. As there was no enhancement of the H–C(2) signals between δ 3.85–3.95 upon irradiation of *Me*–C(7a) the rings should be *cis*-fused. Though the absence of an NOE generally is less conclusive, the similar geometry of H_{ax}–C(2) and H_{ax}–C(6) with respect to Me–C(7a) in the case of a *trans*-fusion corroborates this assignment.

The following final two examples detail short diastereoselective syntheses of tetrahydro-2*H*-pyran systems. They shall exemplarily show the utility of this *Prins*-type cyclization for more-complex target structures, and also provide ideas for the simple construction of suitable starting materials. For the first synthetic sequence, which is illustrated in *Scheme 7*, we made use of the high diastereoselectivity of the α-alkylation

Scheme 6. *Formation of the Octahydrobenzofuranyl Ester* **42**



Scheme 7. *Diastereoselective Synthesis of the Biycylic 'Pyranolactone'* **48**

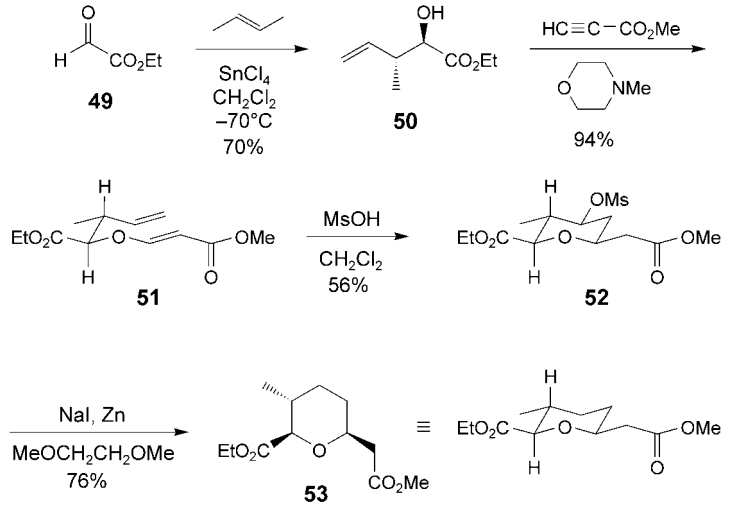


of dianions derived from β-hydroxycarboxylic esters with lithium diisopropylamide (LDA) [13][14]. The lithio dianion of ethyl 2-hydroxybutanoate (**43**) was alkylated with prenyl bromide (=1-bromo-3-methylbut-2-ene) to provide, after work-up and purification by FC, the diastereoisomerically pure (2*RS*)-2-[(1*RS*)-1-hydroxyethyl]-hex-4-enoate **44** [15] in 74% yield. In the next step of the synthesis of **45**, the 3-(alkyloxy-3-oxoprop-1-enyl enol ether moiety was constructed following the protocol of *Suda* [12]. The formate of **44** was prepared in 78% yield by treating **44** with HCOOH and Ac_2O at room temperature for 2 d. Subsequent *Wittig* reaction with the (ethoxycarbonyl)ethylidene ylide **19** in refluxing diglyme provided enol ether **45** in 71% yield after FC. As **45** features a geminally dimethyl-substituted C=C bond, we expected the oxonium ion **46** to cyclize in such a way that the tertiary carbocation **47** would be formed, which could further react intramolecularly with the ester moiety. Indeed, when diester **45** was subjected to the conditions of the *Prins* cyclization employing a threefold excess of MsOH at room temperature for 3 d, the bicyclic 'pyranolactone' **48** was obtained diastereoselectively in 55% yield after purification by FC. As expected, the carbocation **47** must have been formed (see *Scheme 7*), and the positively charged tertiary C-atom must have subsequently been attacked intramolecularly by the carbonyl O-atom under cleavage of the ester to provide **48**. Employing differently substituted allylic halides in the alkylation step of **43** opens up a panoply of related pyran derivatives.

The last example makes use of the *Alder* ene reaction for the construction of homoallylic alcohols, a reaction that also could be carried out with high enantioselectivity, if desired, by using 8-phenylmenthyl glyoxylate as chiral auxiliary [16][17]. Ethyl glyoxylate (=ethyl oxoacetate; **49**) was used as enophile in the $SnCl_4$-catalyzed reaction of (2*E*)-but-2-ene in CH_2Cl_2 at $-70°$. Standard workup after 2 h of reaction time and purification by FC afforded diastereoisomerically pure (2*RS*,3*RS*)-hydroxypentenoate **50** in 70% yield in accord with the general transition state of this reaction (*Scheme 8*). Addition of methyl propiolate (=methyl prop-2-ynoate) in the presence of *N*-methylmorpholine afforded ethyl 2-[(3-methoxy-3-oxoprop-1-enyl)oxy]-3-methylpent-4-enoate (**51**) smoothly and in 94% yield. Exposing a solution of **51** in CH_2Cl_2 to an excess of MsOH at room temperature for 1 h provided the tetrahydro-2*H*-pyran **52** in 56% yield. The all-equatorial configuration was again apparent from the vicinal coupling constants of $H_{ax}-C(2)$, $H_{ax}-C(4)$, and $H_{ax}-C(5)$, ($J=10-18$ Hz). To complete the diastereoselective synthesis of the pyran diester **53**, we reductively removed the methylsulfonyl group of **52** with the reagent system NaI/Zn in 1,2-dimethoxyethane [18][19] at room temperature. Thereby, (2*RS*,3*RS*,6*SR*)-tetrahydro-6-(2-methoxy-2-oxoethyl)-3-methyl-2*H*-pyran-2-carboxylate **53** was obtained in 76% yield after FC.

These examples illustrating the scope of the *Prins*-type cyclization of oxonium ions demonstrate the utility of this reaction for the stereoselective construction of simple and complex tetrahydro-2*H*-pyran and tetrahydrofuran systems. The starting (alkenyloxy)acrylates are easily and stereoselectively accessible, and the cyclization reactions proceed with good to excellent yields, making the presented *Prins*-type cyclization of oxonium ions an attractive and versatile synthetic method.

Scheme 8. *Diastereoselective Synthesis of the Pyrano Diester* **53**



Experimental Part

General. Reagents and solvents: *Fluka* (*puriss.* or *purum*), used without further purification. IR: *Perkin-Elmer 681*, *Nicolet 510-FT-IR*, and *Bruker Vector-22* spectrometer, $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker AC-F-200*, *Bruker AM-400*, and *Bruker Advance-DPX-400* spectrometer; δ in ppm rel. to $SiMe_4$, J in Hz. MS: *Finnigan MAT-212*, *Varian MAT-CH-5*, and *HP Chemstation-6890GC/5973MSD* instrument; in *m/z* (rel. int. in % of the base peak).

(±)-Ethyl (2E/Z)-2-Methyl-3-[(1-methylbut-3-enyl)oxy]prop-2-enoate (**20**). To a soln. of 1-methylbut-3-enyl formate (**18**; 46.0 g, 403 mmol) in di(ethylene glycol) dimethyl ether (=diglyme; 500 ml), ethyl 2-(triphenylphosphoranylidene)propanoate (**19**; 72.4 g, 200 mmol) was added with stirring at r.t. The mixture was then heated to reflux for 5 h allowing the temp. to rise to a maximum of 163°. After the mixture had cooled down to r.t., it was poured into H_2O and extracted with hexane. The combined org. extract was dried (Na_2SO_4), evaporated, and the residue (49.0 g) distilled at 86–87°/0.3 mbar: **20** (29.7 g, 75%), (*E*)/(*Z*) 3:1 (NMR of H–C(3)). Colorless liquid. IR (neat): 1115*s* and 1205*s* (C–O), 1695*s* and 1635*s* (OC=O). ^1H-NMR ($CDCl_3$): 1.26 (*d*, *J* = 6.5, Me–C(1′)); 1.28 (*t*, *J* = 7.0, *Me*CH_2O); 1.75 (*d*, *J* = 1.0, Me–C(2)); 2.40 (*t*, *J* = 7.0, 2 H–C(2′)); 4.03 (*tq*, *J* = 7.0, 7.0, H–C(1′)); 4.21 (*q*, *J* = 7.0, MeCH_2O); 4.95–5.25 (*m*, 2 H–C(4′)); 5.57–6.18 (*m*, H–C(3′)); 6.58 (*q*, *J* = 1.0, H–C(3), (*Z*)-isomer); 7.46 (*q*, *J* = 1.0, H–C(3), (*E*)-isomer).

*(±)-Ethyl (2*RS*)-2-[(2*RS*,4*SR*,6*RS*)- and (2*SR*,4*RS*,6*SR*)-6-Methyltetrahydro-4-[(trifluoroacetyl)oxy]-2H-pyran-2-yl]propanoate* (**22**). CF_3COOH (20.0 ml, 269 mmol) was added dropwise with stirring at −20° to a soln. of **20** (10.0 g, 50.4 mmol) in CH_2Cl_2 (100 ml). The mixture was allowed to warm to r.t., stirred for 40 min, then poured into H_2O, and extracted with Et_2O. The combined org. extract was washed with sat. aq. $NaHCO_3$ soln., evaporated, and the residue (18.0 g) purified by distillation at 70°/0.2 mbar: **22** (14.6 g, 93%) as a 1:1 diastereoisomer mixture (GC). IR (neat): 1170*s* and 1135*s* (C–O), 1730*s* (OC=O), 1780*s* (OC(=O)CF_3), 1220*s* (C–F). ^1H-NMR ($CDCl_3$): 1.10–1.42 (*m*, H_{ax}–C(3′), H_{ax}–C(5′)); 1.14, 1.21, 1.23, 1.24 (4*d*, *J* = 7.0, Me–C(2), Me–C(6′)); 1.26, 1.27 (2*t*, *J* = 7.0, *Me*CH_2O); 2.01–2.13 (*m*, H_{eq}–C(3′), H_{eq}–C(5′)); 2.54, 2.61 (2*dq*, *J* = 8.0, 7.0, H–C(2)); 3.49–3.57 (*m*, H–C(6′)); 3.58–3.65 (*m*, H–C(2′)); 4.12–4.20 (*m*, MeCH_2O); 5.06–5.15 (*m*, H–C(4′)).

*(±)-Ethyl (2*RS*)-2-[(2*RS*,4*SR*,6*RS*)- and (2*SR*,4*RS*,6*SR*)-Tetrahydro-4-hydroxy-6-methyl-2H-pyran-2-yl]propanoate* (**23**). At 0°, 5% aq. K_2CO_3 soln. (500 ml, 181 mmol) was added to a soln. of **22** (13.0 g, 41.6 mmol) in EtOH (100 ml). After vigorous stirring for 1 h, the pH was adjusted to 6 by dropwise addition of citric acid. The mixture was saturated by addition of an excess NaCl and extracted with Et_2O. The crude product (10.0 g) was purified by FC (silica gel, hexane/Et_2O 1:1): **23** (8.20 g, 91%), 1:1 diastereoisomer mixture. Colorless thin oil. R_f 0.18 and 0.22.

Less-Polar Diastereoisomer: IR (neat): 1730*s* (OC=O), 1060*s* (C–O–H), 1145*s* (C–O–C), 3415*m* (br., O–H). ^{1}H-NMR ($CDCl_3$): 1.09–1.17 (*m*, H_{ax}–C(3′), H_{ax}–C(5′)); 1.21 (*d*, *J* = 7.0, Me–C(2)); 1.23 (*d*, *J* = 7.0, Me–C(6′)); 1.26 (*t*, *J* = 7.0, *Me*CH_2O); 1.87 (*s*, OH); 1.88–1.96 (*m*, H_{eq}–C(3′), H_{eq}–C(5′)); 2.52 (*dq*, *J* = 8.0, 7.0, H–C(2)); 3.42 (*dqd*, *J* = 12.0, 7.0, 2.0, H_{ax}–C(6′)); 3.47 (*ddd*, *J* = 12.0, 8.0, 2.0, H_{ax}–C(2′)); 3.80 (*dddd*, *J* = 12.0, 12.0, 4.5, 4.5, H_{ax}–C(4′)); 4.14 (*q*, *J* = 7.0, MeCH_2O). MS (70 eV): 198 (10, $[M-H_2O]^+$), 173 (8, $[M-C_2H_3O]^+$), 152 (13, $[M-H_2O-C_2H_6O]^+$), 131 (17, $C_7H_{15}O_2^+$), 115 (66, $C_6H_{11}O_2^+$), 97 (61, $C_6H_9O^+$), 69 (63, $C_5H_9^+$), 43 (100, $C_2H_3O^+$).

More-Polar Diastereoisomer: IR (neat): 1735*s* (OC=O), 1040*s* (C–O–H), 1145*s* (C–O–C), 3415*m* (br., O–H). ^{1}H-NMR ($CDCl_3$): 1.12 (*d*, *J* = 7.0, Me–C(2)); 1.12–1.22 (*m*, H_{ax}–C(3′), H_{ax}–C(5′)); 1.18 (*d*, *J* = 6.0, Me–C(6′)); 1.26 (*t*, *J* = 7.0, *Me*CH_2O); 1.90–2.02 (*m*, H_{eq}–C(3′), H_{eq}–C(5′)); 1.93 (*s*, OH); 2.57 (*dq*, *J* = 8.0, 7.0, H–C(2)); 3.44 (*dqd*, *J* = 11.0, 6.0, 2.0, H_{ax}–C(6′)); 3.51 (*ddd*, *J* = 13.5, 8.0, 2.0, H_{ax}–C(2′)); 3.80 (*dddd*, *J* = 12.0, 12.0, 4.5, 2.0, H_{ax}–C(4′)); 4.16 (*q*, *J* = 7.0, MeCH_2O). MS (70 eV): 198 (10, $[M-H_2O]^+$), 173 (11, $[M-C_2H_3O]^+$), 144 (20, $[M-C_4H_8O]^+$), 131 (25, $C_7H_{15}O_2^+$), 115 (100, $C_6H_{11}O_2^+$), 97 (66, $C_6H_9O^+$), 73 (100, $C_3H_5O_2^+$), 45 (82, $C_2H_5O^+$), 28 (91, CO^+).

*(±)-(2*E*)-Methyl 3-(2-Methylbut-3-enyloxy)prop-2-enoate* (**24**). At 0–10°, 4-methylmorpholine (25.0 g, 248 mmol) was added to a stirred soln. of 2-methylbut-3-en-1-ol (20.0 g, 232 mmol) and methyl prop-2-ynoate (20.0 g, 238 mmol) in Et_2O (250 ml). After stirring at 15° for 1 h, stirring was continued at r.t. overnight, prior to pouring the mixture in Et_2O/H_2O 1:1. The org. phase was washed with 2N AcOH to neutrality, evaporated, and the resulting residue distilled at 59–60°/0.2 mbar **24** (34.3 g, 87%). Colorless liquid. IR (neat): 1135*s* and 1205*s* (C–O), 1625*s* and 1645*s* (C=C), 1715*s* (OC=O). ^{1}H-NMR ($CDCl_3$): 1.10 (*d*, *J* = 7.0, Me–C(2′)); 2.64 (*'sept.'*, *J* = 7.0, H–C(2′)); 3.65–3.85 (*m*, CH_2(1′)); 3.74 (*s*, MeO); 4.97–5.34 (m, H–C(2), CH_2(4′)); 5.86 (*ddd*, *J* = 17.0, 9.0, 7.0, H–C(3′)); 7.64 (*d*, *J* = 14.0, H–C(3)). MS (70 eV): 139 (1, $[M-OMe]^+$), 84 (23, $C_5H_8O^+$), 69 (75, $[C_5H_8O-Me]^+$), 41 (100, $C_3H_5^+$).

*(±)-Methyl 2-{(2*RS*,4*RS*,5*RS*)- and (2*RS*,4*SR*,5*RS*)-Tetrahydro-5-methyl-4-[(trifluoroacetyl)oxy]-2*H*-pyran-2-yl}acetate* (**25** and **26**, resp.). To a soln. of **24** (8.50 g, 49.9 mmol) in CH_2Cl_2 (100 ml) at −5°, CF_3COOH (20.0 ml, 269 mmol) was added dropwise with stirring. Stirring was continued at −5° for 2 h and at r.t. for 64 h. The mixture was poured into H_2O, the product extracted with Et_2O, the combined extract washed with sat. aq. $KHCO_3$ soln., dried (Na_2SO_4), and evaporated, and the residue (14.2 g) purified by FC (silica gel, hexane/Et_2O 1:1): **25**/**26** 6:1 (10.5 g, 74%). R_f 0.54. IR (neat): 1170*s* (C–O), 1225*s* (C–F), 1785*s* (OC(=O)CF_3), 1745*s* (OC=O). ^{1}H-NMR ($CDCl_3$), **25**: 0.88 (*d*, *J* = 7.0, Me–C(5′)); 1.53 (*q*, *J* = 11.0, H_{ax}–C(3′)); 1.90–2.00 (*m*, H–C(5′)); 2.11 (*ddd*, *J* = 11.0, 6.0, 2.5, H_{eq}–C(3′)); 2.47 (*dd*, *J* = 15.0, 5.0, H_b–C(2)); 2.61 (*dd*, *J* = 15.0, 7.0, H_a–C(2)); 3.17 (*t*, *J* = 11.0, H_{ax}–C(6′)); 3.71 (*s*, Me); 3.79–3.91 (*m*, H_{ax}–C(2′)); 3.94 (*dd*, *J* = 11.0, 5.0, H_{eq}–C(6′)); 4.81 (*ddd*, *J* = 11.0, 11.0, 6.0, H_{ax}–C(4′)); **26**: 1.09 (*d*, *J* = 7.0, Me–C(5′)); 1.72 (*q*, *J* = 11.0, H_{ax}–C(3′)); 1.90–2.00 (*m*, H–C(5′)); 2.11 (*ddd*, *J* = 11.0, 6.0, 2.5, H_{eq}–C(3′)); 2.49 (*dd*, *J* = 15.0, 5.0, H_b–C(2)); 2.64 (*dd*, *J* = 15.0, 7.0, H_a–C(2)); 3.17 (*t*, *J* = 11.0, H_{ax}–C(6′)); 3.71 (*s*, MeO); 3.81 (*dd*, *J* = 11.0, 3.0, H_{eq}–C(6′)); 3.79–3.91 (*m*, H_{ax}–C(2′)); 4.81 (*ddd*, *J* = 11.0, 6.0, 6.0, H_{eq}–C(4)). MS (70 eV): 253 (1, $[M-OMe]^+$), 211 (8, $C_8H_{10}O_3F_3^+$), 170 (15, $[M-C_2HO_2F_3]^+$), 155 (32, $[M-C_2HO_2F_3-Me]^+$), 138 (15, $[M-C_2HO_2F_3-Me]^+$), 110 (47, $C_6H_6O_2^+$), 97 (100, $C_2OF_3^+$), 69 (87, CF_3^+), 43 (81, $C_3H_7^+$).

*Methyl (2*E*)-3-[(3*E*)-Pent-3-enyloxy]prop-2-enoate* (**27**). Methyl prop-2-yonate (7.00 g, 83.3 mmol) was added at r.t. to a stirred soln. of (3*E*)-pent-3-en-1-ol (7.00 g, 81.3 mmol) in Et_2O (100 ml). After subsequent addition of 4-methylmorpholine (200 mg, 1.98 mmol), stirring was continued at r.t. overnight. The solvent was evaporated, and the residue distilled at 60–65°/0.1 mbar: **27** (12.3 g, 89%). IR (neat): 1140*s* (C–O), 1625*s* and 1640*s* (C=C), 1715*s* (OC=O). ^{1}H-NMR ($CDCl_3$): 1.67 (*dq*, *J* = 7.0, 2.0, Me(5′)); 2.38 (*'qquint.'*, *J* = 7.0, 1.0, CH_2(2′)); 3.69 (*s*, MeO); 3.84 (*t*, *J* = 7.0, CH_2(1′)); 5.20 (*d*, *J* = 13.0, H–C(2)); 5.41 (*dtq*, *J* = 16.0, 7.0, 1.0, H–C(3)); 5.56 (*dqt*, *J* = 16.0, 7.0, 1.0, H–C(4′)); 7.64 (*d*, *J* = 13.0, H–C(3′)). MS (70 eV): 170 (1, M^+), 138 (5, $[M-MeOH]^+$), 101 (4, $[M-C_5H_9]^+$), 69 (94, $C_5H_9^+$), 59 (6, CO_2Me^+), 41 (100, $C_3H_5^+$).

*(±)-Methyl 2-{(2*RS*,3*RS*,4*RS*)-Tetrahydro-3-methyl-4-[(methylsulfonyl)oxy]-2*H*-pyran-2-yl}acetate* (**28**). To a soln. of **27** (4.60 g, 27.0 mmol) in CH_2Cl_2 (70 ml) at r.t. MsOH (4.10 g, 43.0 mmol) was added dropwise *via* syringe within 10 min under stirring upon which the temp. was allowed to rise to a maximum of 33°. After 45 min of stirring at r.t., the mixture was poured into Et_2O (250 ml) and neutralized by addition of 1% aq. $NaHCO_3$ soln. (500 ml). The aq. phase was extracted with Et_2O (200 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the semi-crystalline crude material (5.10 g) recrystallized from ^{t}BuOMe: **28** (3.00 g, 41%). M.p. 102–103° (^{t}BuOMe). IR (neat): 953*s* and 939*s* (S–O), 1168*s* (SO_2, sym.), 1058*s* (C–O), 1726*s* (C=OO). ^{1}H-NMR ($CDCl_3$): 1.02 (*d*, *J* = 6.5, Me–C(3′)); 1.67 (*tq*, *J* = 10.0, 6.5, H_{ax}–C(3′); 1.92 (*tq*, *J* = 12.0, 5.0, H_{ax}–C(5′)); 2.19 (*ddt*, *J* = 12.0, 5.0, 2.0, H_{eq}–C(5′)); 2.46 (*dd*, *J* = 15.0, 9.0, H_b–C(2)); 2.68 (*dd*, *J* = 15.0, 2.0, H_a–C(2)); 3.05 (*s*, $MeSO_3$); 3.46 (*dd*, *J* = 10.0, 2.0, H_{ax}–C(6′)); 3.53 (*ddd*, *J* = 10.0, 9.0, 2.0,

H_{ax}–C(2′)); 3.71 (*s*, MeO); 4.01 (*ddd*, *J* = 10.0, 5.0, 2.0, H_{eq}–C(6′)); 4.45 (*'td'*, *J* = 10.0, 5.0, H_{ax}–C(4′)). ^{13}C-NMR ($CDCl_3$): 13.2 (*q*, Me–C(3′)); 33.5 (*t*, C(5′)); 38.7 (*t*, C(2)); 38.8 (*q*, $MeSO_3$); 41.1 (*d*, C(3′)); 51.8 (*q*, MeO); 65.1 (*t*, C(6′)); 78.3 (*d*, C(2′)); 82.9 (*d*, C(4′)); 171.4 (*s*, C(1)). MS (70 eV): 267 (1, $[M+H]^+$), 193 (4, $[M-C_3H_5O_2]^+$), 170 (21, $[M-CH_4O_3S]^+$), 155 (19, $[M-CH_4O_3S-CH_3]^+$), 139 (7, $[M-CH_4O_3S-OCH_3]^+$), 97 (88, $[M-C_3H_5O_2-CH_4O_3S]^+$), 69 (100, $C_5H_9^+$), 41 (45, $C_3H_5^+$).

*Methyl (2*E*)-3-[(3*Z*)-Pent-3-enyloxy]prop-2-enoate* (**29**). As described for **27**, with methyl prop-2-yonate (8.41 g, 100 mmol), (3*Z*)-pent-3-en-1-ol (8.61 g, 100 mmol), Et_2O (100 ml), and 4-methylmorpholine (1.00 g, 9.89 mmol): **29** (15.0 g, 88%). IR (neat): 1140*s* (C–O), 1625*s* and 1645*s* (C=C), 1715*s* (OC=O). ^{1}H-NMR ($CDCl_3$): 1.64 (*dq*, *J* = 7.0, 1.0, MeC(5′)); 2.46 (*'qquint.'*, *J* = 7.0, 0.5, CH_2(2′)); 3.69 (*s*, MeO); 3.85 (*t*, *J* = 7.0, CH_2(1′)); 5.21 (*d*, *J* = 12.0, H–C(2)); 5.38 (*dtq*, *J* = 9.0, 7.0, 1.0, H–C(3)); 5.61 (*dqt*, *J* = 9.0, 7.0, 1.0, H–C(4′)); 7.59 (*d*, *J* = 12.0, H–C(3′)). MS (70 eV): 170 (1, M^+), 155 (1, $[M-Me]^+$), 138 (2, $[M-MeOH]^+$), 101 (3, $[M-C_5H_9]^+$), 69 (100, $C_5H_9^+$), 59 (6, CO_2Me^+), 41 (84, $C_3H_5^+$).

*(±)-Methyl 2-[(2*RS*,3*SR*,4*RS*)-Tetrahydro-3-methyl-4-[(methylsulfonyl)oxy]-2*H*-pyran-2-yl]acetate* (**30**). At 0°, MsOH (5.0 ml, 77 mmol) was added dropwise with stirring to a soln. of **29** (8.50 g, 49.9 mmol) in CH_2Cl_2 (100 ml). Stirring was continued for 15 min at 10°, prior to pouring into Et_2O (400 ml), and washing with 1% aq. $NaHCO_3$ soln. After drying (Na_2SO_4), evaporation gave a viscous oil (16.0 g). The starting materials and by-products were removed from the oil by prolonged drying under high vacuum: **30** (12.8 g, 96%). IR (neat): 1175*s* (SO_2, sym), 950*s* and 900*s* (S–O), 1735*s* (OC=O), 1345*s* (SO_2, asym). ^{1}H-NMR ($CDCl_3$): 1.02 (*d*, *J* = 7.0, Me–C(3′)); 1.78–1.84 (*m*, H_{eq}–C(5′)); 2.00 (*ddd*, *J* = 24.0, 12.5, 5.0, H_{ax}–C(5′)); 2.18–2.24 (*m*, H_{eq}–C(3′)); 3.04 (*s*, $MeSO_3$); 2.47 (*dd*, *J* = 15.5, 5.0, H_b–C(2)); 2.62 (*dd*, *J* = 15.5, 9.0, H_a–C(2)); 3.50 (*ddd*, *J* = 12.0, 12.0, 3.0, H_{ax}–C(6′)); 3.70 (*s*, MeO); 3.89 (*ddd*, *J* = 9.0, 5.0, 3.0, H_{ax}–C(2′)); 4.01 (*ddd*, *J* = 12.0, 9.0, 3.0, H_{eq}–C(6′)); 4.91 (*dt*, *J* = 11.0, 5.0, H_{ax}–C(4′)). MS (70 eV): 193 (3, $[M-C_3H_5O_2]^+$), 170 (7, $[M-CH_4O_3S]^+$), 155 (9, $[M-CH_4O_3S-Me]^+$), 139 (4, $[M-CH_4O_3S-OMe]^+$), 97 (34, $[M-C_3H_5O_2-CH_4O_3S]^+$), 69 (78, $C_5H_9^+$), 43 (100, $C_3H_7^+$).

*(2*E*)-Ethyl 3-[(4-Methylpent-3-enyl)oxy]acrylate* (**31**). At r.t., 4-methylpent-3-en-1-ol (10.0 g, 99.8 mmol) was added to a stirred soln. of ethyl prop-2-yonate (10.0 g, 102 mmol) and 4-methylmorpholine (10.0 g, 98.9 mmol) in Et_2O (100 ml), and the mixture was stirred for 18 h. The mixture was poured in Et_2O/H_2O 1:1, the org. layer washed with 2N AcOH to neutrality, evaporated, and the residue (22.0 g) was distilled at 78–82°/0.1 mbar: **31** (17.0 g, 86%). Colorless liquid. IR (neat): 1130*s* and 1205*s* (C–O), 1625*s* and 1640*s* (C=C), 1710*s* (OC=O). ^{1}H-NMR ($CDCl_3$): 1.27 (*t*, *J* = 7.0, *Me*CH_2O); 1.63 (*d*, *J* = 1.0, Me–C(4′) *trans* to C(2′)); 1.71 (*d*, *J* = 1.0, Me–C(4′) *cis* to C(2′)); 2.39 (*q*, *J* = 7.0, CH_2(2′)); 3.81 (*t*, *J* = 7.0, CH_2(1′)); 4.16 (*J* = 7.0, MeC*H*$_2$O); 5.11 (*t sept.*, *J* = 7.0, 1.0, H–C(3′)); 5.19 (*d*, *J* = 13.0, H–C(2)); 7.58 (*d*, *J* = 13.0, H–C(3)).

*(±)-Ethyl [(2*RS*,3*RS*)-Tetrahydro-3-(1-methylethenyl)furan-2-yl]acetate* (**32**) and *(±)-Ethyl [Tetrahydro-3-(1-methylethylidene)furan-2-yl]acetate* (**33**). At r.t., MsOH (0.1 ml, 1.5 mmol) was added to a stirred soln. of **31** (2.00 g, 10.1 mmol) in CH_2Cl_2 (50 ml). Stirring was continued at r.t. for 90 min, prior to adding in turn Et_2O (5.0 ml), sat. aq. $KHCO_3$ soln. (5.0 ml), and H_2O (5.0 ml). After vigorous stirring for 10 min, the aq. layer was extracted with Et_2O, the combined org. extract dried (Na_2SO_4) and evaporated, and the resulting residue purified by FC (silica gel, hexane/Et_2O 9:1); **32**/**33** (800 mg, 40%), *ca.* 1:1 mixture (GC). Separation by prep. GC afforded pure samples for spectroscopic characterization.

Data of **32**: ^{1}H-NMR ($CDCl_3$): 1.22 (*t*, *J* = 7.0, *Me*CH_2O); 1.71 (*s*, CH_2=C(*Me*)); 1.89–1.94 (*m*, H_b–C(4′)); 2.01 (*ddd*, *J* = 16.0, 7.0, 5.0, H_a–C(4′)); 2.18 (*dd*, *J* = 15.0, 6.0, H_b–C(2)); 2.30 (*dd*, *J* = 15.0, 7.0, H_a–C(2)); 2.84 (*qd*, *J* = 7.0, 1.0, H–C(3′)); 3.68 (*q*, *J* = 8.0, H_b–C(5′)); 3.91 (*td*, *J* = 8.0, 5.0, H_a–C(5′)); 4.05 (*qd*, *J* = 7.0, 2.0, MeC*H*$_2$O); 4.22 (*dt*, *J* = 8.0, 7.0, H–(2′)); 4.68 (*quint.*, *J* = 0.5, 1 H, C*H*$_2$=C(Me)); 4.77 (*quint.*, *J* = 0.5, 1 H, C*H*$_2$=C(Me)).

Data of **33**: ^{1}H-NMR ($CDCl_3$): 1.25 (*t*, *J* = 7.0, *Me*CH_2O); 1.63 (br. *s*, MeC=C(3′) *cis* to C(2′)); 1.65 (*d*, *J* = 1.0, Me–C=C(3′) *trans* to C(2′)); 2.29 (*dd*, *J* = 14.0, 9.0, H_b–C(2)); 2.35 (*dd*, *J* = 14.0, 4.0, H_a–C(2)); 2.38–2.44 (*m*, CH_2(4′); 3.74 (*dt*, *J* = 9.0, 8.0, H_b–C(5′)); 3.89 (*dt*, *J* = 9.0, 8.0, H_a–C(5′)); 4.08 (*q*, *J* = 7.0, MeC*H*$_2$O); 4.76–4.81 (*m*, H–C(2′)).

*(±)-Ethyl (2*Z*)-3-(Tetrahydro-2,2-dimethylfuran-3-yl)prop-2-enoate* (**37**). $BF_3 \cdot Et_2O$ (30.0 ml, 239 mmol) was added at r.t. to a stirred soln. of **31** (28.0 g, 141 mmol) in CH_2Cl_2 (200 ml). After stirring for 18 h at r.t., the reaction was quenched by pouring into H_2O/Et_2O 1:2 (1 l). After extraction with CH_2Cl_2, the org. layer was dried (Na_2SO_4) and evaporated. The crude material (29.0 g) was taken up in Et_2O (150 ml), and 50% aq. KOH soln. was added at r.t. After stirring for 1 h at 40°, quenching with H_2O/Et_2O (500 ml) provided, after separation and evaporation of the org. layer, the crude product (19.5 g), which was purified by distillation at 70–75°/0.3 mbar: **37** (16.5 g, 59%). IR (neat): 1185*s* (O–CO), 1720*s* (OC=O), 1045*m* (C–O–C), 1645*m* (C=C). ^{1}H-NMR ($CDCl_3$): 1.11, 1.28 (2*s*, 2Me–C(2′)); 1.30 (*t*, *J* = 7.0, *Me*CH_2O); 1.82 (*ddd*, *J* = 17.5, 10.0, 8.0,

H_b–C(4′)); 2.24 (*ddd*, *J* = 17.5, 7.0, 4.5, H_a–C(4′)); 3.85–3.98 (*m*, H–C(3′), CH_2(5′)); 4.19 (*q*, *J* = 7.0, Me*C*H_2O); 5.85 (*dd*, *J* = H–C(2)); 6.08 (*td*, *J* = 11.0, 1.0, H–C(3)). ^{13}C-NMR ($CDCl_3$): 14.2 (*q*, *Me*CH_2O); 23.1, 27.6 (2*q*, 2*Me*–C(2′)); 33.0 (*t*, C(4′)); 46.5 (*d*, C(3′)); 60.0 (*t*, Me*C*H_2O); 65.6 (*t*, C(5′)); 83.3 (*s*, C(2′)); 120.8 (*d*, C(2)); 148.9 (*d*, C(3)); 166.1 (*s*, C(1)). MS (70 eV): 198 (3, M^+), 183 (20, $[M - Me]^+$), 168 (3, $[M - CH_2O]^+$), 153 (7, $[M - MeCH_2O]^+$), 140 (69, $[M - C_3H_6O]^+$), 125 (15, $[M - C_3H_5O_2]^+$), 112 (92, $C_8H_{16}^+$), 95 (68, $C_7H_{11}^+$), 84 (81, $C_6H_{12}^+$), 67 (100, $C_5H_7^+$), 43 (81, $C_3H_7^+$).

(±)-3-(But-3-enyl)tetrahydro-2-methylfuran-3-ol (**39**). To a stirred suspension of Mg turnings (6.10 g, 251 mmol) in Et_2O (10.0 ml), 4-bromobut-1-ene (3.00 g, 22.2 mmol) was added and the reaction was started by occasional heating with a heat gun. The remainder of the 4-bromobut-1-ene (30.0 g, 222 mmol) was added dropwise at reflux temp., and, after 10 min of stirring at this temp., a soln. of dihydro-2-methylfuran-3(2*H*)-one (**38**; 20.0 g, 200 mmol) in Et_2O (140 ml) was added dropwise. After heating to reflux for 1 h, the mixture was poured into sat. aq. NH_4Cl soln./ice 1:1. The aq. layer was extracted with Et_2O, the combined Et_2O extract dried (Na_2SO_4) and evaporated, and the residue (10.3 g) distilled over a short *Vigreux* column to provide **39** (10.6 g, 34%) at 98°/0.1 mbar. IR (neat): 1080*s* and 1100*s* (O–C), 3410*s* (O–H), 1640*m* (C=C). ^{1}H-NMR ($CDCl_3$): 1.19 (*d*, *J* = 7.0, Me–C(2)); 1.49 (*ddd*, *J* = 13.0, 11.0, 5.0, H_b–C(1′)); 1.68 (*ddd*, *J* = 13.0, 10.0, 5.0, H_a–C(1′)); 1.79 (br. *s*, OH); 1.92–2.35 (*m*, CH_2(4), CH_2(2′)); 3.54 (*q*, *J* = 7.0, H–C(2)); 3.79 (*ddd*, *J* = 14.0, 8.0, 6.0, H_b–C(5)); 3.99 (*dd*, *J* = 14.0, 7.0, H_a–C(5)); 4.99 (*dq*, *J* = 10.0, 2.0, H–C(4′) *trans* to C(2′)); 5.06 (*dq*, *J* = 16.0, 2.0, H–C(4′) *cis* to C(2′)); 5.86 (*ddt*, *J* = 16.0, 10.0, 6.0, H–C(3′)). MS (70 eV): 156 (2, M^+), 141 (18, $[M^+ - Me]$), 112 (20, $C_2H_4O^+$), 97 (59, $C_6H_9O^+$), 83 (77, $C_5H_7O^+$), 70 (68, $C_4H_6O^+$), 53 (67, $C_4H_5^+$), 43 (100, $C_3H_7^+$).

*(±)-(3a*RS*,6*RS*,7a*RS*)-Octahydro-7a-methylbenzofuran-6-yl Formate* (**42**). At r.t. with stirring, **39** (500 mg, 3.20 mmol) was dissolved in HCOOH (5.0 ml). Stirring was continued at r.t. for 30 min, and then at 60° for 1 h. Then, $HClO_4$ (2 drops) was added, and the mixture was stirred at r.t. for 15 h, prior to adding in turn Et_2O (50 ml) and H_2O (50 ml). The org. layer was washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), evaporated, and the resulting residue purified by FC (silica gel, hexane/Et_2O): **42** (200 mg, 37%). R_f 0.28. IR (neat): 1720*s* (OC=O), 1180*s* (C–O–C). ^{1}H-NMR ($CDCl_3$): 1.17–1.27 (*m*, H_{eq}–C(4)); 1.31 (*s*, Me–C(7a)); 1.52–1.83 (*m*, H_{ax}–C(4), CH_2(5), CH_2(7)); 1.89–2.01 (*m*, CH_2(3), H–C(3a)); 3.88 (*dd*, *J* = 15.0, 8.0, H_b–C(2)); 3.92 (*ddd*, *J* = 15.0, 9.0, 6.0, H_a–C(2)); 4.80–4.87 (*m*, H–C(6)); 8.02 (*s*, HCOO). NOE-DIFF ($CDCl_3$): 1.31 (Me–C(7a)) → 4.80–4.87 (H–C(6), 17%). ^{13}C-NMR ($CDCl_3$): 22.2 (*t*, C(4)); 25.5 (*q*, *Me*–C(7a)); 26.3 (*t*, C(3)); 29.5 (*t*, C(5)); 38.6 (*t*, C(7)); 42.5 (*d*, C(3a)); 64.8 (*t*, C(2)); 70.8 (*d*, C(6)); 80.9 (*s*, C(7a)); 160.5 (*d*, OC=O). MS (70 eV): 101 (3, $[M - CO - C_4H_7]^+$), 58 (17, $C_4H_{10}^+$), 43 (100, $C_2H_3O^+$), 28 (93, CO^+).

*(±)-Ethyl (2*RS*)-2-[(1*RS*)-1-Hydroxyethyl]-5-methylhex-4-enoate* (**44**). Under N_2, 1.6M MeLi in Et_2O (250 ml, 400 mmol) was added dropwise at 0° to a stirred soln. of ^{i}Pr$_2$NH (60 ml, 428 mmol) in dry THF (200 ml). The mixture was cooled to −78°, and between −78° and −50° ethyl 2-hydroxybutanoate (**43**; 26.4 g, 200 mmol) was added within 10 min with vigorous stirring, followed by a soln. of prenyl bromide (36.0 g, 242 mmol) in dry HMPTA (= hexamethylphosphoric trianide; 50 ml) was added dropwise in such a way that the temp. rose to 0°. Stirring was continued at this temp. for further 10 min prior to neutralization with 50% aq. citric acid and pouring into Et_2O/H_2O/sat. aq. $NaHCO_3$ soln. 1:1:1. The aq. layer was extracted with Et_2O, the combined org. extract dried (Na_2SO_4) and evaporated, and the residue (48.0 g) purified by FC (silica gel, hexane/Et_2O 1:1): **44** (29.5 g, 74%). R_f 0.41. IR (neat): 1730*s* (OC=O), 1180*m* (C–O), 1380*m* and 1445*m* (Me), 3480*m* (O–H). ^{1}H-NMR ($CDCl_3$): 1.24 (*d*, *J* = 7.0, Me(2′)); 1.27 (*t*, *J* = 7.0, *Me*CH_2O); 1.62, 1.69 (2*s*, 2Me–C(5)); 2.30–2.41 (*m*, H–C(2), CH_2(3), OH); 3.91, 3.92 (2 *quint.*, H–C(1′)); 4.16, 4.17 (2*q*, *J* = 7.0, MeCH_2O); 5.05–5.09 (*m*, H–C(4)). MS (70 eV): 201 (1, $[M + H]^+$), 182 (20, $[M - H_2O]^+$), 167 (6, $[M - H_2O - Me]^+$), 139 (18, $[M - H_2O - C_3H_7]^+$), 127 (4, $[M - CO_2Et]^+$), 109 (100, $[M - CO_2Et - H_2O]^+$), 69 (87, $C_5H_9^+$).

*(±)-Ethyl (2*RS*)-2-{(1*RS*)-1-{[(1*E*)-Ethoxy-2-methyl-3-oxoprop-1-enyl]oxy}ethyl}-5-methylhex-4-enoate* (**45**). Under N_2, a mixture of Ac_2O (7.00 g, 68.6 mmol) and $HCOO_2H$ (4.00 g, 86.9 mmol) was stirred for 2 h at 50°. Then **44** (10.0 g, 49.9 mmol) was added in one batch, and the mixture was stirred at r.t. for 2 d. The mixture was poured into H_2O/sat. $NaHCO_3$ soln./hexane 1:1:1. The aq. layer was extracted with hexane, the combined org. layer dried ($MgSO_4$) and evaporated, and the crude material (10.0 g) bulb-to-bulb distilled: formate of **44** (8.90 g, 78%), sufficiently pure for further transformation. This formate (4.00 g, 17.5 mmol) was dissolved under N_2 in di(ethylene glycol) dimethyl ether (90.0 ml), and ethyl 2-(triphenylphosphoranylidene)-propanoate (**19**; 6.30 g, 17.4 mmol) was added in one batch. The mixture was heated to reflux for 6 h, and after it had cooled to r.t., poured into H_2O. The product was extracted with hexane, the combined org. extract dried (Na_2SO_4) and evaporatored, and the residue (4.20 g) purified by FC (silica gel, hexane/Et_2O 2:1): **45** (3.90 g, 71%). Colorless liquid. R_f 0.54. IR (neat): 1120*s* and 1190*s* (C–O–C), 1700*s* and 1730*s* (OC=O), 1630*s*

(C=C), 1380*m* and 1445*m* (Me). ^{1}H-NMR ($CDCl_3$): 1.24, 1.27 (2*d*, *J* = 7.0, 2 *Me*CH_2O); 1.32 (*d*, *J* = 7.0, Me(2′)); 1.60, 1.69 (2*s*, 2MeC(5)); 1.70 (*d*, *J* = 1.0, Me–C(2″)); 2.19–2.36 (*m*, CH_2(3)); 2.60 (*ddd*, *J* = 9.0, 8.0, 5.0, H–C(2)); 4.10–4.22 (*m*, 2MeCH_2O, H–C(1′)); 5.04–5.09 (*m*, H–C(4)); 7.33 (*q*, *J* = 1.0, H–C(1″)). MS (70 eV): 312 (1, M^+), 267 (2, $[M - OEt]^+$), 182 (10, $C_{11}H_{18}O^+$), 137 (16, $[C_{11}H_{18}O - OEt]^+$), 109 (61, $C_8H_{13}^+$), 69 (100, $C_5H_9^+$).

*(±)-Ethyl (2*RS*,3*RS*,4a*RS*,8*SR*,8a*RS*)-Hexahydro-2,5,5,8-tetramethyl-7-oxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-carboxylate* (**48**). At –40° (cooling in a dry ice/^{i}PrOH bath), MsOH (0.4 ml, 6 mmol) was added with stirring to a soln. of **45** (1.00 g, 3.20 mmol) in CH_2Cl_2 (50 ml). After further stirring for 10 min at –35°, the cooling bath was removed, and the mixture was stirred at r.t. for 1 d. Since GC still indicated starting material **45**, the mixture was again cooled to –35°, and another portion of MsOH (0.2 ml, 3 mmol) was added. Then the mixture was stirred for 2 d prior to pouring into hexane/H_2O/sat. aq. $NaHCO_3$ soln. 1:1:1. The aq. layer was extracted with hexane, the combined org. extract dried ($MgSO_4$) and evaporated, and the residue (1.20 g) purified by FC (silica gel, hexane/Et_2O 2:1): **48** (500 mg, 55%). Liquid, which slowly crystallized. R_f 0.14. M.p. 48–50° (hexane/Et_2O). ^{1}H-NMR ($CDCl_3$): 1.30 (*d*, *J* = 7.0, Me–C(8)); 1.32 (*d*, *J* = 7.0, Me–C(2)) ; 1.38 (*t*, *Me*CH_2O); 1.42 (2*s*, 2Me–C(5)); 1.54 (*ddd*, *J* = 13.0, 13.0, 5.0, H_{ax}–C(4)); 2.13 (*ddd*, *J* = 13.0, 4.0, 2.0, H_{eq}–C(4)); 2.44 (*ddd*, *J* = 14.0, 10.0, 4.0 H_{ax}–C(4a)); 2.51 (*dq*, *J* = 11.0, 7.0, H_{ax}–C(8)); 2.64 (*ddd*, *J* = 5.0, 3.0, 2.0, H–C(3)); 3.32 (*dd*, *J* = 11.0, 10.0, H_{ax}–C(8a)); 3.72 (*qd*, *J* = 7.0, 3.0, H_{ax}–C(2)); 4.17, 4.20 (2*q*, *J* = 7.0, MeCH_2O). MS (70 eV): 284 (7, M^+), 269 (10, $[M - Me]^+$), 239 (20, $[M - C_3H_9]^+$), 211 (37, $[M - C_3H_5O_2]^+$), 170 (51, $C_9H_{14}O_3^+$), 109 (39, $C_7H_9O^+$), 96 (100, $C_6H_8O^+$), 69 (71, $C_5H_9^+$), 43 (100, $C_3H_7^+$).

*(±)-Ethyl (2*RS*,3*RS*)-2-Hydroxy-3-methylpent-4-enoate* (**50**). At –70° under N_2, –70° cold (2*E*)-but-2-ene (50 ml) was added to a stirred soln. of ethyl glyoxylate (=ethyl 2-oxoacetate; **49**; 15.0 g, 147 mmol) in dry CH_2Cl_2 (1.00 l). During 10 min, $SnCl_4$ (60.0 g, 230 mmol) was added dropwise with stirring, upon which the temp. was allowed to rise to –63°. The mixture was stirred at –70° for 2 h, then Et_2O (500 ml) was added. The mixture was allowed to warm up to –30° prior to carefully pouring into sat. aq. $KHCO_3$ soln. and stirring for 1 h (pH 7–8). The org. layer was washed with sat. aq. $KHCO_3$ soln., dried (Na_2SO_4), evaporated and the residue (23.0 g) purified by FC (silica gel, hexane/Et_2O 1:1): **50** (16.3 g, 70%). Colorless liquid. R_f 0.39. IR (neat): 1730*s* (C=O), 1130*s* and 1220*s* (C–O), 3490*s* (O–H), 1640*m* (C=C). ^{1}H-NMR ($CDCl_3$): 1.16 (*d*, *J* = 7.0, Me–C(3)); 1.30 (*t*, *J* = 7.0, *Me*CH_2O); 2.64–2.68 (*m*, H–C(3)); 4.10 (*d*, *J* = 3.0, H–C(2)); 4.23, 4.26 (2*q*, *J* = 7.0, MeCH_2O); 4.72 (br. *s.*, OH); 5.07, 5.08 (2*ddd*, *J* = 16.0, 3.0, 2.0, CH_2(5)); 5.76 (*ddd*, *J* = 16.0, 10.0, 8.0, H–C(4)). MS (70 eV): 158 (1, M^+), 104 (58, $[M - C_4H_6]^+$), 85 (21, $C_5H_9O^+$), 76 (75, $C_3H_8O_2^+$), 55 (100, $C_4H_7^+$).

*(±)-Ethyl (2*RS*,3*RS*)-2-{[(1*E*)-3-Methoxy-3-oxoprop-1-enyl]oxy}-3-methylpent-4-enoate* (**51**). Methyl prop-2-ynoate (8.00 g, 95.2 mmol) and 4-methylmorpholine (2.00 g, 19.8 mmol) were added in turn at r.t. under N_2 to a stirred soln. of **50** (11.8 g, 74.6 mmol). Stirring was continued for 15 h at r.t., prior to pouring the mixture in Et_2O/1N aq. AcOH 1:1. The aq. layer was extracted with Et_2O, the combined org. extract dried (Na_2SO_4) and evaporated, and the resulting residue distilled at 90–100°/0.2 mbar: **51** (16.9 g, 94%). Colorless liquid. IR (neat): 1135*s* and 1195*s* (C–O), 1715s and 1750*s* (OC=O), 1630*s* and 1640*s* (C=C). ^{1}H-NMR ($CDCl_3$): 1.07 (*d*, *J* = 7.0, Me–C(3)); 1.24 (*t*, *J* = 7.0, *Me*CH_2O); 2.81 (‘*sext.*’, *J* = 7.0, H–C(3)); 3.65 (*s*, Me–OCO); 4.21, 4.22 (2*q*, *J* = 7.0, MeCH_2O); 4.24 (*d*, *J* = 7.0, H–C(2)); 5.05 (*d*, *J* = 10.0, H–C(5) *trans* to C(3)); 5.06 (*d*, *J* = 14.0, H–C(5) *cis* to C(3)); 5.23 (*d*, *J* = 14.0, H–C(2′)); 5.80 (*ddd*, *J* = 14.0, 10.0, 7.0, H–C(4)); 7.66 (*d*, *J* = 14.0, H–C(1′)).

*(±)-Ethyl (2*RS*,3*RS*,4*SR*,6*SR*)-Tetrahydro-6-(2-methyoxy-2-oxoethyl)-3-methyl-4-[(methylsulfonyl)oxy]-2*H*-pyran-2-carboxylate* (**52**). MsOH (5.00 g, 52.0 mmol) was added with stirring at 10° to a soln. of **51** (9.00 g, 37.1 mmol) in CH_2Cl_2 (100 ml). After the cooling bath was removed, the mixture was stirred 1 h at r.t. The mixture was then diluted with Et_2O (300 ml) and washed with sat. aq. $NaHCO_3$ soln., the org. layer dried (Na_2SO_4) and evaporated, and the residue (14.0 g) purified by FC (silica gel, Et_2O/hexane 1:1): **52** (7.00 g, 56%) as a viscous oil which slowly crystallized. Recrystallization from ^{t}BuOMe furnished **52** (3.00 g, 23%). Colorless crystals. R_f 0.27. M.p. 93–95° (^{t}BuOMe). IR (neat): 1175*s* (SO_2, sym.), 1740*s* (OC=O), 940s and 930*s* (S–O), 1340*s* (SO_2, asym). ^{1}H-NMR ($CDCl_3$): 1.02 (*d*, *J* = 7.0, Me–C(3)); 1.30 (*t*, *J* = 8.0, *Me*CH_2O); 1.74 (*dd*, *J* = 18.0, 10.0, H_{ax}–C(5)); 1.96 (*dqd*, *J* = 10.0, 7.0, 6.0, H_{ax}–C(3)); 2.34 (*ddd*, *J* = 10.0, 6.0, 2.0, H_{eq}–C(5)); 2.49 (*dd*, *J* = 14.0, 7.0, H_b–C(1′)); 2.53 (*dd*, *J* = 14.0, 7.0, H_a–C(1′)); 3.06 (*s*, $MeSO_3$); 3.69 (*s*, MeOCO); 3.72 (*d*, *J* = 10.0, H_{ax}–C(2)); 3.92–3.98 (*m*, H–C(6)); 4.23, 4.24 (2*q*, *J* = 8.0, MeCH_2O); 4.52 (*ddd*, *J* = 10.0, 10.0, 6.0, H_{ax}–C(4)). MS (70 eV): 339 (1, $[M + H]^+$), 243 (2, $[M - SO_3Me]^+$), 211 (1, $[M - SO_3Me - MeOH]^+$), 169 (47, $C_9H_{13}O_3^+$), 95 (100, $C_6H_7O^+$).

*(±)-Ethyl (2*RS*,3*RS*,6*SR*)-Tetrahydro-6-(2-methoxy-2-oxoethyl)-3-methyl-2*H*-pyran-2-carboxylate* (**53**). Under N_2, NaI (5.00 g, 33.4 mmol) and Zn powder (6.00 g, 91.8 mmol) were added in turn at r.t. to a stirred soln. of **52** (3.00 g, 8.87 mmol) in 1,2-dimethoxyethane (50 ml). Stirring was continued at r.t. for 3 h, after which

the mixture was poured into Et_2O (400 ml), and the insolubles were removed by filtration. After washing with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ soln., the org. phase was dried (Na_2SO_4), evaporated, and the residue (2.50 g) purified by FC (silica gel, Et_2O/hexane 1:1): **53** (1.65 g, 76%). Colorless liquid. R_f 0.38. IR (neat): 1740*s* (C=OO), 1080*s* and 1190*s* (C–O). ^{1}H-NMR ($CDCl_3$): 0.86 (*d*, *J* = 7.0, Me–C(3)); 1.29 (*t*, *J* = 7.0, *Me*CH_2O); 1.45 (*dddd*, *J* = 14.0, 14.0, 11.0, 4.0, H_{ax}–C(5)); 1.69–1.89 (*m*, H–C(3), CH_2(4), H_{eq}–C(5)); 2.45 (*dd*, *J* = 15.0, 6.0, H_b–C(1′)); 2.69 (*dd*, *J* = 15.0, 6.0, H_a–C(1′)); 3.68 (*s*, MeOCO); 3.62 (*d*, *J* = 10.0, H_{ax}–C(2)); 3.75–3.83 (*m*, H–C(6)); 4.22 (*q*, *J* = 7.0, MeCH_2O). MS (70 eV): 243 (1, $[M-H]^+$), 212 (3, $[M-MeOH]^+$), 198 (3, $[M-EtOH]^+$), 185 (6, $[M-CO_2Me]^+$), 171 (91, $[M-CO_2Et]^+$), 139 (100, $[M-CO_2Et-MeOH]^+$), 97 (79, $C_6H_9O^+$), 59 (31, $C_2H_3O^+$), 43 (56, $C_3H_7^+$).

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