EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201501128

Aldol Additions of Titanium and Boron Enolates of Achiral and Chiral δ-Lactones to Achiral Model Aldehydes: Simple and Induced Diastereoselectivities

Fabian Weber,[a] Fabian Becker,[a] Manfred Keller,[a] Harald Hillebrecht,[b] and Reinhard Brückner*[a]

Dedicated to Dr. Klaus Brückner at the occasion of his 90th anniversary

Keywords: Aldol reactions / β-Hydroxy esters / δ-Lactones / Boron enolates / Titanium enolates / Diastereoselectivity / Configuration determination

We studied the steric course of aldol additions of $CpTiCl_2$ (novel) or Bu_2B enolates of the unsubstituted δ-lactone and of the four monomethylated δ-lactones to isobutyraldehyde, crotonaldehyde, and *para*-bromobenzaldehyde. The titanium enolates reacted *syn*-selectively with >95:5 *ds* in most cases. The boron enolates reacted *anti*-selectively without exception (*ds* = 98:2 to 92:8). These selectivities paired with a preferred *trans*-orientation of the α-hydroxyalkyl substituents relative to the lactone's β- or γ-methyl group and with a preferred *cis*-orientation relative to the lactone's δ-methyl group. Our preparation of γ-methyl-δ-lactone (**20**) features a tandem glycol cleavage/lactol→lactone conversion with cat. TEMPO/stoichiom. $PhI(OAc)_2$, which we believe is novel.

Introduction

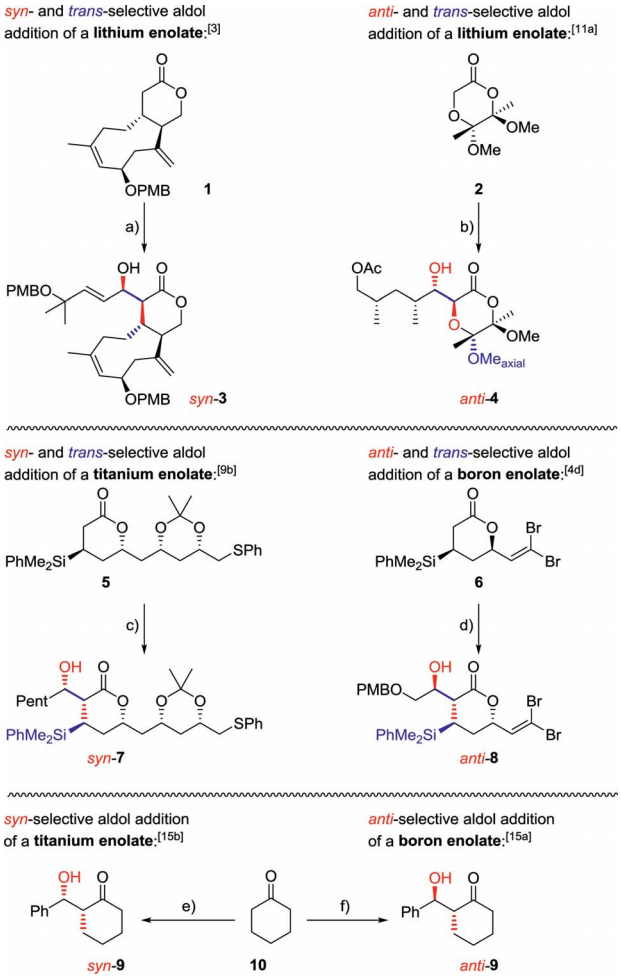
The aldol addition is an exceedingly powerful tool in organic synthesis.[1] Among its many specialized applications is the aldol addition of δ-lactones to aldehydes.[2–9] It introduces an α-hydroxyalkyl group at C-α of a δ-lactone. Thereby, the latter is incorporated into more complex structures. Analogous aldol additions allow functionalization of "δ-lactone variants", such as those that contain two heteroatoms in the cycle rather than one.[10–14] Conversely, cyclohexanones represent isocyclic variants of δ-lactones. Their enolates aldol-add to aldehydes, too.[15,16] The enolates of "heterocyclic cyclohexanones" such as pyran-4-ones (= 4-oxacyclohexanones),[17] piperidin-4-ones (= 4-azacyclohexanones),[18] thian-4-ones (= 4-thiacyclohexanones),[19] and 1,3-dioxane-5-ones (= 3,5-dioxacyclohexanones)[20] react likewise.

Each of the aldol additions mentioned above may form, in principle, a maximum of at least two diastereomers, if the reactants are achiral, and a maximum of at least four diastereomers if at least one reactant is chiral. This is because aldol additions can proceed with or without simple diastereoselectivity (no matter which reactants) and with or without induced diastereoselectivity (if at least one reactant is chiral). High simple diastereoselectivity is rarely encountered in aldol additions of acyclic *lithium* enolates.[1] *Cyclic lithium* enolates are not generally exempt from this rule. Accordingly, lithium enolates of the six-membered rings enumerated in the first paragraph – and of δ-lactones, which are the focus of this paper, in particular – aldol-add with little or without simple diastereoselectivity.[2] A few exceptions are known, though.[15d,15e] For δ-lactone enolates this is exemplified in the upper third of Scheme 1. The lithium enolate of lactone **1** aldol-adds to an α,β-unsaturated aldehyde with *perfect syn* selectivity.[3] In contrast the lithium enolate of lactone **2** and a variety of aldehydes give *anti*-aldols with up to 100% *ds*.[11a]

The only *syn*-selective aldol additions of α-unsubstituted δ-lactones described to date, to the best of our knowledge, have been performed in our group and proceed via $CpCl_2Ti^{IV}$ enolates.[9,21] Arguably, the most (and only?) reliable method of making *anti*-aldols from α-unsubstituted δ-lactones is via their dialkylboron enolates.[4] This propensity extends to *anti*-selective aldol additions from δ-lactone analogues with an extra heteroatom in the six-membered ring.[10,13,14] Scheme 1 illustrates these selectivities in lines 3 and 4, starting from the chiral δ-lactones **5**[9b] and **6**.[4d] The *syn* and *anti* selectivities of these aldol additions were per-

[a] Institut für Organische Chemie der Albert-Ludwigs-Universität, Albertstraße 21, 79104 Freiburg, Germany
E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de
http//www.brueckner.uni-freiburg.de
[b] Institut für Anorganische und Analytische Chemie der Albert-Ludwigs-Universität, Albertstraße 21, 79104 Freiburg, Germany

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201501128.

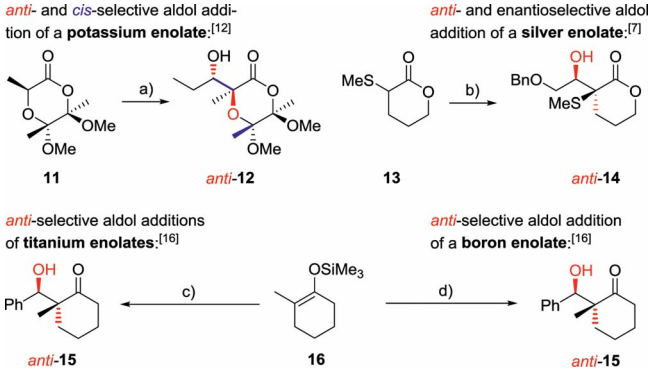


Scheme 1. Highly diastereoselective aldol additions of α-unsubstituted six-membered ring enolates from the literature. Considering them pairwise reveals their synthetic value but also suggests the absence of easy explanations for the respective kind of stereocontrol. One suspects a medley of factors, which – in the absence of high-caliber calculational support – looks intractable. Reagents and conditions: **a)** LDA (0.25 M in THF, 3 equiv.), THF, –78 °C, 1 h; aldehyde (1.5 equiv.), –78 °C, 2 h; 50%;[3] **b)** LiHMDS (1.0 M in hexane, 1.1 equiv.), THF, –78 °C 15 min; aldehyde (1.0 equiv.), –78 °C, 30 min; 79%;[11a] **c)** iPr_2NH (1.3 equiv.), nBuLi (1.25 equiv.), Et_2O, –78 °C, 60 min; addition of **5**, Et_2O, 2 h; addition of $CpTiCl_3$ (1.4 equiv.), 24 h; addition of hexanal (2.2 equiv.), 24 h; 82%, *anti*/*syn* 100:0;[9b] **d)** iPr_2NEt (1.6 equiv.), nBu$_2$BOTf (1.5 equiv.), CH_2Cl_2, room temp.→–78 °C; **6**, CH_2Cl_2, –78 °C, 2 h; addition of PMBO-CH_2-CHO (2.0 equiv.), –78 °C, 3 h; aq. H_2O_2 (30%), MeOH, room temp., 14 h; 71%, *syn*/*anti* 100:0;[4d] **e)** LDA, THF, –78 °C; $BrTi(NEt_2)_2$, –78 °C; solvent removed at room temp.; redissolved in pentane and cooled to –78 °C; benzaldehyde, –78 °C; >70%; *syn*/*anti* 97:3 (no more details given);[15b] **f)** iPrNEt$_2$ (1.1 equiv.), c-C_5H_9($t$$C_6H_{13}$)BOTf (1.1 equiv.), THF, –78 °C, 30 min, PhCHO (1.0 equiv.) 30 min, –78 °C, 1 h, 0 °C; 73%, no *syn* diastereomer detected in the ^{1}H NMR spectrum of the crude product.[15a]

fect – as perfect as the respective induced diastereoselecitivities, which arose additionally.

The dichotomy of the *syn*- versus *anti*-selective aldol additions of the titanium versus boron enolates of the substituted δ-lactones of Scheme 1 is complemented by a related dichotomy of aldol additions of the unsubstituted cyclohexanone enolates (Scheme 1, bottom): the $(Et_2N)_3Ti^{IV}$ enolate of the cyclohexanone aldol-adds to benzaldehyde with 97:3 *syn*/*anti* selectivity.[15b] The cyclopentyl(*tert*-hexyl)boron enolate reacts analogously with more than 96:4 *anti*/*syn* selectivity.[15a]

Little to nothing is known about the scope of these methods of simple diastereocontrol. Turning from aldol additions of α-unsubstituted δ-lactones (cf. above) to aldol additions of α-*substituted* δ-lactones, the upper part of Scheme 2 shows two pertinent examples.[12,7] They are both *anti*-selective and yet proceed via enolates strikingly different from the Bu_2B enolate of lactone **6**,[4d] which forms the aldol *anti*-**8** of Scheme 1. The *anti*-addition of lactone **11**[12] was effected via the potassium enolate, the *anti*-addition of lactone **13**[7] via the silver enolate. Of course, these findings imply nothing about what the *syn*/*anti* selectivities of the corresponding $CpCl_2Ti^{IV}$ and Bu_2B enolates would have been. Nonetheless it must be pointed out that there need not be a Ti versus B dichotomy of the simple diastereoselectivity as lines 3–5 of Scheme 1 might suggest: the $(i$PrO$)_3Ti^{IV}$ *and* the Bu_2B enolate of α-methylcyclohexanone (both accessed from the silyl enol ether **16**, namely by an indirect and by a direct transmetalation, respectively) aldol-added to benzaldehyde with high *anti* selectivity.[16] Differently expressed, the aldol additions of six-membered cyclic α-substituted ester and ketone enolates as represented in Scheme 2 tend to give *anti*-configured aldol adducts no matter what the counterion is. The $CpCl_2Ti^{IV}$ and Bu_2B enolates of α-methyl-δ-lactone revealed *anti* preferences – or at least only a small *syn* preference – in their aldol additions as well (see below).



Scheme 2. Highly diastereoselective aldol additions of α-substituted six-membered ring enolates from the literature. Reagents and conditions: **a)** KHMDS (1.05 equiv.), THF, –78 °C, 15 min; propanal (2.0 equiv.), –78 °C, 1 h; 53%, only *anti*;[12] **b)** DBU/$AgPF_6$/(*R*)-MeO-BIPHEP (3 mol-% each), toluene, –50 °C, 15 h, 92%, *anti*/*syn* >95:5, 99% *ee*;[7] **c)** for the $Ti(OiPr)_3$ enolate: **16** (1.1 equiv.), BuLi (1.1 equiv.), THF, 0 °C, 30 min; $TiCl(OiPr)_3$ (1.1 equiv.) –72 °C, 2 h; solvent exchanged for hexane; –72 °C, benzaldehyde, 1 h; 94%, *anti*/*syn* 95:5; the $TiCl_3$ enolate reacted with benzaldehyde at –72 °C in CH_2Cl_2 for 1 h: 29%, *anti*/*syn* 88:12;[16] **d)** the BBu_2 enolate reacted at –72 °C in Et_2O for 2 h: 60%, *anti*/*syn* 99.5:0.5.[16]

Bearing in mind the facts delineated so far we wondered what the scope of our *syn*- versus *anti*-favoring aldol additions **5**→*syn*-**7**[9b] and **6**→*anti*-**8**[4d] from Scheme 1 would be (Figure 1). Would the simple diastereoselectivity vary if

our enolates originated from unsubstituted δ-lactone (**17**) or α-methyl-δ-lactone (**18**): that is, from δ-lactones, which would aldol-add without the interference of induced diastereoselectivity? Or, if our enolates were derived from β- (**19**), γ- (**20**) or δ-monomethyl-δ-lactone (**21**): that is, from δ-lactones that would aldol-add such that simple diastereoselectivity might be reinforced or attenuated by the interference of induced diastereocontrol? We addressed these questions by employing isobutyraldehyde (**22**), crotonaldehyde (**23**), and 4-bromobenzaldehyde (**24**) as representative electrophiles. We opted for 4-bromobenzaldehyde rather than benzaldehyde hoping that the aldol adducts obtained from the former would crystallize and therefore lend themselves for structure elucidation by X-ray crystallography.

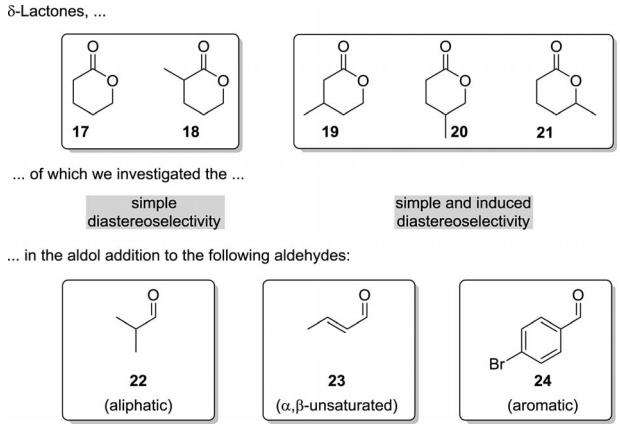


Figure 1. Substrates of the aldol additions of this study.

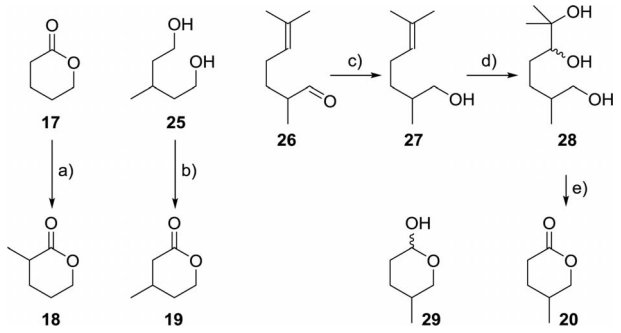
Synthesis of the δ-Lactone Starting Materials

Of the δ-lactones required for this study (Figure 1), the parent compound **17** and δ-methyl-δ-lactone (**21**) were commercially available. α-Methyl-δ-lactone (**18**), β-methyl-δ-lactone (**19**), and γ-methyl-δ-lactone (**20**) were synthesized as shown in Scheme 3.

(1) We obtained α-methyl-δ-lactone (**18**) in 42% yield by methylating the lithium enolate of δ-lactone (**17**) with methyl iodide.[22,23]

(2) The synthesis of β-methyl-δ-lactone (**19**) by the oxidation of 3-methylpentane-1,5-diol (**25**) with MnO_2 was described in the literature (81% yield).[24] In our hands this reaction gave irreproducible results (→ 46–82% **19** plus up to 54% of the corresponding lactol, which proved inseparable by flash chromatography[25]). We achieved the same oxidation reproducibly in 58% yield by using catalytic TEMPO and stoichiometric bleach as the oxidants.[26]

(3) We synthesized γ-methyl-δ-lactone (**20**) via the surmised intermediacy of the lactol **29**. For **29** a two-step access from melonal (**26**) via the unsaturated alcohol **27** had been described.[27] Melonal (**26**) gave an 89% yield of this alcohol **27** after treatment with $NaBH_4$ in MeOH. The olefin moiety of **27** was dihydroxylated.[28] This provided a 72% yield of the triol **28**. This, 10 mol-% TEMPO,[26a] and 2 equiv. of $PhI(OAc)_2$[26b] were subjected to a glycol cleavage (→ lactol **29**) / oxidation (→ lactone **20**) tandem reaction in 68% yield. Effecting such an overall transformation



Scheme 3. Synthesis of the methyl-δ-lactones that were not obtained commercially. Reagents and conditions: **a)** *i*$PrNH_2$ (1.1 equiv.), BuLi (1.1 equiv.), THF, –78 °C, 30 min; addition of **17**, –78 °C, 30 min; MeI (1.5 equiv.), –78 °C, 30 min, –35 °C, 1 h; 42%; **b)** TEMPO (5 mol-%), bleach (total content of chlorine approx. 10%, approx. 2.0 equiv.), KBr (15 mol-%), CH_2Cl_2/satd. aq. $NaHCO_3$ solution, room temp., 30 min; 58%; **c)** $NaBH_4$ (2.0 equiv.), MeOH, room temp., 1 h; 89% (ref.[27] with $NaBH_4$ in EtOH: 93%); **d)** $K_2OsO_2(OH)_4$ (0.2 mol-%), $(DHQ)_2PHAL$ (0.4 mol-%), $K_3Fe(CN)_6$ (2.2 equiv.), K_2CO_3 (2.2 equiv.), $MeSO_2NH_2$ (1.0 equiv.), tBuOH/H_2O (1:1), room temp. 1 d; 72%; **e)** TEMPO (10 mol-%), $PhI(OAc)_2$ (2.2 equiv.), $NaHCO_3$ (20 equiv.), CH_2Cl_2, room temp., 30 min; 68%.

with this reagent mix is unprecedented to the best of our knowledge. We had found these conditions "accidentally" – when trying to oxidize a different secondary/tertiary glycol to the corresponding *tert*-hydroxy ketone and achieving a glycol cleavage instead.[29]

Results and Discussion

Being in possession of the desired δ-lactones **17**–**21** (cf. Figure 1) we investigated how their $CpCl_2Ti$ and Bu_2B enolates aldol-add to the aldehydes **22**–**24**. As a rule, these $CpCl_2Ti$ enolate additions proceeded well under the conditions of the corresponding prototypical aldol addition **5**→*syn*-**7**[9b] (Scheme 1). An exception was found in the $CpCl_2Ti$ enolate aldol additions of α-methyl-δ-lactone (**18**), as detailed below. The Bu_2B enolate aldol additions of the δ-lactones **17**–**21** required modifying the conditions of the prototypical aldol addition **6**→*anti*-**8**[4d] (Scheme 1). Orienting additions of the boron enolate of β-methyl-δ-lactone (**19**) to 4-bromobenzaldehyde (**24**) led to no more than 30% conversion[30] under the previously described conditions.[4d] Under otherwise identical conditions we had much better levels of conversion[30] – and isolated an 82% yield of the aldol adduct **38** – by combining the metal source and the base in a different order with the present lactone **19** than with the previously used lactone **6**. Originally, we had added Bu_2BOTf to a solution of NEt_3 in CH_2Cl_2 at –5 °C, cooled that solution to –78 °C, and then added the lactone. Now, we mixed the lactone and Bu_2BOTf at –78 °C and added NEt_3 15 min later.

The outcomes of the 30 lactone enolate aldol additions that we undertook are compiled in Tables 1 and 2. Table 1 contains the results of the 2×6 aldol additions delivering aldol adducts with two stereocenters; Table 2 represents the outcome of the 2×9 aldol additions that furnished aldol

adducts with three stereocenters. Differently expressed, the aldol additions of this study's lactone enolates, which are achiral – and hence cannot be subject to induced diastereocontrol – are compiled in Table 1. The aldol additions of this study's lactone enolates, which are chiral – and, hence, may experience induced diastereocontrol – are the topic of Table 2.

Adding unsubstituted δ-lactone (**17**) to the aldehydes **22**–**24** afforded the aldols **30**–**32** (Table 1, Entries 1–3). They were diastereomerically almost pure, the $CpCl_2Ti$ enolate of **17** reacting with *syn*/*anti* >95:5 to 97:3 and the Bu_2B enolate with *anti*/*syn* 93:7 to 96:4.

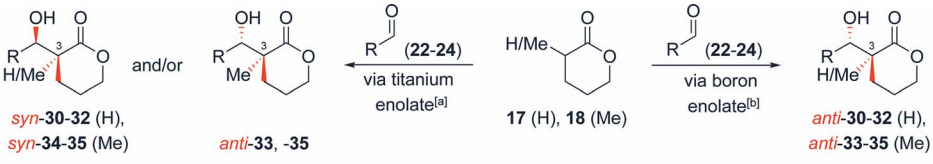
This stereocomplementarity and the separability of all *syn,anti* mixtures by flash chromatography[25] allowed us to gain 400 MHz ^{1}H NMR spectra of the six pure aldol diastereomers. This allowed us to assess the *syn*/*anti* ratios in the crude aldol products ^{1}H-NMR-spectroscopically. We established the *syn* configuration of the major aldol diastereomer *syn*-**32** (Table 1, Entry 3, left) from the $CpCl_2Ti$ enolate of δ-lactone (**17**) and *para*-bromobenzaldehyde (**24**) by X-ray crystallography (Figure 2, first line, left). Making doubly sure, we established the *anti* configuration of the major aldol diastereomer *anti*-**32** (Table 1, Entry 3, right), which resulted from the Bu_2B enolate of δ-lactone (**17**) and *para*-bromobenzaldehyde (**24**), by X-ray crystallography, too (Figure 2, first line, right). The *syn* versus *anti* assignments of the aldol adducts **30** and **31** (Entries 1 and 2, Table 1) are based on the following analogies:

(1) The diastereoselectivities of the formation reactions were stereocomplementary starting from $CpCl_2Ti$ versus Bu_2B enolates, and uniformly high. This fits well with the assumption that the titanium enolates of Entries 1–3 of Table 1 aldol-add *syn*-selectively and the corresponding boron enolates *anti*-selectively.

(2) If so assigned, the ring-protons 3-H (numbering: Table 1) of the aldol adducts **30**–**32** are deshielded in the three pairs of *syn* versus *anti* diastereomers.[31]

The aldol adducts **30**–**32** derived from the unsubstituted δ-lactone (**17**) and the aldehydes **22**–**24** (Table 1, Entries 1–3) are sterically less hindered than the aldol adducts **33**–**35** (Table 1, Entries 4–6). The latter compounds contain a quaternary stereocenter and are the result of adding α-methyl-δ-lactone (**18**) to the same three aldehydes. The titanium-mediated aldol additions of α-methyl-δ-lactone (**18**) responded to the increased hindrance by the loss – or, as assessed later (see below), the partial reversal (from a *syn* to an *anti* preference[32]) – of simple diastereocontrol. In contrast, the boron-mediated aldol additions of the same hindered lactone **18** were nearly as diastereoselective (*ds* = 92:8 to >95:5; Table 1, Entries 4–6) as the analogous reactions of the unsubstituted lactone **17** (*ds* = 93:7 to 96:4; Table 1, Entries 1–3).

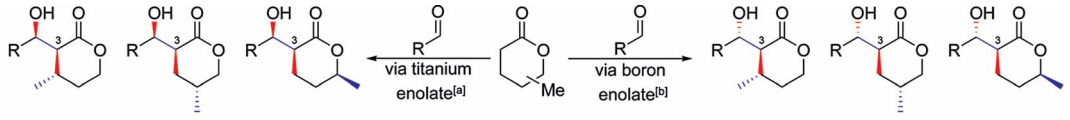
Table 1. Simple diastereoselectivity in the aldol additions of titanium and boron enolates of the achiral δ-lactones of Figure 1. The 3D structure of each aldol adduct whose compound number is highlighted by a grey background was determined by an X-ray crystal structural analysis (cf. Figure 2).



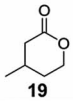
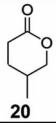
Entry	Lactone	R	Aldol addition of titanium enolate[a]			Aldol addition of boron enolate[b]		
			Major product	Diastereomer ratio in the crude product[c] *syn:anti*	Yield[d]	Major product	Diastereomer ratio in the crude product[c] *anti:syn*	Yield[d]
1		*i*Pr-	*syn*-**30**	>95:5[e,f]	72%	*anti*-**30**	96:4	67%
2		Me-CH=CH-	*syn*-**31**	>95:5[f]	65%	*anti*-**31**	93:7	64%
3	**17**	4-Br-C_6H_4-	*syn*-**32**	97:3	66%	*anti*-**32**	95:5	72%
4		*i*Pr-	*anti*-**33**	37:63	(60%)	*anti*-**33**	>95:5[f]	84%
5		Me-CH=CH-	*syn*-**34**	59:41	61%[g]	*anti*-**34**	93:7	45%
6	**18**	4-Br-C_6H_4-	— (**35**)	50:50	72%	*anti*-**35**	92:8	78%

[a] Reagents and conditions: iPr_2NH (1.2 equiv.), BuLi (1.1 equiv.), Et_2O, –78 °C, 1 h; addition of lactone **17** or **18**, –78 °C, 1 h; $CpTiCl_3$ (1.4 equiv.), –78 °C, 18 h; aldehyde **22**–**24** (2.0 equiv.), –78 °C, 24 h. [b] Reagents and conditions: Lactone **17** or **18**, Bu_2BOTf (1.6 equiv.), CH_2Cl_2, –78 °C, 15 min; NEt_3 (1.6 equiv.),–78 °C, 1 h; aldehyde **22**–**24** (2.0 equiv.), –78 °C, 3 h. [c] Determined by integrating baseline-separated signals in the 400 MHz ^{1}H NMR spectrum of the crude product (which signals these were is specified in the Experimental Section). [d] Yields without parentheses are either the yield of the only isolated diastereomer[f] or the combined yield of the separated diastereomers, always after purification by flash chromatography on silica gel.[25] The yield with parentheses refers to the *syn*-**30**/*anti*-**30** mixture isolated after purification by flash chromatography on silica gel.[25] [e] Crude "**30**" was so contaminated by side products that its 400 MHz ^{1}H NMR spectrum did not allow the diastereomeric composition to be determined. Therefore, "**30**" was purified by flash chromatography on silica gel[25] "to some extent". This means that we combined all fractions that contained the product (according to TLC analysis) with the three fractions that eluted before the product and with the three fractions that eluted after the product. The diastereomer ratio[f] in the Table refers to the chromatographed product just described. [f] No ^{1}H NMR signal corresponding to the minor diastereomer was detected. [g] Isolated yield of a pure 65:35 mixture of the diastereomers.

Table 2. Simple and induced diastereoselectivity in the aldol additions of titanium and boron enolates of the chiral δ-lactones of Figure 1. The 3D structure of each aldol adduct whose compound number is highlighted by a grey background was determined by an X-ray crystal structural analysis (cf. Figure 2).



syn,trans-**36**-**38** *syn,trans*-**39**-**41** *syn,cis*-**42**-**44** *anti,trans*-**36**-**38** *anti,trans*-**39**-**41** *anti,cis*-**42**-**44**

Entry	Lactone	R	Aldol addition of titanium enolate[a]					Aldol addition of boron enolate[b]				
			Major product[c]	Diastereomer ratio in the crude product[c]			Yield[d]	Major product[c]	Diastereomer ratio in the crude product[c]			Yield[d]
				syn:anti	*syn,trans:syn,cis*	*anti,trans:anti,cis*			*anti:syn*	*anti,trans:anti,cis*	*syn,trans:syn,cis*	
1	 **19**	*i*Pr-	*syn,trans*-**36**	96:4[e]	>95:5[e,f]	>95:5[e,f]	76%	*anti,trans*-**36**	98:2	>95:5[f]	>95:5[f]	79%
2		Me-CH=CH-	*syn,trans*-**37**	97:3	>95:5[f]	>95:5[f]	75%	*anti,trans*-**37**	94:6	>95:5[f]	>95:5[f]	75%
3		4-Br-C_6H_4-	*syn,trans*-**38**	95:5	>95:5[f]	>95:5[f]	80%	*anti,trans*-**38**	97:3	91:9	>95:5[f]	82%
4	 **20**	*i*Pr-	*syn,trans*-**39**	>95:5[e,f]	72:28[e]	—	60%	*anti,trans*-**39**	>95:5[e,f]	75:25[e]	—	70%
5		Me-CH=CH-	*syn,trans*-**40**	93:7	73:27	23:77	(59%)	*anti,trans*-**40**	93:7	78:22	>95:5[f]	(74%)
6		4-Br-C_6H_4-	*syn,trans*-**41**	97:3	68:32	70:30	(75%)	*anti,trans*-**41**[g]	93:7	73:27[g]	41:59	(82%)
7	 **21**	*i*Pr-	*syn,cis*-**42**	99:[e]	14:86[e]	<5[f]:95[e]	75%	*anti,cis*-**42**	94:6	24:76	<5:95[f]	62%
8		Me-CH=CH-	*syn,cis*-**43**	>95:5[f]	27:73	—	(71%)	*anti,cis*-**43**	94:6	25:75	<5:95[f]	(73%)
9		4-Br-C_6H_4-	*syn,cis*-**44**	98:2	27:73	37:63	52%[h]	*anti,cis*-**44**	94:6	24:76	<5:95[f]	(83%)

[a] Reagents and conditions: *i*Pr_2NH (1.2 equiv.), BuLi (1.1 equiv.), Et_2O (0.16 M), –78 °C, 1 h; lactone, –78 °C, 1 h; $CpTiCl_3$ (1.4 equiv.), –78 °C, 18 h; aldehyde (2.0 equiv.), –78 °C, 24 h. [b] Reagents and conditions: Bu_2BOTf (1.6 equiv.), CH_2Cl_2 (0.16 M), –78 °C, 15 min; NEt_3 (1.6 equiv.), –78 °C, 1 h; aldehyde (2.0 equiv.), –78 °C, 3 h. [c] Determined by integrating baseline-separated signals in the 400 MHz ^{1}H NMR spectrum of the crude product (which signals these were is specified in the Experimental Section). [d] Yields without parentheses refer to the pure main diastereomer isolated after purification by flash chromatography on silica gel.[25] If a mixture of *cis*,*trans* diastereomers was isolated, its yield is given in parentheses. [e] Crude "*syn*,*trans*-**36**", crude "**39**", and crude "**42**" were so contaminated by side products that the corresponding 400 MHz ^{1}H NMR spectrum did not allow the diastereomeric composition to be determined. Therefore, "**36**", "**39**", and "**42**" were purified by flash chromatography on silica gel[25] "to some extent". This means that we combined all respective fractions that contained the product (according to TLC analysis) with the three fractions that eluted before the product and with the three fractions that eluted after the product. The respective diastereomer ratios in the Table[f] refer to the chromatographed products just described. [f] No ^{1}H NMR signal corresponding to the indicated minor diastereomer was detected. [g] Three diastereomers from this aldol adduct portfolio were subjected to X-ray crystallography: *anti*,*trans*-**41** (Figure 2), *syn*,*trans*-**41** (Figure 2), and a co-crystal of *syn*,*trans*-**41** and *anti*,*trans*-**41** (Figure 3). [h] 12% of a mixture of diastereomers were isolated separately, as were 17% *syn*,*trans*-**44**; the total yield of aldol adduct was 81%.

The near-identical *magnitudes* of simple diastereocontrol in the boron-mediated aldol additions of lactones **18** versus **17** suggested that the *directions* of simple diastereocontrol were identical, too. Consequently, the major diastereomers of the boron-based aldol adducts **33**–**35** were considered *anti* diastereomers. This notion was corroborated by crystallizing the major diastereomer of the boron- and *para*-bromobenzaldehyde-based aldol adduct **35**. An X-ray crystal structure analysis confirmed its *anti* configuration (Figure 2, second line, right). If the configurations of *anti*-**33** and *anti*-**34** were assigned correctly for analogy (see above), the *syn*,*anti* selectivity of each of the titanium-mediated aldol additions of α-methyl-δ-lactone (**18**) could be quantified ^{1}H NMR spectroscopically as follows (Table 1, Entries 4–6): the titanium enolate of lactone **18** added to isobutyraldehyde (**22**) with a weak *anti* preference (→ *anti*/*syn* 63:37), to crotonaldehyde (**23**) with a weak *syn* preference (→ *syn*/*anti* 59:41), and to 4-bromobenzaldehyde (**24**) with no preference at all (→ *syn*/*anti* 50:50). This contrasts with the >95:5 *syn* selectivities of the aldol additions of the titanium enolate of the unhindered lactone **17** to the same aldehydes.[33]

Table 2 summarizes the 18 aldol additions altogether of the $CpCl_2Ti$ enolates ("left-bound" reactions) and of the Bu_2B enolates ("right-bound" reactions) of β- (**19**, Entries 1–3), γ- (**20**, Entries 4–6), and δ-methyl-δ-lactone (**21**, Entries 6–9) to our aldehydes **22**–**24**. Each of these additions might have led, in principle, to up to four diastereomers. The corresponding ratios of *syn*- to *anti*-aldol(s) measure the extent of simple diastereocontrol, and the ratios of *cis*- to *trans*-(hydroxyalkyl)methyl-δ-lactone(s) gauge the degree of induced diastereoselectivity. In the actual experiments, we identified – ^{1}H-NMR-spectroscopically (400 MHz, $CDCl_3$) – as few as two aldol adducts in eight aldol additions, three aldol adducts in six aldol additions, and the maximum number of four aldol adducts in four aldol additions. Overall, Table 2 documents the obtention of 31 of the 36 conceivable different aldol products. The content of the major diastereomer in the crude aldol mixtures ranged from 66% (*syn*,*trans*-**41**) to 98% (*anti*,*trans*-**36**). From 11 of our total of 18 aldol additions the major diastereomer was isolated as a pure product. In one case (*syn*,*cis*-**44**) the second most abundant diastereomer (*syn*,*trans*-**44**) was also isolated as a pure compound. From

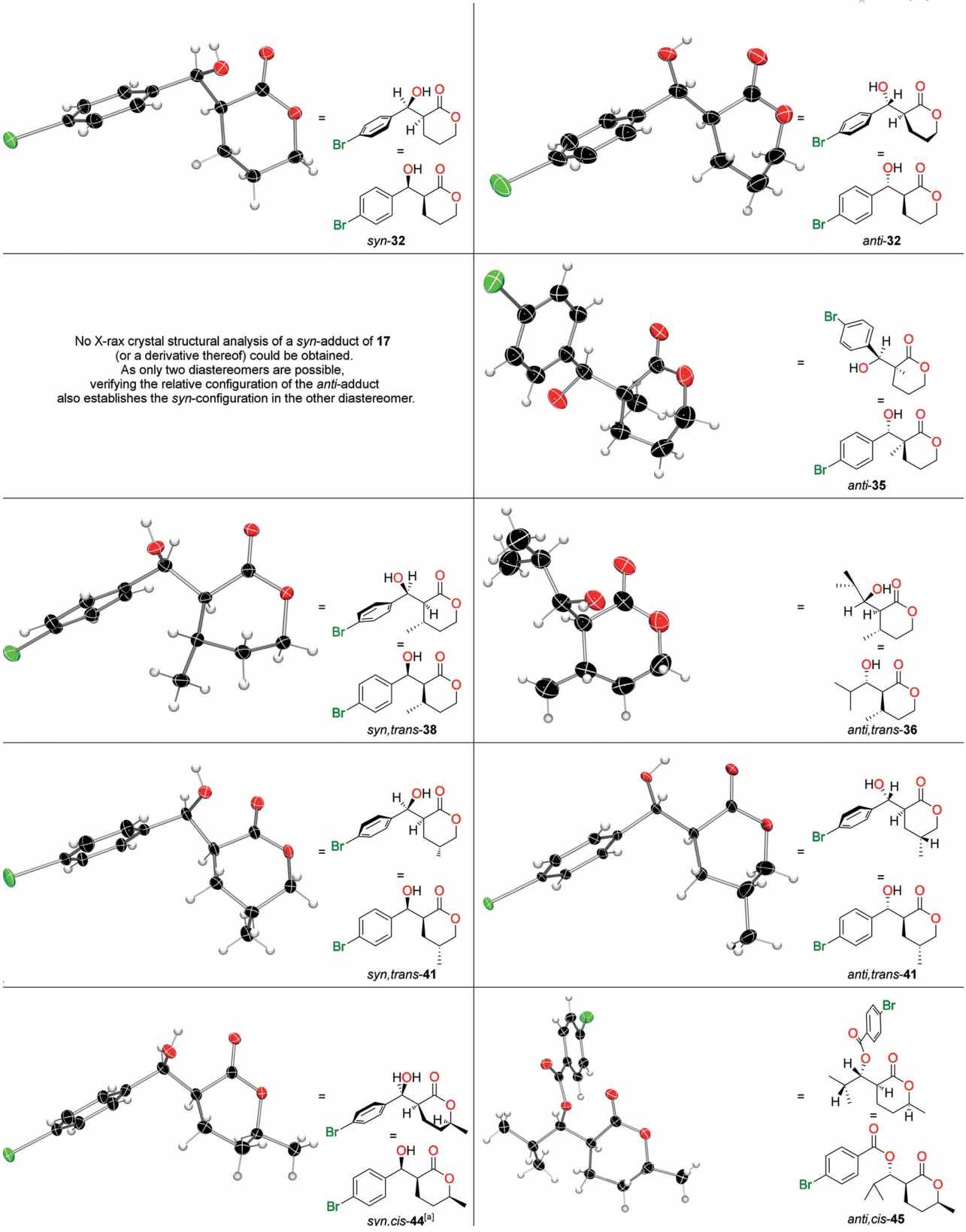


Figure 2. Elucidation of the configurations of the main diastereomers by X-ray structural analysis: the 4-bromobenzaldehyde adducts *syn*-**32**,[41] *anti*-**32**,[42] *anti*-**35**,[43] *syn*,*trans*-**38**,[44] *syn*,*trans*-**41**,[45] *anti*,*trans*-**41**,[46] and *syn*,*cis*-**44**,[47][a] the isobutanal adduct *anti*,*trans*-**36**,[48] and the 4-bromobenzoate *anti*,*cis*-**45**[49] of the isobutanal adduct *anti*,*cis*-**42**. [a] Compound *syn*,*cis*-**44** crystallized in an acentric space group. Its X-ray structure has been inverted in the presentation *in this Figure* for the sake of endowing the stereocenter at C-α of each δ-lactone consistently with an *S* configuration. The genuine X-ray structure is shown in the Supporting Information.

the remaining seven aldol additions we could only isolate two-compound mixtures consisting of the major *cis* and the major *trans* isomer.[34]

The configurational assignments of the 18 major diastereomers of the aldol products **36**–**44** of Table 2 began with assigning the *syn* configuration to each major aldol product from the $CpCl_2Ti$ enolates of lactones **19**–**21** and the aldehydes **22**–**24** ("left-bound" reactions); of these aldols, we recognized *syn*-**36**–**41** as *syn*,*trans*-**36**–**41** and *syn*-**42**–**44** as *syn*,*cis*-**42**–**44**. Similarly, we assigned the *anti* configuration to each major aldol product **36**–**44** from the corresponding Bu_2B enolates and the same set of aldehydes (Table 2, "right-bound" reactions); of these, we recognized *anti*-**36**–**41** as *anti*,*trans*-**36**–**41** and *anti*-**42**–**44** as *anti*,*cis*-**42**–**44**. Six of the 18 preceding attributions are based on X-ray crystallographic evidence (Figure 2, lines 3–5); twelve are extrapolated by analogy. Each extrapolation concerned an enolate, which, by adding to *one* aldehyde, had afforded crystals that had been subjected to X-ray crystallography. Accordingly, we did not go beyond assuming that the identical enolate added to the *other two* aldehydes essentially with the identical stereoselectivity.

The titanium and boron enolates of β-methyl-δ-lactone (**19**) afforded a total of seven aldol adducts (Table 2, Entries 1–3). Six of them yielded their stereostructures either to X-ray analyses (*anti*,*trans*-**36**, *syn*,*trans*-**38**) or to the already mentioned assumption that the identical enolates added to the *other two* aldehydes essentially with identical stereoselectivities. The seventh aldol product was identified ^{1}H-NMR-spectroscopically as *anti*,*cis*-**38** in the aldol mixture obtained from Bu_2B-**19** and *para*-bromobenzaldehyde (**24**; Table 2, Entry 3, right).[35]

The aldol additions of γ-methyl-δ-lactone (**20**) led to all 12 conceivable aldol adducts **39**–**41** (Table 2, Entries 4–6). The stereostructures of the six major diastereomers were recognized directly by X-ray analyses (*syn*,*trans*-**41**[36,37] and *anti*,*trans*-**41**[37,38]) or indirectly by extrapolating the underlying selectivities to the analogous aldolizations (see above). Additionally, we possessed an X-ray structural analysis of a mixture of the aldols *syn*,*cis*-**41** and *syn*,*trans*-**41**[37,38] (Figure 3). By the exclusion principle this allowed us to assign stereostructure *anti*,*cis*-**41** to the fourth aldol diastereomer with the constitution **41**. Accordingly, when the aldol **41** resulted from the titanium enolate, the major (*syn*,*trans*-**41**) and the second most abundant diastereomer (*syn*,*cis*-**41**) were *trans*,*cis* isomers. So were the major (*anti*,*trans*-**41**) and the second most abundant diastereomer (*anti*,*cis*-**41**) of the aldol **41** formed from the boron enolate. These findings suggest that the second most abundant diastereomers in the γ-methyl-δ-lactone-derived aldols **39** and **40** are *cis* isomers of the dominating *trans* species. This interpretation is corroborated by ^{1}H NMR analogies.[39]

The aldol additions of δ-methyl-δ-lactone (**21**) furnished a full set of the 12 conceivable aldol adducts, too (**42**–**44**, Table 2, Entries 7–9). The 3D structures of the six major diastereomers were elucidated by X-ray crystallography (*syn*,*cis*-**44**, *para*-bromobenzoate *anti*,*cis*-**45** of aldol *anti*,*cis*-**42**) or plausible analogies as described above. Moreover, we reasoned similarly as when we considered each second most abundant aldol **39**–**41** as the *cis* isomer of the *trans*-configured major aldol. However, in the aldols **42**–**44** we classified the second most abundant diastereomers as *trans* isomers of the dominating *cis* isomers. These assignments were corroborated by ^{1}H NMR analogies.[39,40]

In a nutshell, the stereoselectivities of Table 2 can be described as follows:

(1) The $CpCl_2Ti$ enolate additions of Table 2 gave *syn*-aldols with *ds* = 93:7 to 99:1. This resembles the *syn* selectivity of the aldolizations of the $CpCl_2Ti$ enolate of the unsubstituted δ-lactone (**17**; *syn*/*anti* >95:5 to 97:3; Table 1, Entries 1–3).

(2) The Bu_2B enolate additions of Table 2 gave *anti*-aldol products with *ds* = 93:7 to 98:2. This is akin to the *anti* selectivity of the aldolizations of the Bu_2B enolate of the unsubstituted δ-lactone (**17**; *anti*/*syn* 92:8 to ca. 96:4; Table 1, Entries 1–3).

(3) The aldol additions of the $CpCl_2Ti$ and the Bu_2B enolate of β-methyl-δ-lactone (**19**) were highly *trans*-selective (*trans*/*cis* >94:6; Table 2, Entries 1–3). The underlying 1,2-asymmetric inductions appears plausible in terms of a repulsive steric effect of the neighboring methyl group.

(4) The aldol additions of the $CpCl_2Ti$ and the Bu_2B enolate of γ-methyl-δ-lactone (**20**) were moderately *trans*-selective (*trans*/*cis* = 68:32 to 78:22; Table 2, Entries 4–6).

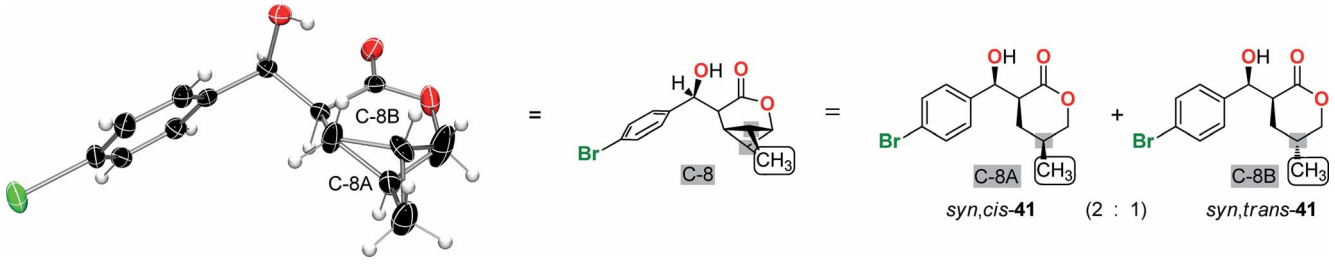


Figure 3. Along with the thin flat needles of the aldol adduct *syn*,*trans*-**41**[37] (X-ray structure: Figure 2) we found one large plate-like crystal. It turned out to be a co-crystal of the same aldol adduct *syn*,*trans*-**41** and its diastereomer *syn*,*cis*-**41** in a 1:2 ratio. The X-ray structure[50] of this crystal is shown here. In the first analysis (not depicted), the nucleus C-8 (≡ X-ray numbering for the methyl-substituted carbon atom) was refined as an unexplainably elongated ellipsoid. This could be resolved into two distinct positions: C-8A and C-8B, with site occupation factors in a ratio of 2 (for *syn*,*cis*-**41**) to 1 (for *syn*,*trans*-**41**). Obviously, very small amounts of residual *syn*,*cis*-**41** co-precipitated with *syn*,*trans*-**41** in a 2:1 ratio towards the end of the crystallization of what had been the 33:67 (!) *syn*,*cis*-**41**/*syn*,*trans*-**41** mixture, which we had isolated from our titanium-mediated aldol addition.

The respective 1,3-asymmetric induction seems inexplicable in terms of a direct interaction with the methyl group, which looks fairly remote.

(5) The aldol additions of the $CpCl_2Ti$ and the Bu_2B enolate of δ-methyl-δ-lactone (**21**) were moderately *cis*-selective (*cis*/*trans* = 73:27 to 76:24), reaching 86:14 in one instance (Table 2, Entries 7–9). Superficially, the underlying 1,4-asymmetric induction looks contrasteric, but evidently the methyl group at C-δ and a suitably oriented incoming aldehyde should be separated too much from one another for any steric interaction to occur.

A straightforward interpretation – at least to an extent – of the dichotomy of the simple diastereoselectivities of our titanium- versus boron-mediated aldol additions is based on the assumption that they proceed via cyclic transition states. There is no reason to doubt that, in compliance with the Zimmerman–Traxler model,[51] the Bu_2B enolates, which must be "*trans*"-configured, react via chair-like transition states chair-**51a**–**e** (Figure 4). In these "chairs", the aldehyde substituent R is oriented equatorially. Thus, these additions should lead to boron aldolates *anti*-**50a**–**e**. This is true no matter whether or where the lactone is methylated. If (!) the *syn* selectivity of the aldol additions of the $CpCl_2Ti$ enolates **46a** and **46c**–**e** is also determined in six-membered cyclic transition states **48a** and **48c**–**e**, the latter must accommodate the aldehyde substituent axially (Figure 4). This is a necessity both if these transitions states represent chairs **48a** and **48c**–**e** or boats **48a** and **48c**–**e**. We believe it is more likely that the $CpCl_2Ti$ enolates **46a** and **46c**–**e** react via the transition states boat- rather than chair-**48a** and **48c**–**e**. This is because the α-methylated $CpCl_2Ti$ enolate **46b** does not exhibit the *syn* selectivity of all other $CpCl_2Ti$ enolates (**46a** and **46c**–**e**). α-Methylation should destabilize specifically the transition state boat-**48b** by allyl^{1,3} strain, while no comparable effect would be expected in a chair-like transition state. The selective destabilization of the transition state boat-**48b** might act in favor of an equatorial aldehyde substituent in the respective transition state (not depicted in Figure 4) and the formation of an *anti*-aldol, accordingly.[32] Of course, one may speculate whether a $CpCl_2Ti$(enolate) is too weak a Lewis acid for capturing an aldehyde in a Zimmerman–Traxler transition state. A hint in that direction might be that $CpTiCl_3$ scarcely releases HCl fumes when handled in laboratory air. In any event an alternative is that our $CpCl_2Ti$ enolates aldol-add via an acyclic transition state.[52]

Figure 5 is an attempt at interpreting the induced diastereoselectivities of the aldol additions of our *chiral* enolates. The respective stereocontrol is independent of the metal moiety. Accordingly, the partaking $CpCl_2Ti$ *and* Bu_2B enolates are condensed to single formulas **52c**–**e** in Figure 5. The structure variation **c**–**e** is the locant variation of the methyl group. In the $CpCl_2Ti$ and Bu_2B enolates **52c** the methyl group resides at C^{β}, in the enolates **52d** at C^{γ}, and in the enolates **52e** at C^{δ}. We presume that each enolate **52c**–**e** represents either the best "half-chair"-like[53] substructure $\mathbf{52c}_{\text{half-chair}}$–$\mathbf{e}_{\text{half-chair}}$ of the transition state of its aldol additions or the best "half-boat"-like[54] substructure $\mathbf{52c}_{\text{half-boat}}$–$\mathbf{e}_{\text{half-boat}}$ of the transition state of its aldol additions.[55] We cannot assess what the favored structure might be, because we are even unaware of δ-lactone enolate equilibrium structures. How the hybridization of the endocyclic O atom and the associated ring-strain add up to an optimized transition state structure must be considered an unknown. Be this as it may, we suppose that, moreover, the carbonyl group of the incoming aldehyde targets the nucleophilic center C^{α} of the relevant enolate **52c**–**e** via an *axial* trajectory. This is inferred from understanding the HOMO of these enolates as a π-type orbital and from optimizing its overlap with the LUMO of the incipient aldehyde. An axial attack of the aldehyde upon C^{α} looks least hindered by a methyl group at the immediately neighboring

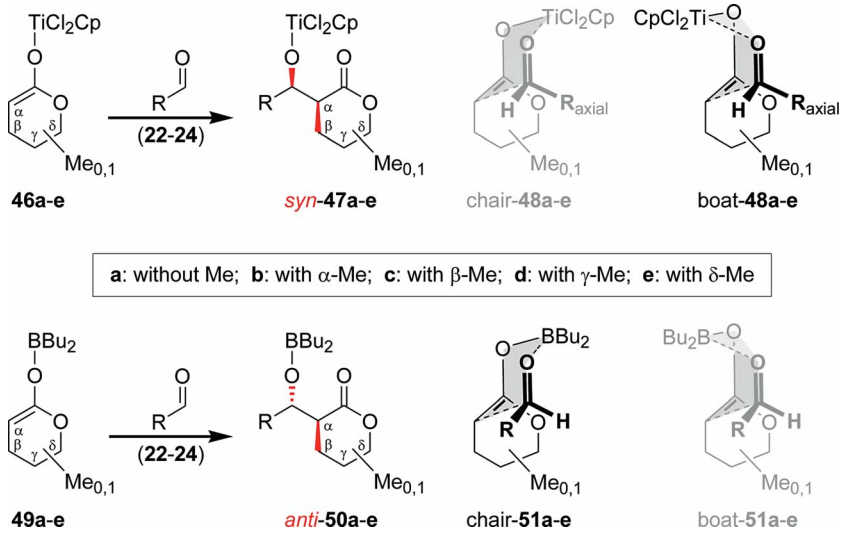


Figure 4. Aldol additions of the titanium and boron enolates of the unsubstituted δ-lactone (**17**) and the analogous δ-lactones methylated at C-α (**18**), C-β (**19**), C-γ (**20**), or C-δ (**21**) to isobutyraldehyde (**22**), crotonaldehyde (**23**), and 4-bromobenzaldehyde (**24**): interpretation of the metal-dependent – and in one case ($CpCl_2Ti$ enolate **46b**) methyl-dependent – simple diastereoselectivities (details: see text).

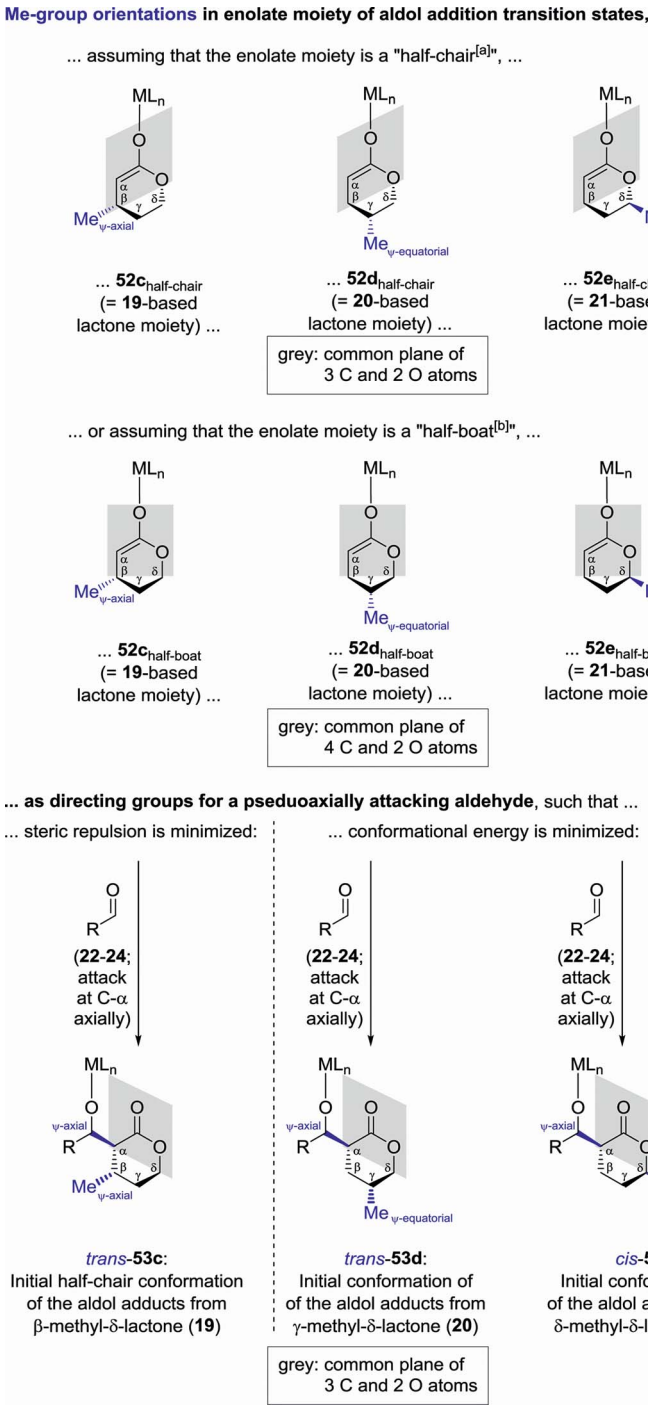


Figure 5. Aldol additions of the titanium and boron enolates of the unsubstituted δ-lactone (**17**) and the analogous δ-lactones methylated at C-β (**19**), C-γ (**20**), or C-δ (**21**) to isobutyraldehyde (**22**), crotonaldehyde (**23**), and 4-bromobenzaldehyde (**24**): conformation-based hypotheses for explaining the metal-independent induced diastereoselectivities (details: see text). [a] The term "half-chair" has a substrate-dependent meaning in conformational analysis. In the enolates labeled "half-chair" *here*, we use the term as for cyclohexene; this understanding was extended to δ-lactones (see the reference cited in ref. 40); the identical conformation was used – its conformational preference being corroborated by molecular mechanics calculations – for δ-lactone enolates in ref.[55]. [b] The term "half-boat" is used here to describe a conformation in which five ring-atoms are coplanar and one atom projects out of the plane. This structure is homologous to the envelope conformation of a five-membered ring.

C^{β} if this attack is *antiperiplanar* to the C^{β}–Me bond. This would be tantamount to a preference of the enolates **52c**$_{\text{half-chair}}$ or **52c**$_{\text{half-boat}}$ for forming aldolates **53c** (Figure 5). That is, the high *trans* selectivity of the aldol additions of β-methyl-δ-lactone (**19**; Table 2, Entries 1–3) would be a steric effect. In contrast, the induced diastereoselectivities of the aldol additions of γ-methyl-δ-lactone (**20**; Table 2, Entries 4–6) and δ-methyl-δ-lactone (**21**; Table 2, Entries 7–9) are moderate – and diverging: **20** reacts with a *trans* preference while **21** shows a *cis* preference. Our speculation is that the *trans* preference of the aldol additions of the enolates **52d**$_{\text{half-chair}}$ or **52d**$_{\text{half-boat}}$ and the *cis* preference of the aldol additions of the enolates **52e**$_{\text{half-chair}}$ or **52e**$_{\text{half-boat}}$ are a conformational effect. As Figure 5 points out, the *trans* preference of the aldol additions **52d**→**53d** allows the C^{γ}–Me bond to be oriented (pseudo)equatorially both in the enolate subunit **52d** of the transition state and in the initially formed half-chair conformer **53d** of the aldol adduct. Similarly, the *cis* preference of the aldol additions **52e**→**53e** allows the C^{δ}–Me bond to be oriented (pseudo)equatorially both in the enolate subunit **52e** of the transition state and in the initially formed half-chair conformer **53e** of the aldol adduct.

Experimental Section

General Working Technique and Analytic Techniques

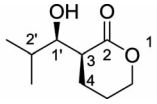
Working Technique: All reactions that did not require water were carried out under dry N_2. Reaction flasks were dried in an oven (65 °C) and under reduced pressure with a heat gun prior to use. Liquids were added with syringe and cannula through a rubber septum. Solids were added in a countercurrent of dry N_2. Reactions that were conducted in the presence of water were carried out without inert gas atmosphere. **Solvents**: tetrahydrofuran (THF) was distilled from potassium and dichloromethane (CH_2Cl_2) over CaH_2 under dry N_2 prior to use. Other solvents, which were obtained commercially as "dry" or "extra dry" solvents, were used without further purification. Cyclohexane (*c*-C_6H_{12}), ethyl acetate (EtOAc), methanol (MeOH), ethanol (EtOH), dichloromethane (CH_2Cl_2), and *tert*-butyl methyl ether (TBME) for workup and column chromatography were distilled prior to use with a rotary evaporator to remove high-boiling fractions. Diethyl ether (Et_2O), pentane, and chloroform ($CHCl_3$) for workup and column chromatography were obtained as p.a. grade solvents and used without further purification. **Grignard reagents** were stored in a freezer in Schlenk flasks with PTFE screw caps and PTFE valves. Prior to use, they were titrated with salicylaldehyde phenylhydrazone.[56] **Chromatography**: Thin layer chromatography (TLC) on Merck silica plates with glass as supporting material (TLC Silicagel 60 F_{254}) was used to monitor reactions and assess purification procedures. If possible, chromatograms were marked in UV light at 254 nm and subsequently stained with permanganate stain (2 g $KMnO_4$, 4 g $NaHCO_3$, 100 mL of H_2O) or vanillin stain (4.5 g vanillin, 75 mL EtOH, 4 mL conc. H_2SO_4). Macherey–Nagel & Co silica gel 60® (230–400 mesh) was used for flash column chromatography.[25] Chromatography conditions are documented at the respective experiment in the following manner: d × h (cm), V (mL), solv1:solv2, a:b to c:d, Fx–Fy. This means: a column with the inner diameter d cm was packed with

h cm silica gel. Fractions of the size V mL were collected. The product was eluted with the solvents solv1 and solv2 in the ratio a:b. The ratio – if not stated otherwise – was changed every 12 fractions in the following series (a:b marks the starting point, c:d marks the end point): 100:0, 100:1, 50:1, 20:1, 10:1, 5:1, 3:1, 2:1, 1:1, 1:2, 1:3, 0:100. Fx–Fy were the fractions containing the product. **Melting points** were determined with a Büchi melting point apparatus and use of open glass capillaries.[57] **Nuclear magnetic resonance spectroscopy**: NMR spectra were recorded by Dr. M. Keller, F. Reinbold, and M. Schonhard with a Bruker Avance 400 spectrometer [^{1}H (400 MHz), ^{13}C (100 MHz), DQF-COSY, edHSQC, and HMBC experiments] and a Bruker DRX 500 spectrometer [^{1}H (500 MHz), ^{13}C (126 MHz), DQF-COSY, edHSQC ("C,H-COSY"), and HMBC experiments] or with an automated Varian Mercury VX 300 spectrometer [^{1}H (300 MHz)]. Spectra were referenced internally by the ^{1}H and ^{13}C NMR signals of the solvent [$CDCl_3$: 7.26 ppm (^{1}H) and 77.10 ppm (^{13}C)]. ^{1}H NMR spectroscopic data are reported as follows: chemical shift (δ in ppm), multiplicity (s for singlet; d for doublet; t for triplet; m for multiplet; m_c for symmetrical multiplet; br. for broad signal), coupling constant(s) (Hz; ^3J couplings unless otherwise noted), integral, and specific assignment. ^{13}C NMR spectroscopic data are reported in terms of chemical shift and assignment. For AB signals the high-field part was named A and the low-field part B. The atom numbering used for NMR assignments follows the IUPAC nomenclature. **IR spectra** were recorded with a Perkin–Elmer Paragon 1000 FT-IR spectrometer for a film of the substance on an NaCl plate. **High-resolution mass spectra** (HRMS) were recorded by Dr. J Wörth and C. Warth with a Thermo Exactive mass spectrometer equipped with an orbitrap analyzer. Ionization methods: electron spray ionization (ESI; spray voltage: 4–5 kV) or atmospheric pressure chemical ionization (APCI; spray current: 5 μA). **Elemental analyses** were obtained by F. Tönnies and A. Siegel with an Elementar Vario El CHNS analyzer. **X-ray crystal structure analyses** were conducted by Dr. M. Keller with a Nonius Kappa-CCD diffractometer and by Prof. Dr. H. Hillebrecht with a Bruker SMART APEX2 CCD diffractometer and use of Mo-K_α radiation from a microsource.[58]

General Procedure A – Titanium-Mediated Preparation of *syn*-Aldols: A solution of LDA was prepared by adding BuLi (2.2–2.4 M in hexane, 1.1 mmol, 1.1 equiv.) to a stirred solution of iPr$_2$NH (0.16 mL, 0.12 g, 1.2 mmol, 1.2 equiv.) in Et_2O (6 mL) at –78 °C. After the system had been stirred for 1 h at –78 °C a solution of the appropriate δ-lactone (1.0 mmol) in Et_2O (1 mL) was added within 30 min by syringe pump at –78 °C. After the system had been stirred for 1 h at –78 °C, solid $CpTiCl_3$ (0.31 g, 1.4 mmol, 1.4 equiv.) was added in one portion. Upon addition of $CpTiCl_3$ the clear solution turns red and after stirring overnight at –78 °C a colorless precipitate forms. The appropriate aldehyde (2.0 mmol, 2.0 equiv.) was added at –78 °C, either as a solution in Et_2O (1 mL) within 1 h by syringe pump [isobutyraldehyde (**22**)] or in one portion [crotonaldehyde (**23**), 4-bromobenzaldehyde (**24**)]. After the system had been stirred overnight at –78 °C the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (2 mL) at –78 °C. The mixture was warmed to room temperature, diluted with Et_2O (10 mL), and filtered through a pad of celite®. The residue was washed with Et_2O (50 mL). The combined filtrates were dried with $MgSO_4$ and the solvent was evaporated under reduced pressure. The *syn*-aldols were obtained as colorless oils, which were purified by flash chromatography.[25]

General Procedure B – Boron-Mediated Preparation of *anti*-Aldols: Bu_2BOTf (0.36 mL, 0.41 g, 1.5 mmol, 1.5 equiv.) was added to a solution of the appropriate δ-lactone (1.0 mmol) in CH_2Cl_2 (6 mL) at –78 °C. After the system had been stirred for 15 min at –78 °C, NEt_3 (0.22 mL, 0.16 g, 1.6 mmol, 1.6 equiv.) was added and the solution was stirred for 1 h at –78 °C. The appropriate aldehyde (2.0 mmol, 2.0 equiv.) was added to this solution, either as a solution in CH_2Cl_2 (1 mL) within 1 h by syringe pump [isobutyraldehyde (**22**)] or in one portion [crotonaldehyde (**23**), 4-bromobenzaldehyde (**24**)] at –78 °C. After the system had been stirred for 3 h at –78 °C the reaction was quenched by addition of aqueous phosphate buffer (20 mM, pH 7, 4 mL), MeOH (2 mL), and H_2O_2 (30%, 1 mL). The mixture was warmed to room temperature and stirred for 1 h at room temperature. CH_2Cl_2 (10 mL) was added to the mixture, the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous Na_2SO_3 solution (5 mL) and dried with $MgSO_4$, and the solvent was evaporated under reduced pressure. The *anti*-aldols were obtained as colorless oils, which were purified by flash chromatography.[25]

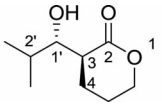
***rel*-(*S*)-3-[(*R*)-1-Hydroxy-2-methylpropyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*-30)**



Following the **General Procedure A** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 15–20) rendered the product as a colorless oil (124 mg, 72%). *syn*/*anti* >95:5. [The 300 MHz ^{1}H NMR spectrum of the crude product was too contaminated by byproducts to integrate any signals. A short column chromatographic separation (2.0 × 10 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 9–18) was conducted to get rid of most byproducts. The 400 MHz ^{1}H NMR spectrum of the product thus obtained still contained no baseline-separated signals of *anti*-**30**. Integration of the signals at δ = 4.25–4.35 (6-H_2, both diastereomers) versus δ = 3.85–3.94 (1′H, *syn*-**30**) resulted in *syn*/*anti* 100:0]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.87 (d, $J_{2'\text{-Me},2'}$ = 6.8 Hz, 3 H, 2′-Me), 1.05 (d, $J_{3',2'}$ = 6.5 Hz, 3 H, 3′-H_3), 1.69 (dqq, $J_{2',1'}$ = 9.8 Hz, $J_{2',3'}$ = $J_{2',2'\text{-Me}}$ = 6.6 Hz, 1 H, 2′-H), 1.89–1.99 (m, 4 H, 4-H_2, 5-H_2)^A, 2.46 (br. s, 1 H, OH), 2.67–2.73 (m, 1 H, 3-H)^A, 3.89 (br. d, $J_{1',2'}$ = 9.5 Hz, 1 H, 1′-H), 4.30–4.34 (m, 2 H, 6-H_2) ppm; ^{A}the indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(previously assigned) ↔ δ_H(distinguished)]: δ = 3.98 (1′-H) ↔ δ = 2.67–2.73 (3-H); δ = 2.67–2.73 (3-H) ↔ δ = 1.89–1.99 (4-H_2, 5-H_2) and δ = 4.30–4.34 (6-H_2) ↔ δ = 1.89–1.99 (4-H_2, 5-H_2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.27 (C-4)^A, 18.88 (C-2-Me)^A, 19.76 (C-3′)^A, 22.38 (C-5)^A, 29.91 (C-2′)^A, 43.14 (C-3)^A, 68.66 (C-6)^A, 75.85 (C-1′)^A, 174.96 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.27 (C-4) ↔ δ = 1.89–1.99 (4-H_2, 5-H_2, downfield part which has no crosspeak to 6-H_2 in the DQF-COSY spectrum); δ = 18.88 (C-2-Me) ↔ δ = 0.87 (2-Me); δ = 19.76 (C-3′) ↔ δ = 1.05 (3′-H_3); δ = 22.38 (C-5) ↔ δ = 1.89–1.99 (4-H_2, 5-H_2, highfield part which has a crosspeak to 6-H_2 in the DQF-COSY spectrum); δ = 29.91 (C-2′) ↔ δ = 1.69 (2′-H); δ = 43.14 (C-3) ↔ δ = 2.67–2.73 (3-H); δ = 68.66 (C-6) ↔ δ = 4.30–4.34 (6-H_2); δ = 75.85 (C-1′) ↔ δ = 3.89 (1′-H) ppm. IR (film): $\tilde{\nu}$ = 3450, 2960, 1720, 1475, 1400, 1260, 1170, 1080, 995, 910, 740 cm^{-1}. HRMS (pos. APCI,

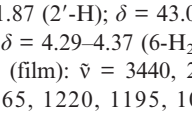
MeOH): calcd. for $C_9H_{17}O_3$ [M + H]$^+$ 173.11722; found 173.11728 (+0.3 ppm). $C_9H_{16}O_3$ (172.22): calcd. C 62.77, H 9.36; found C 62.51, H 9.43.

***rel*-(*S*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-30)**



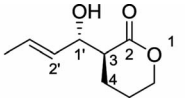
Following the **General Procedure B** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 13–17) rendered the product as a colorless oil (115 mg, 67%). *syn*/*anti* 4:96 [determined by integration of the signals at δ = 2.57 (3-H, *anti*-**30**) vs. δ = 2.67–2.73 (3-H, *syn*-**30**) in the 400 MHz ^{1}H NMR spectrum of the crude product]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.91 (d, $J_{2'\text{-Me},2'}$ = 6.8 Hz, 3 H, 2′-Me), 1.03 (d, $J_{3',2'}$ = 6.8 Hz, 3 H, 3′-H_3), 1.58 (m_c, possibly interpretable as ddt, J_{gem} = 13.2 Hz, $J_{4\text{-H}(1),3}$ = 11.8 Hz, $J_{4\text{-H}(1),5}$ = 7.2 Hz, 1 H, 4-H^1)^A, 1.86 (qqd, $J_{2',2'\text{-Me}}$ = $J_{2',3'}$ = 6.8 Hz, $J_{2',1'}$ = 3.8 Hz, 1 H, 2′-H), 1.93 (m_c, 2 H, 5-H_2)^A, 2.02 [m_c, possibly interpretable as ddt, J_{gem} = 13.3 Hz, $J_{4\text{-H}(2),3}$ = 8.0 Hz, $J_{4\text{-H}(2),5}$ = 6.6 Hz, 1 H, 4-H^2]^A, 2.56 [ddd, $J_{3,4\text{-H}(1)}$ = 11.8 Hz, $J_{3,4\text{-H}(2)}$ = $J_{3,1'}$ = 7.8 Hz, 1 H, 3-H]^A, 3.57 (ddd, $J_{1',3}$ = 7.6 Hz, $J_{1',\text{OH}}$ = $J_{1',2'}$ = 3.8 Hz, 1 H, 1′-H)^A, 3.76 (d, $J_{\text{OH},1'}$ = 3.4 Hz, 1 H, OH), 4.29–4.34 (m, 2 H, 6-H_2)^A ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 1.87 (2′-H) ↔ δ = 3.58 (1′-H); δ = 3.58 (1′-H) ↔ δ = 3.57 (3-H); δ = 3.57 (3-H) ↔ δ = 1.59 (4-H^1); δ = 3.57 (3-H) ↔ δ = 2.03 (4-H^2); δ = 1.59 (4-H^1) ↔ δ = 1.93 (5-H_2) and δ = 2.03 (4-H^2) ↔ δ = 1.93 (5-H_2); δ = 1.93 (5-H_2) ↔ δ = 4.29–4.37 (6-H_2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.00 (C-2′-Me)^A, 20.19 (C-3′)^A, 21.34 (C-4)^A, 21.93 (C-5)^A, 29.30 (C-2′)^A, 43.03 (C-3)^A, 68.15 (C-6)^A, 75.85 (C-1′)^A, 175.95 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 15.00 (C-2′-Me) ↔ δ = 0.92 (2′-Me); δ = 20.19 (C-3′) ↔ δ = 1.04 (3′-H_3); δ = 21.34 (C-4) ↔ δ = 1.59 (4-H^1) and 2.03 (4-H^2); δ = 21.93 (C-5) ↔ δ = 1.93 (5-H_2); δ = 29.30 (C-2′) ↔ δ = 1.87 (2′-H); δ = 43.03 (C-3) ↔ δ = 3.57 (3-H); δ = 68.15 (C-6) ↔ δ = 4.29–4.37 (6-H_2); δ = 75.85 (C-1′) ↔ δ = 3.58 (1′-H) ppm. IR (film): $\tilde{\nu}$ = 3440, 2960, 2360, 2340, 1710, 1475, 1400, 1315, 1265, 1220, 1195, 1085, 1055, 1000, 940, 655 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_9H_{17}O_3$ [M + H]$^+$ 173.11777; found 173.11800 (+1.3 ppm). $C_9H_{16}O_3$ (172.22): calcd. C 62.77, H 9.36; found C 62.68, H 9.42.

***rel*-(*S*)-3-[(*R,trans*)-1-Hydroxybut-2-enyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*-31)**



Following the **General Procedure A** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 20–26) rendered the product as a colorless oil (110 mg, 65%). *syn*/*anti* >95:5 [the 400 MHz ^{1}H NMR spectrum of the crude product contained no signals clearly attributable to *anti*-**31**]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.68 (m_c, possibly interpretable as ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.6 Hz, $^5J_{4',1'}$ = 0.9 Hz, 3 H, 4′-H_3), 1.70–1.81 (m, 1 H, 4-H^1)^A, 1.83–1.96 (m, 3 H, 4-H^2, 5-H_2)^A, 2.66 (m_c, 1 H, 3-H)^A, 3.17 (m_c, possibly interpretable as br. d, $J_{\text{OH},1'}$ = 5.0 Hz, 1 H, OH)^A, 4.21–4.33 (m, 2 H, 6-H_2), 4.47 (br. s, 1 H, 1′-H), 5.47 (m_c, possibly interpretable as ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 6.8 Hz, $J_{2',4'}$ = 1.6 Hz, 1 H, 2′-H)^A, 5.73 (dq, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.5 Hz, 1 H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.47 (1′-H) ↔ δ = 5.47 (2′-H); δ = 4.47 (1′-H) ↔ δ = 3.17 (OH); δ = 4.47 (1′-H) ↔ δ = 2.66 (3-H); δ = 2.66 (3-H) ↔ δ = 1.70–1.81 (4-H^1); δ = 2.66 (3-H) ↔ δ = 1.83–1.96 (4-H^2, 5-H_2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.73 (C-4′)^A, 19.69 (C-4)^A, 22.25 (C-5)^A, 45.75 (C-3)^A, 69.07 (C-6)^A, 72.10 (C-1′)^A, 128.67 (C-3′)^A, 129.69 (C-2′)^A, 173.90 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 17.73 (C-4′) ↔ δ = 1.68 (4′-H_3); δ = 19.69 (C-4) ↔ δ = 1.70–1.81 (4-H^1) and 1.83–1.96 (4-H^2, 5-H_2); δ = 22.25 (C-5) ↔ δ = 1.83–1.96 (4-H^2, 5-H_2); δ = 45.75 (C-3) ↔ δ = 2.66 (3-H); δ = 69.07 (C-6) ↔ δ = 4.21–4.33 (6-H_2); δ = 72.10 (C-1′) ↔ δ = 4.47 (1′-H); δ = 128.67 (C-3′) ↔ δ = 5.73 (3′-H); δ = 129.69 (C-2′) ↔ δ = 5.47 (2′-H) ppm. IR (film): $\tilde{\nu}$ = 3445, 2975, 2880, 1725, 1450, 1400, 1350, 1260, 1165, 1080, 970, 735, 645 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_9H_{15}O_3$ [M + H]$^+$ 171.10212; found 171.10290 (+1.3 ppm).

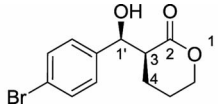
***rel*-(*S*)-3-[(*S,trans*)-1-Hydroxybut-2-enyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-31)**



Following the **General Procedure B** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 12–16) rendered the product as a colorless oil (109 mg, 64%, *anti*-**31**/*syn*-**31** 93:7). *syn*/*anti* 7:93 [determined by integration of the signals at δ = 2.52 (3-H, *anti*-**31**) vs. δ = 2.71 (3-H, *syn*-**31**) in the 400 MHz ^{1}H NMR spectrum of the crude product]. ^{1}H NMR (400.13 MHz, $CDCl_3$, contains 7% *syn*-**31**): δ = 1.50 [m_c, possibly interpretable as dddd, J_{gem} = 13.2 Hz, $J_{4\text{-H}(1),3}$ = 11.8 Hz, $J_{4\text{-H}(1),5}$ = 7.6 and 7.1 Hz, 1 H, 4-H^1]^A, 1.72 (ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.7 Hz, $^5J_{4',1'}$ = 0.5 Hz, 3 H, 4′-H_3), 1.86–2.04 (m, 3 H, 5-H_2, 4-H^2)^A, 2.50 [m_c, possibly interpretable as ddd, $J_{3,4\text{-H}(1)}$ = 11.8 Hz, $J_{3,4\text{-H}(2)}$ = $J_{3,1'}$ = 7.9 Hz, 1 H, 3-H]^A, 3.98 (br. s, 1 H, OH), 4.24 (br. dd, $J_{1',3}$ = $J_{1',2'}$ = 7.9 Hz, 1 H, 1′-H), 4.29–4.33 (m, 2 H, 6-H_2), 5.46 (ddq, $J_{2',3'}$ = 15.2 Hz, $J_{2',1'}$ = 7.8 Hz, $^4J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H), 5.77 (dqd, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 0.9 Hz, 1 H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.25 (1′-H) ↔ δ = 2.51 (3-H); δ = 2.51 (3-H) ↔ δ = 1.51 (4-H^1); δ = 2.51 (3-H) ↔ δ = 1.87–2.05 (5-H_2 4-H^2); δ = 4.30–4.34 (6-H_2) ↔ δ = 1.87–2.05 (5-H_2 4-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, contains 7% *syn*-**31**): δ = 17.80 (C-4′)^A, 21.59 (C-4)^A, 21.83 (C-5)^A, 45.21 (C-3)^A, 68.51 (C-6)^A, 73.53 (C-1′)^A, 129.87 (C-2′)^A, 129.96 (C-3′)^A, 175.26 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were

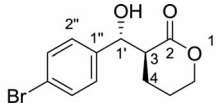
identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 17.80 (C-4′) ↔ δ = 1.73 (4′-H_3); δ = 21.59 (C-4) ↔ δ = 1.51 (4-H^1) and 1.87–2.05 (5-H_2 4-H^2); δ = 21.83 (C-5) ↔ δ = 1.87–2.05 (5-H_2 4-H^2); δ = 45.21 (C-3) ↔ δ = 2.51 (3-H); δ = 68.51 (C-6) ↔ δ = 4.30–4.34 (6-H_2); δ = 73.53 (C-1′) ↔ δ = 4.25 (1′-H); δ = 129.87 (C-2′) ↔ δ = 5.47 (2′-H); δ = 129.96 (C-3′) ↔ δ = 5.78 (3′-H) ppm. IR (film): $\tilde{\nu}$ = 3430, 2915, 2360, 1720, 1450, 1400, 1255, 1220, 1165, 1080, 1030, 970, 770, 640 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_9H_{15}O_3$ $[M + H]^+$ 171.10212; found 171.10220 (+0.5 ppm).

***rel*-(*S*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*-32)**



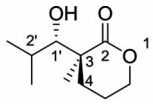
Following the **General Procedure A** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 14–21) rendered the product as a colorless solid (189 mg, 66%). *syn*/*anti* 97:3 [determined by integration of the signals at δ = 4.80 (1′-H, *anti*-**32**) vs. δ = 5.47 (1′-H, *syn*-**32**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 71 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.48–1.58 (m, 1 H, 4-H^1)^A, 1.73–1.91 (m, 3 H, 4-H^2, 5-H_2)^A, 2.77 (m_c, possibly interpretable as ddd, $J_{3,4}$ = 10.4 and 7.8 Hz, $J_{3,1'}$ = 2.6 Hz, 1 H, 3-H), 3.26 (d, $J_{OH,1'}$ = 4.6 Hz, 1 H, OH), 4.23–4.32 (m, 2 H, 6-H_2), 5.47 (dd, $J_{1',OH} = J_{1',3}$ = 3.3 Hz, 1 H, 1′-H), 7.23 (m_c, 2 H, 2 × *ortho*-H), 7.47 (m_c, 2 H, 2 × *meta*-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.77 (3-H) ↔ δ = 1.48–1.58 (4-H^1); δ = 2.77 (3-H) ↔ δ = 1.73–1.91 (4-H^2, 5-H_2); δ = 4.23–4.32 (6-H_2), ↔ δ = 1.73–1.91 (4-H^2, 5-H_2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.80 (C-4)^A, 22.19 (C-5)^A, 47.13 (C-3)^A, 69.07 (C-6)^A, 71.22 (C-1′)^A, 121.24 (C-*para*), 127.56 (2 × C-*ortho*)^A, 131.48 (2 × C-*meta*)^A, 139.97 (C-*ipso*), 173.93 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 17.80 (C-4) ↔ δ = 1.48–1.58 (4-H^1) and 1.73–1.91 (4-H^2, 5-H_2); δ = 22.19 (C-5) ↔ δ = 1.73–1.91 (4-H^2, 5-H_2); δ = 47.13 (C-3) ↔ δ = 2.77 (3-H); δ = 69.07 (C-6) ↔ δ = 4.23–4.32 (6-H_2); δ = 71.22 (C-1′) ↔ δ = 5.47 (1′-H); δ = 127.56 (2 × C-*ortho*) ↔ δ = 7.23 (2 × *ortho*-H); δ = 131.48 (2 × C-*meta*) ↔ δ = 7.47 (2 × *meta*-H) ppm. IR (film): $\tilde{\nu}$ = 3450, 2965, 1720, 1490, 1460, 1400, 1350, 1250, 1165, 1070, 1030, 1010, 960, 830, 775 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.02773; found 299.02774 (±0.0 ppm).

***rel*-(*S*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-32)**



Following the **General Procedure B** the title compound was prepared from δ-lactone (**17**, 100 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 15–20) rendered the product as a colorless solid (206 mg, 72%). *syn*/*anti* 5:95 [determined by integration of the signals at δ = 2.69 (3-H, *anti*-**32**) vs. δ = 2.78 (3-H, *syn*-**32**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 66 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.38 [m_c, possibly interpretable as dddd, J_{gem} = 13.7 Hz, $J_{4\text{-}H(1),3}$ = 12.1 Hz, $J_{4\text{-}H(1),5\text{-}H(1)} = J_{4\text{-}H(1),5\text{-}H(2)}$ = 7.7 Hz, 1 H, 4-H^1]^A, 1.50 [m_c, possibly interpretable as dddd, J_{gem} = 14.1 Hz, $J_{4\text{-}H(2),3}$ = 7.3 Hz, $J_{4\text{-}H(2),5\text{-}H(1)}$ = 6.6 Hz, $J_{4\text{-}H(2),5\text{-}H(2)}$ = 6.0 Hz, $^4J_{4\text{-}H(2),6\text{-}H(2)}$ = 0.7 Hz, 1 H, 4-H^2]^A, 1.74–1.91 (m, 2 H, 5-H_2)^A, 2.67 [ddd, $J_{3,4\text{-}H(1)}$ = 12.0 Hz, $J_{3,1'}$ = 8.7 Hz, $J_{3,4\text{-}H(2)}$ = 7.8 Hz, 1 H, 3-H], 4.25–4.36 (m, 2 H, 6-H_2), 4.60 (br. s, 1 H, OH), 4.80 (d, $J_{1',3}$ = 8.7 Hz, 1 H, 1′-H), 7.25 (m_c, 2 H, 2 × *ortho*-H), 7.49 (m_c, 2 H, 2 × *meta*-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.67 (3-H) ↔ δ = 1.38 (4-H^1); δ = 2.67 (3-H) ↔ δ = 1.50 (4-H^2); δ = 4.25–4.36 (6-H_2) ↔ δ = 1.74–1.91 (5-H_2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.65 (C-4)^A, 21.71 (C-5)^A, 46.59 (C-3)^A, 68.58 (C-6)^A, 74.46 (C-1′)^A, 122.23 (C-4′′), 128.79 (C-2′′, C-6′′), 131.74 (C-3′′, C-5′′), 139.23, (C-1′′), 175.31 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 21.65 (C-4)^A ↔ δ = 1.38 (4-H^1) and 1.50 (4-H^2); δ = 21.71 (C-5)^A ↔ δ = 1.74–1.91 (5-H_2); δ = 46.59 (C-3)^A ↔ δ = 2.67 (3-H); δ = 68.58 (C-6)^A ↔ δ = 4.25–4.36 (6-H_2); δ = 74.46 (C-1′)^A ↔ δ = 4.80 (1′-H) ppm. IR (film): $\tilde{\nu}$ = 3440, 2960, 1715, 1490, 1400, 1350, 1265, 1165, 1085, 1070, 1010, 965, 840, 775, 735 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{12}H_{14}O_3Br$ $[M + H]^+$ 285.01263; found 285.01300 (+1.3 ppm).

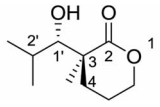
***rel*-(*S*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-33) by Ti-Mediated Aldol Addition**



Following the **General Procedure A** the title compound was prepared from α-methyl-δ-lactone (**18**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 20 cm, 15 mL, pentane/Et_2O 1:2, 8–20) rendered the product as a colorless oil (112 mg, 60%). *syn*/*anti* 37:63 [determined by integration of the signals at δ = 1.39 (3-Me, *anti*-**33**) vs. δ = 1.42 (3-Me, *syn*-**33**) in the 400 MHz ^{1}H NMR spectrum of the crude product]. ^{1}H NMR (400.13 MHz, $CDCl_3$, *syn*/*anti* 37:63 mixture of diastereomers): δ = 0.87 [d, $J_{2'\text{-}Me,2'}$ = 6.8 Hz, 3 H, 2′-Me (*syn*-**33**)], 0.98 [d, $J_{2'\text{-}Me,2'}$ = 6.9 Hz, 3 H, 2′-Me (*anti*-**33**)], 1.02 [d, $J_{3'\text{-}H3,2'}$ = 6.6 Hz, 3 H, 3′-H_3 (*anti*-**33**)], 1.05 [d, $J_{3'\text{-}H3,2'}$ = 6.8 Hz, 3 H, 3′-H_3 (*syn*-**33**)], 1.39 [d, $^4J_{3\text{-}Me,4}$ = 0.4 Hz, 3 H, 3-Me (*anti*-**33**)], 1.41 [s, 3 H, 3-Me (*syn*-**33**)], 1.55–1.62 [m, 1 H, 4-H^1 (*syn*-**33**)], 1.69–1.77 [m, 1 H, 4-H^1 (*anti*-**33**)], 1.80–1.91 [m, 3 H, probably 4-H^2 (*anti*-**33**), 5-H^1 (both diastereomers), 2′-H (*anti*-**33**)], 1.91–2.10 [m, 3 H, probably 4-H^2 (*syn*-**33**), 5-H^2 (both diastereomers), 2′-H (*syn*-**33**)], 2.87 [d, $J_{OH,1'\text{-}H}$ = 4.0 Hz, 1 H, OH (*anti*-**33**)], 3.24 [d, $J_{OH,1'}$ = 8.4 Hz, 1 H, OH (*syn*-**33**)], 3.51 [dd, $J_{1',OH}$ = 8.5 Hz, $J_{1',2'}$ = 2.9 Hz, 1 H, 1′-H (*syn*-**33**)], 3.70 [dd, $J_{1',2'}$ = 4.8 Hz, $J_{1',OH}$ = 4.0 Hz, 1 H, 1′-H (*anti*-**33**)] 4.24–4.33 [m, 1 H, 6-H^1 (both diastereomers)], 4.39–4.47 [m, 1 H, 6-H^2 (both diastereomers)] ppm. IR (film): $\tilde{\nu}$ = 3445, 2975, 2880, 1725, 1450, 1400, 1350, 1260, 1165, 1080, 970, 735, 645 cm^{-1}. HRMS (pos.

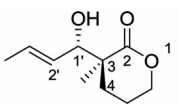
APCI, MeOH): calcd. for $C_9H_{19}O_3$ [M + H]$^+$ 187.13342; found 187.13320 (–1.2 ppm). $C_9H_{18}O_3$ (174.24): calcd. C 64.49, H 9.74; found C 64.22, H 10.02.

***rel*-(*S*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-33) by B-Mediated Aldol Addition**



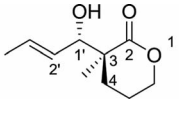
Following the **General Procedure B** the title compound was prepared from α-methyl-δ-lactone (**18**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 20 cm, 15 mL, pentane/Et_2O 1:1, 11–30) rendered the product as a colorless oil (157 mg, 84%). *syn*/*anti* <5:95 [the 400 MHz ^{1}H NMR spectrum of the crude product contained no signals clearly attributable to *syn*-**33**]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.92 (d, $J_{2'\text{-Me},2'}$ = 6.9 Hz, 3 H, 2′-Me), 0.99 (d, $J_{3',2'}$ = 6.6 Hz, 3 H, 3′-H$_3$), 1.36 (d, $^4J_{3\text{-Me},4}$ = 0.4 Hz, 3 H, 3-Me), 1.66–1.74 (m, 1 H, 4-H^1)^A, 1.77–1.88 (m, 3 H, 4-H^2, 5-H^1, 2′-H)^A, 1.93–2.05 (m, 1 H, 5-H^2)^A, 3.00 (br. s, 1 H, OH), 3.67 (d, $J_{1',2'}$ = 5.1 Hz, 1 H, 1′-H), 4.24 [m$_c$, possibly interpretable as ddd, J_{gem} = 11.3 Hz, $J_{6\text{-H}(1),5}$ = 11.3 Hz and 3.5 Hz, 1 H, 6-H^1], 4.41 [m$_c$, possibly interpretable as dddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(1),5}$ = 4.9 Hz and 2.8 Hz, $^4J_{6\text{-H}(1),4\text{-H}(1)}$ = 2.2 Hz, 1 H, 6-H^2] ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 3.67 (1′-H) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H); δ = 4.24 (6-H^1) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H) and δ = 4.41 (6-H^2) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H); δ = 4.24 (6-H^1) ↔ δ = 1.93–2.05 (5-H^2) and δ = 4.41 (6-H^2) ↔ δ = 1.93–2.05 (5-H^2); δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H) ↔ δ = 1.66–1.74 (4-H^1) and δ = 1.93–2.05 (5-H^2) ↔ δ = 1.66–1.74 (4-H^1); δ = 1.93–2.05 (5-H^2) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H) and δ = 1.66–1.74 (4-H^1) ↔ 1.77–1.88 (4-H^2, 5-H^1, 2′-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 18.39 (C-3′)^A, 20.23 (C-5)^A, 21.71 (C-2′-Me)^A, 23.27 (C-3-Me)^A, 28.20 (C-4)^A, 30.33 (C-2′)^A, 46.29 (C-3)^A, 70.30 (C-6)^A, 79.66 (C-1′)^A, 176.85 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 18.39 (C-3′) ↔ δ = 0.99 (3′-H$_3$); δ = 20.23 (C-5) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H) and 1.93–2.05 (5-H^2); δ = 21.71 (C-2′-Me) ↔ δ = 0.92 (2′-Me); δ = 23.27 (C-3-Me) ↔ δ = 1.36 (3-Me); δ = 28.20 (C-4) ↔ δ = 1.66–1.74 (4-H^1) and 1.77–1.88 (4-H^2, 5-H^1, 2′-H); δ = 30.33 (C-2′) ↔ δ = 1.77–1.88 (4-H^2, 5-H^1, 2′-H); δ = 70.30 (C-6) ↔ δ = 4.24 (6-H^1) and 4.41 (6-H^2); δ = 79.66 (C-1′) ↔ δ = 3.67 (1′-H). IR (film): $\tilde{\nu}$ = 3450, 2965, 2880, 2360, 1710, 1465, 1400, 1265, 1215, 1165, 1140, 1115, 1075, 1040, 1015, 1000, 950, 770, 755, 720, 675, 650 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_9H_{19}O_3$ [M + H]$^+$ 187.13342; found 187.13370 (+1.5 ppm). $C_9H_{18}O_3$ (174.24): calcd. C 64.49, H 9.74; found C 64.24, H 9.53.

***rel*-(*S*)-3-[(*R,trans*)-1-Hydroxybut-2-enyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*-34)**



Following the **General Procedure A** the title compound was prepared from α-methyl-δ-lactone (**18**, 150 mg, 1.32 mmol) and crotonaldehyde (**23**, 0.30 mL, 256 mg, 3.65 mmol, 2.8 equiv.). Purification by flash chromatography[25] (2.5 × 20 cm, 15 mL, pentane/Et_2O 1:2, fractions 14–27) rendered a mixture of diastereomers as an off-white solid (145 mg, 61%, *syn*-**34**/*anti*-**34** 64:36). *syn*/*anti* 59:41 [determined by integration of the signals at δ = 1.26 (3-Me, *syn*-**34**) vs. δ = 1.32 (3-Me, *anti*-**34**) in the 300 MHz ^{1}H NMR spectrum of the crude product], m.p. (for the *syn*-**34**/*anti*-**34** 64:36 mixture): 53 °C. An analytical sample of *syn*-**34** (!) was obtained by flash chromatography (cf. footnote 33); it eluted slightly faster than *anti*-**34** and was obtained as a colorless oil. Analytical data for *syn*-34 (!): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (s, 3 H, 3-Me), 1.49 [dddd, J_{gem} = 13.3 Hz, $J_{4\text{-H}(1),5\text{-H}(2)}$ = 5.0 Hz, $J_{4\text{-H}(1),5\text{-H}(1)}$ = 3.6 Hz, $J_{4\text{-H}(1),6\text{-H}(2)}$ = 2.0 Hz, 1 H, 4-H^1]^A, 1.73 (ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.7 Hz, $^5J_{4',1'}$ = 0.5 Hz, 3 H, 4′-H$_3$), 1.83 [dddd, J_{gem} = 14.2 Hz, $J_{5\text{-H}(1),4\text{-H}(1)}$ = 8.5 Hz, $J_{5\text{-H}(1),4\text{-H}(2)}$ = 4.1 Hz, $J_{5\text{-H}(1),6\text{-H}(1)}$ = 4.0 Hz, 1 H, 5-H^1]^A, 1.95 [ddddd, J_{gem} = 14.4 Hz, $J_{5\text{-H}(2),4\text{-H}(2)}$ = 11.7 Hz, $J_{5\text{-H}(2),6\text{-H}(1)}$ = 10.6 Hz, $J_{5\text{-H}(2),4\text{-H}(1)}$ = 4.4 Hz, $J_{5\text{-H}(2),6\text{-H}(2)}$ = 3.9 Hz, 1 H, 5-H^2]^A, 2.10 [ddd, J_{gem} = 13.2 Hz, $J_{4\text{-H}(2),5\text{-H}(2)}$ = 11.9 Hz, $J_{4\text{-H}(2),5\text{-H}(1)}$ = 4.1 Hz, 1 H, 4-H^2]^A, 2.68 (d, $J_{OH,1'}$ = 5.9 Hz, 1 H, OH), 4.22 (dd, $J_{1',2'}$ = 7.3 Hz, $J_{1',OH}$ = 5.6 Hz, 1 H, 1′-H)^A superimposed by 4.26 [m$_c$, possibly interpretable as ddd, J_{gem} = $J_{6\text{-H}(1),5\text{-H}(2)}$ = 10.9 Hz, $J_{6\text{-H}(1),5\text{-H}(1)}$ = 3.5 Hz, 1 H, 6-H^1], 4.38 [dddd, J_{gem} = 10.9 Hz, $J_{6\text{-H}(2),5\text{-H}(1)}$ = 4.5 Hz, $J_{6\text{-H}(2),5\text{-H}(2)}$ = 3.5 Hz, $J_{6\text{-H}(2),4\text{-H}(1)}$ = 2.1 Hz, 1 H, 6-H^2], 5.42 (ddq, $J_{2',3'}$ = 15.2 Hz, $J_{2',1'}$ = 7.9 Hz, $J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H), 5.77 (dqd, $J_{3',2'}$ = 15.2 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 1.0 Hz, 1 H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 5.42 (2′-H) ↔ δ = 4.22 (1′-H); δ = 4.26 (6-H^1) ↔ δ = 1.83 (5-H^1) and δ = 4.38 (6-H^2) ↔ δ = 1.83 (5-H^1); δ = 4.26 (6-H^1) ↔ δ = 1.95 (5-H^2) and δ = 4.38 (6-H^2) ↔ δ = 1.95 (5-H^2); δ = 1.83 (5-H^1) ↔ δ = 1.49 (4-H^1) and δ = 1.95 (5-H^2) ↔ δ = 1.49 (4-H^1); δ = 1.83 (5-H^1) ↔ δ = 2.10 (4-H^2) and δ = 1.95 (5-H^2) ↔ δ = 2.10 (4-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.97 (C-4′)^A, 20.74 (C-5)^A, 24.16 (C-3-Me)^A, 27.99 (C-4)^A, 47.32 (C-3)^A, 70.25 (C-6)^A, 78.54 (C-1′)^A, 128.46 (C-2′)^A, 130.79 (C-3′)^A, 176.80 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.97 (C-4′) ↔ δ = 1.73 (4′-H$_3$); δ = 20.74 (C-5) ↔ δ = 1.83 (5-H^1) and 1.95 (5-H^2); δ = 24.16 (C-3-Me) ↔ δ = 1.26 (3-Me); δ = 27.99 (C-4) ↔ δ = 1.49 (4-H^1) and 2.10 (4-H^2); δ = 70.25 (C-6) ↔ δ = 4.26 (6-H^1) and 4.38 (6-H^2); δ = 78.54 (C-1′) ↔ δ = 4.22 (1′-H); δ = 128.46 (C-2′) ↔ δ = 5.42 (2′-H); δ = 130.79 (C-3′) ↔ δ = 5.77 (3′-H). IR (film): $\tilde{\nu}$ = 3445, 2965, 2940, 2360, 2340, 1710, 1450, 1400, 1375, 1270, 1150, 1110, 1070, 1020, 970, 930, 770, 650 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{17}O_3$ [M + H]$^+$ 185.11777; found 185.11760 (Δ = 0.9 ppm). $C_{10}H_{16}O_3$ (184.23): calcd. C 65.19, H 8.75; found C 64.92, H 8.93.

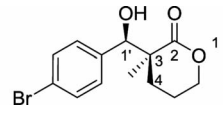
***rel*-(*S*)-3-[(*S,trans*)-1-Hydroxybut-2-enyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-34)**



Following the **General Procedure B** the title compound was prepared from α-methyl-δ-lactone (**18**, 114 g, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, pentane/Et_2O 1:3, 7–13) rendered the product as a colorless oil (83 mg, 45%). *syn*/*anti* 7:93 [determined by integration of the signals at δ = 1.26 (3-Me, *syn*-**34**)

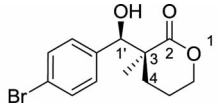
vs. δ = 1.32 (3-Me, *anti*-**34**) in the 400.13 MHz ^{1}H NMR spectrum of the crude product]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.31 (s, 3 H, 3-Me), 1.57–1.63 (m, 1 H, 4-H^1)^A, 1.73 (ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.7 Hz, $^5J_{4',1'}$ = 0.7 Hz, 3 H, 4′-H$_3$), 1.78–1.87 (m, 2 H, 4-H^2, 5-H^1)^A, 1.91–2.03 (m, 1 H, 5-H^2)^A, 3.48 (d, $J_{OH,1'}$ = 2.2 Hz, 1 H, OH), 4.21 (ddq, $J_{1',2'}$ = 7.3 Hz, $J_{1',OH}$ = 2.1 Hz, $^4J_{1',3'}$ = $^5J_{1',4'}$ = 0.7 Hz, 1 H, 1′-H)^A, 4.28 [m$_c$, possibly interpretable as ddd, J_{gem} = 10.8 Hz, $J_{6\text{-}H(1),5}$ = 10.8 and 3.4 Hz, 1 H, 6-H^1], 4.42 [m$_c$, possibly interpretable as dddd, J_{gem} = 11.1 Hz, $J_{6\text{-}H(1),5}$ = 4.8 and 3.7 Hz, $^4J_{6\text{-}H(1),4\text{-}H}$ = 1.9 Hz, 1 H, 6-H^2], 5.53 (ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 7.3 Hz, $^4J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H), 5.80 (dqd, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 1.0 Hz, 1 H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 5.53 (2′-H) ↔ δ = 4.21 (1′-H); δ = 4.28 (6-H^1) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1) and δ = 4.42 (6-H^2) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1); δ = 4.28 (6-H^1) ↔ δ = 1.91–2.03 (5-H^2) and δ = 4.42 (6-H^2) ↔ δ = 1.91–2.03 (5-H^2); δ = 1.78–1.87 (4-H^2, 5-H^1) ↔ δ = 1.57–1.63 (4-H^1) and δ = 1.91–2.03 (5-H^2) ↔ δ = 1.57–1.63 (4-H^1); δ = 1.91–2.03 (5-H^2) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1) and δ = 1.57–1.63 (4-H^1) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.96 (C-4′)^A, 20.48 (C-5)^A, 20.78 (C-3-Me)^A, 30.36 (C-4)^A, 45.96 (C-3)^A, 70.48 (C-6)^A, 77.41 (C-1′)^A, 127.89 (C-2′)^A, 130.65 (C-3′)^A, 177.25 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.96 (C-4′) ↔ δ = 1.73 (4′-H$_3$); δ = 20.48 (C-5) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1) and 1.91–2.03 (5-H^2); δ = 20.78 (C-3-Me) ↔ δ = 1.31 (3-Me); δ = 30.36 (C-4) ↔ δ = 1.78–1.87 (4-H^2, 5-H^1) and 1.57–1.63 (4-H^1); δ = 70.48 (C-6) ↔ δ = 4.28 (6-H^1) and 4.42 (6-H^1); δ = 77.41 (C-1′) ↔ δ = 4.21 (1′-H); δ = 127.89 (C-2′) ↔ δ = 5.53 (2′-H); δ = 130.65 (C-3′) ↔ δ = 5.80 (3′-H). IR (film): $\tilde{\nu}$ = 3450, 2965, 2940, 2880, 2360, 1710, 1480, 1455, 1400, 1375, 1345, 1305, 1265, 1215, 1165, 1135, 1110, 1190, 1170, 1020, 970, 950, 840, 800, 745, 705, 675, 647 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{17}O_3$ [M + H]$^+$ 185.11777; found 185.11800 (+2.8 ppm). $C_{10}H_{16}O_3$ (184.23): calcd. C 65.19, H 8.75; found C 64.92, H 8.93.

***rel*-(*S*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*-35)**



Following the **General Procedure A** the title compound was prepared from α-methyl-δ-lactone (**18**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 410 mg, 2.00 mmol, 2.2 equiv.). Purification by flash chromatography[25] (3.0 × 20 cm, 20 mL, pentane/Et_2O 2:1 to 1:2, 45–73) rendered the product as a colorless solid (132 mg, 44%). Additionally, a fraction containing *anti*-**35** (33–43, 95 mg, 32%) was collected (overall yield: 227 mg, 76%). *syn*/*anti* 50:50 [determined by integration of the signals at δ = 4.94 (1′-H, *syn*-**35**) vs. δ = 4.99 (1′-H, *anti*-**35**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 69 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.28 [dddd, J_{gem} = 13.4 Hz, $J_{4\text{-}H(1),5\text{-}H(1)}$ = 5.2 Hz, $J_{4\text{-}H(1),5\text{-}H(2)}$ = 3.3 Hz, $^4J_{4\text{-}H(1),6\text{-}H(2)}$ = 2.0 Hz, 1 H, 4-H^1]^A, 1.37 [d, $^4J_{3\text{-}Me,4\text{-}H(1)}$ = 0.4 Hz, 3 H, 3-Me], 1.70 [ddddd, J_{gem} = 13.7 Hz, $J_{5\text{-}H(1),4\text{-}H(1)}$ = 5.0 Hz, $J_{5\text{-}H(1),4\text{-}H(2)}$ = $J_{5\text{-}H(1),6\text{-}H(1)}$ = $J_{5\text{-}H(1),6\text{-}H(2)}$ = 3.6 Hz, 1 H, 5-H^1]^A, 1.80 [ddd, J_{gem} = 13.4 Hz, $J_{4\text{-}H(2),5\text{-}H(2)}$ = 11.8 Hz, $J_{4\text{-}H(2),5\text{-}H(1)}$ = 3.4 Hz, 1 H, 4-H^2]^A, 1.92 [ddddd, J_{gem} = 13.8 Hz, $J_{5\text{-}H(2),4\text{-}H(2)}$ = 11.7 Hz, $J_{5\text{-}H(2),6\text{-}H(1)}$ = 10.5 Hz, $J_{5\text{-}H(2),6\text{-}H(2)}$ = 4.9 Hz, $J_{5\text{-}H(2),4\text{-}H(1)}$ = 3.3 Hz, 1 H, 5-H^2]^A, 4.17 [ddd, J_{gem} = $J_{6\text{-}H(1),5\text{-}H(2)}$ = 10.9 Hz, $J_{6\text{-}H(1),5\text{-}H(1)}$ = 3.8 Hz, 1 H, 6-H^1], 4.29 (d, $J_{OH,1'\text{-}H}$ = 1.7 Hz, 1 H, OH), 4.40 [dddd, J_{gem} = 11.2 Hz, $J_{6\text{-}H(2),5\text{-}H(2)}$ = 5.0 Hz, $J_{6\text{-}H(2),5\text{-}H(1)}$ = 3.4 Hz, $^4J_{6\text{-}H(2),4\text{-}H(1)}$ = 1.9 Hz, 1 H, 6-H^2], 4.94 (d, $J_{1'\text{-}H,OH}$ = 1.7 Hz, 1 H, 1′-H) 7.28 (m$_c$, 2 × *ortho*-H), 7.46 (m$_c$, 2 × *meta*-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 4.17 (6-H^1) ↔ δ = 1.70 (5-H^1) and δ = 4.40 (6-H^2) ↔ δ = 1.70 (5-H^1); δ = 4.17 (6-H^1) ↔ δ = 1.92 (5-H^2) and δ = 4.40 (6-H^2) ↔ δ = 1.92 (5-H^2); δ = 1.70 (5-H^1) ↔ δ = 1. 28 (4-H^1) and δ = 1.92 (5-H^2) ↔ δ = 1.28 (4-H^1); δ = 1.70 (5-H^1) ↔ δ = 1.80 (4-H^2) and δ = 1.92 (5-H^2) ↔ δ = 1.80 (4-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.02 (C-5, C-3-Me)^A, 29.92 (C-4)^A, 46.43 (C-3)^A, 70.67 (C-6)^A, 77.27 (C-1′)^A, 122.13 (C-*para*), 129.81 (2 × C-*ortho*), 131.15 (2 × C-*meta*), 137.73 (C-*ipso*), 177.44 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in a spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 20.02 (C-5) ↔ δ = 1.70 (5-H^1) and 1.92 (5-H^2); δ = 20.02 (C-3-Me) ↔ δ = 1.37 (3-Me); δ = 29.92 (C-4) ↔ δ = 1.28 (4-H^1) and 1.80 (4-H^2); δ = 70.67 (C-6) ↔ δ = 4.17 (6-H^1) and 4.40 (6-H^2); δ = 77.27 (C-1′) ↔ δ = 4.94 (1′-H). IR (film): $\tilde{\nu}$ = 3840, 3430, 2960, 2360, 1700, 1490, 1400, 1265, 1220, 1165, 1135, 1075, 1010, 945, 840, 770, 645 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02828; found 299.02800 (Δ = 0.9 ppm). $C_{13}H_{15}BrO_3$ (299.16): calcd. C 52.19, H 5.05; found C 52.56, H 5.21.

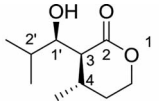
***rel*-(*S*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-3-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*-35)**



Following the **General Procedure B** the title compound was prepared from α-methyl-δ-lactone (**18**, 1.18 mg, 10.3 mmol) and 4-bromobenzaldehyde (**24**, 2.27 g, 12.3 mmol, 1.2 equiv.). Purification by flash chromatography[25] (5.0 × 20 cm, 50 mL, pentane/Et_2O 10:1 to 2:1, 27–33) rendered the product as a colorless solid (2.34 g, 78%). *syn*/*anti* 8:92 [determined by integration of the signals at δ = 4.94 (1′-H, *syn*-**35**) vs. δ = 4.99 (1′-H, *anti*-**35**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 76 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1. 23 [dddd, J_{gem} = 13.4 Hz, $J_{4\text{-}H(1),5\text{-}H(1)}$ = 4.9 Hz, $J_{4\text{-}H(1),5\text{-}H(2)}$ = 3.5 Hz, $^4J_{4\text{-}H(1),6\text{-}H(2)}$ = 2.1 Hz, 1 H, 4-H^1]^A superimposed by 1.25 (s, 3 H, 3-Me), 1.75 [ddddd, J_{gem} = 14.5 Hz, $J_{5\text{-}H(1),4\text{-}H(1)}$ = 4.5 Hz, $J_{5\text{-}H(1),4\text{-}H(2)}$ = $J_{5\text{-}H(1),6\text{-}H(1)}$ = $J_{5\text{-}H(1),6\text{-}H(2)}$ = 3.7 Hz, 1 H, 5-H^1]^A, 1.89 [ddddd, J_{gem} = 14.4 Hz, $J_{5\text{-}H(2),4\text{-}H(2)}$ = 12.2 Hz, $J_{5\text{-}H(2),6\text{-}H(1)}$ = 11.0 Hz, $J_{5\text{-}H(2),6\text{-}H(2)}$ = 4.6 Hz, $J_{5\text{-}H(2),4\text{-}H(1)}$ = 3.5 Hz, 1 H, 5-H^2]^A, 2.17 [ddd, J_{gem} = 13.1 Hz, $J_{4\text{-}H(2),5\text{-}H(2)}$ = 12.4 Hz, $J_{4\text{-}H(2),5\text{-}H(1)}$ = 4.0 Hz, 1 H, 4-H^2]^A, 3.10 (d, $J_{OH,1'\text{-}H}$ = 5.6 Hz, 1 H, OH), 4.22 [ddd, J_{gem} = $J_{6\text{-}H(1),5\text{-}H(2)}$ = 11.0 Hz, $J_{6\text{-}H(1),5\text{-}H(1)}$ = 3.5 Hz, 1 H, 6-H^1], 4.39 [dddd, J_{gem} = 11.0 Hz, $J_{6\text{-}H(2),5\text{-}H(2)}$ = 4.6 Hz, $J_{6\text{-}H(2),5\text{-}H(1)}$ = 3.3 Hz, $J_{6\text{-}H(2),4\text{-}H(1)}$ = 2.1 Hz, 1 H, 6-H^2], 5.00 (d, $J_{1'\text{-}H,OH}$ = 5.5 Hz, 1 H, 1′-H), 7.22 (m$_c$, 2 H, 2 × *ortho*-H), 7.48 (m$_c$, 2 H, 2 × *meta*-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned

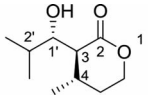
unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.22 (6-H^1) ↔ δ = 1.75 (5-H^1) and δ = 4.39 (6-H^2) ↔ δ = 1.75 (5-H^1); δ = 4.22 (6-H^1) ↔ δ = 1.89 (5-H^2) and δ = 4.39 (6-H^2) ↔ δ = 1.89 (5-H^2); δ = 1.75 (5-H^1) ↔ δ = 1. 23 (4-H^1) and δ = 1.89 (5-H^2) ↔ δ = 1. 23 (4-H^1); δ = 1.75 (5-H^1) ↔ δ = 2.17 (4-H^2) and δ = 1.89 (5-H^2) ↔ δ = 2.17 (4-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.37 (C-5)^A, 24.60 (C-3-Me)^A, 27.22 (C-4)^A, 48.16 (C-3)^A, 70.49 (C-6)^A, 78.61 (C-1′)^A, 122.09, (C-*para*), 129.49 (2 × C-*ortho*), 131.24 (2 × C-*meta*), 138.62 (C-*ipso*), 176.56 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 20.37 (C-5) ↔ δ = 1.75 (5-H^1) and 1.89 (5-H^2); δ = 24.60 (C-3-Me) ↔ δ = 1.25 (3-Me); δ = 27.22 (C-4) ↔ δ = 1.23 (4-H^1) and 2.17 (4-H^2); δ = 70.49 (C-6) ↔ δ = 4.22 (6-H^1) and 4.39 (6-H^2); δ = 78.61 (C-1′) ↔ δ = 5.00 (1′-H). IR (film): $\tilde{\nu}$ = 3840, 3735, 2990, 2870, 2360, 2340, 1700, 1395, 1220, 1140, 1075, 775, 675 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02828; found 299.02870 (+1.4 ppm). $C_{13}H_{15}BrO_3$ (299.16): calcd. C 52.19, H 5.05; found C 52.24, H 5.08.

***rel*-(3*S*,4*S*)-3-[(*R*)-1-Hydroxy-2-methylpropyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-36)**



Following the **General Procedure A** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 12–19) rendered the product as a colorless oil (142 mg, 76%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 96:0:4:0; *syn*/*anti* 96:4; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* >95:5. [The 300 MHz ^{1}H NMR spectrum of the crude product was too contaminated by byproducts to integrate any signals. A short column chromatographic separation (2.0 × 10 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 8–20) was conducted to get rid of most byproducts and a 400 MHz ^{1}H NMR spectrum of the product thus obtained was recorded. Integration of the signals at δ = 1.02 (3′-H$_3$, *anti*,*trans*-**36**) vs. δ = 1.12 (4-Me, *syn*,*trans*-**36**) as well as δ = 2.50 (3-H, *syn*,*trans*-**36**) vs. δ = 3.22 (1′-H, *anti*,*trans*-**36**) resulted in *syn*/*anti* 96:04. The NMR contained no signal clearly attributable to *syn*,*cis*-**36** or *anti*,*cis*-**36**.] ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.97 (d, $J_{3',2'}$ = 5.4 Hz, 3 H, 3′-H$_3$), 0.99 (d, $J_{2'\text{-Me},2'}$ = 5.3 Hz, 3 H, 2′-Me), 1.13 (d, $J_{4\text{-Me},4}$ = 6.7 Hz, 3 H, 4-Me)^A, 1.58 [m$_c$, possibly interpretable as dddd, J_{gem} = 14.1 Hz, $J_{5\text{-H}(1),4}$ = 9.2 Hz, $J_{5\text{-H}(1),6}$ = 8.7 and 4.9 Hz, 1 H, 5-H^1]^A, 1.86 (dqq, $J_{2',1'}$ = 7.7 Hz, $J_{2',3'}$ = $J_{2',2'\text{-Me}}$ = 6.7 Hz, 1 H, 2′-H), 1.97 [m$_c$, possibly interpretable as dddd, J_{gem} = 14.2 Hz, $J_{5\text{-H}(2),4}$ = 5.0 Hz, $J_{5\text{-H}(2),6}$ = 5.0 and 3.4 Hz, 1 H, 5-H^2]^A, 2.24 [dqdd, $J_{4,5\text{-H}(1)}$ = 9.1 Hz, $J_{4,4\text{-Me}}$ = $J_{4,3}$ = 7.0 Hz, $J_{4,5\text{-H}(2)}$ = 5.0 Hz, 1 H, 4-H]^A, 2.52 (dd, $J_{3,4}$ = 7.4 Hz, $J_{3,1'}$ = 3.4 Hz, 1 H, 3-H)^A, 2.86 (d, $J_{1'\text{-OH},1'}$ = 6.7 Hz, 1 H, 1′-OH), 3.82 (ddd, $J_{1',2'}$ = 7.6 Hz, $J_{1',1'\text{-OH}}$ = 6.5 Hz, $J_{1',3}$ = 3.3 Hz, 1 H, 1′-H)^A, 4.33–4.38 (m, 2 H, 6-H$_2$) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.33–4.38 (6-H$_2$) ↔ δ = 1.58 (5-H^1); δ = 4.33–4.38 (6-H$_2$) ↔ δ = 1.97 (5-H^2); δ = 1.58 (5-H^1) ↔ δ = 2.24 (4-H) and δ = 1.97 (5-H^2) ↔ δ = 2.24 (4-H); δ = 2.24 (4-H) ↔ δ = 1.13 (4-Me); δ = 2.24 (4-H) ↔ δ = 2.52 (3-H); δ = 2.52 (3-H) ↔ δ = 3.82 (1′-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 18.44 (C-3′)^A, 20.15 (C-2′-Me)^A, 21.71 (C-4-Me)^A, 26.88 (C-4)^A, 30.78 (C-2′)^A, 31.62 (C-5)^A, 51.60 (C-3)^A, 67.69 (C-6)^A, 77.98 (C-1′)^A, 174.76 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 18.44 (C-3′) ↔ δ = 0.99 (3′-H$_3$); δ = 20.15 (C-2′-Me) ↔ δ = 0.97 (2′-Me); δ = 21.71 (C-4-Me) ↔ δ = 1.13 (4-H$_3$); δ = 26.88 (C-4) ↔ δ = 2.24 (4-H); δ = 30.78 (C-2′) ↔ δ = 1.86 (2′-H); δ = 31.62 (C-5) ↔ δ = 1.58 (5-H^1) and 1.97 (5-H^2); δ = 51.60 (C-3) ↔ δ = 2.52 (3-H); = 67.69 (C-6) ↔ δ = 4.33–4.38 (6-H$_2$); δ = 77.98 (C-1′) ↔ δ = 3.82 (1′-H). IR (film): $\tilde{\nu}$ = 3440, 2960, 1715, 1475, 1400, 1315, 1265, 1230, 1195, 1085, 1055, 1000, 915, 745, 655 cm^{-1}. HRMS (pos. ESI): calcd. for $C_{10}H_{19}O_3$ [M + H]$^+$ 187.13287; found 187.13301 (+0.7 ppm). $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.48, H 9.91.

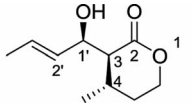
***rel*-(3*S*,4*S*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-36)**



Following the **General Procedure B** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 15–20) rendered the product as a colorless solid (147 mg, 79%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 2:0:98:0; *syn*/*anti* 2:98; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* >95:5 [determined by integration of the signals at δ = 3.82 (1′-H, *syn*,*trans*-**36**) vs. δ = 4.15–4.45 (6-H$_2$, *syn*,*trans*-**36** and *anti*,*trans*-**36**) in the 400 MHz ^{1}H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*cis*-**36** or *anti*,*cis*-**36**], m.p. 41 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.91 (d, $J_{2'\text{-Me},2'}$ = 6.7 Hz, 3 H, 2′-Me)^A, 1.03 (d, $J_{3',2'}$ = 6.6 Hz, 3 H, 3′-H$_3$)^A, 1.11 (d, $J_{4\text{-Me},4}$ = 6.6 Hz, 3 H, 4-Me), 1.58 [m$_c$, possibly interpretable as dddd, J_{gem} = 14.3 Hz, $J_{5\text{-H}(1),4}$ = 6.9 Hz, $J_{5\text{-H}(1),6}$ = 5.6 and 5.0 Hz, 1 H, 5-H^1]^A, 2.01 [m$_c$, possibly interpretable as dddd, J_{gem} = 14.3 Hz, $J_{5\text{-H}(2),4}$ = 6.2 Hz, $J_{5\text{-H}(2),6}$ = 6.2 and 5.7 Hz, 1 H, 5-H^2]^A, 2.18 (dqq, $J_{2',1'}$ = 8.8 Hz, $J_{2',2'\text{-Me}}$ = $J_{2',3'}$ = 6.7 Hz, 1 H, 2′-H)^A superimposed by 2.21 [dddq, $J_{4,3}$ = 8.8 Hz, $J_{4,5\text{-H}(1)}$ = $J_{4,5\text{-H}(2)}$ = $J_{4,4\text{-Me}}$ = 6.6 Hz, 1 H, 4-H]^A, 2.32 (dd, $J_{3,4}$ = 9.0 Hz, $J_{3,1'}$ = 2.0 Hz, 1 H, 3-H)^A, 2.49 (br. d, $J_{OH,1'}$ = 7.8 Hz, 1 H, OH), 3.22 (br. m$_c$, 1 H, 1′-H)^A, 4.27–4.35 (m, 2 H, 6-H$_2$) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 0.91 (2′-Me) ↔ δ = 2.18 (2′-H) and δ = 1.03 (3′-H$_3$) ↔ δ = 2.18 (2′-H); δ = 1.11 (4-Me) ↔ δ = 2.21 (4-H); δ = 2.21 (4-H) ↔ δ = 2.32 (3-H); δ = 2.32 (3-H) ↔ δ = 3.22 (1′-H); δ = 4.27–4.35 (6-H$_2$) ↔ δ = 1.58 (5-H^1); δ = 4.27–4.35 (6-H$_2$) ↔ δ = 2.01 (5-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.43 (C-3′)^A, 19.98 (C-2′-Me)^A, 20.87 (C-4-Me)^A, 29.30 (C-4)^A, 31.27 (C-5)^A, 32.25 (C-2′)^A, 49.79 (C-3)^A, 67.04 (C-6)^A, 77.72 (C-1′)^A, 173.45 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 19.43 (C-3′) ↔ δ = 1.03 (3′-H$_3$); δ = 19.98 (C-2′-Me) ↔ δ = 0.91 (2′-Me); δ = 20.87 (C-4-Me) ↔ δ = 1.11 (4-Me); δ = 29.30 (C-4) ↔ δ = 2.21 (4-H); δ = 31.27 (C-5) ↔ δ = 1.59 (5-

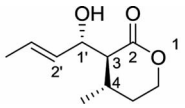
H[1]) and δ = 2.01 (5-H[2]); δ = 32.25 (C-2′) ↔ δ = 2.18 (2′-H); δ = 49.79 (C-3) ↔ δ = 2.32 (3-H); δ = 67.04 (C-6) ↔ δ = 4.27–4.35 (6-H_2); δ = 77.72 (C-1′) ↔ δ = 3.22 (1′-H). IR (film): $\tilde{\nu}$ = 3300, 2955, 2870, 2360, 1720, 1460, 1400, 1255, 1145, 1090, 1055, 945, 915, 745 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{19}O_3$ [M + H]$^+$ 187.13342; found 187.13360 (+1.4 ppm). $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.27, H 10.06.

***rel*-(3*S*,4*S*)-3-[(*R*,*trans*)-1-Hydroxybut-2-enyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-37)**



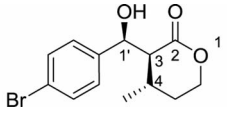
Following the **General Procedure A** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 13–17) rendered the product as a colorless oil (138 mg, 75%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 97:0:3:0; *syn*/*anti* 97:3; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* >95:5 [determined by integration of the signals at δ = 5.53 (2′-H, *syn*,*trans*-**37**) vs. δ = 5.68–5.80 (3′-H, *syn*,*trans*-**37**; 2′-H and 3′-H, *anti*,*trans*-**37**) in the 400 MHz ^{1}H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*cis*-**37** or *anti*,*cis*-**37**]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.07 (d, $J_{4\text{-Me},4}$ = 6.3 Hz, 3 H, 4-Me), 1.60 [m_c, possibly interpretable as dddd, J_{gem} = 15.2 Hz, $J_{5\text{-H}(1),4}$ = $J_{5\text{-H}(1),6\text{-H}(A)}$ = 10.9 Hz, $J_{5\text{-H}(1),6\text{-H}(B)}$ = 4.2 Hz, 1 H, 5-H[1]]^A, 1.73 (m_c, possibly interpretable as ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.5 Hz, $^5J_{4',1'}$ = 0.5 Hz, 3 H, 4′-H_3), 1.81–1.91 (m, 2 H, 4-H, 5-H[2])^A, 2.43 (m_c, possibly interpretable as dd, $J_{3,4}$ = 9.4 Hz, $J_{3,1'}$ = 3.7 Hz, 1 H, 3-H), 3.93 (d, $J_{OH,1'}$ = 9.7 Hz, 1 H, OH), AB-signal; δ_A = 4.23, δ_B = 4.33 ppm, A part additionally split by $J_{6\text{-H}(A),5\text{-H}(1)}$ = 10.9 Hz, $J_{6\text{-H}(A),5\text{-H}(2)}$ = 3.0 Hz, B part additionally split by $J_{6\text{-H}(B),5\text{-H}(1)}$ = $J_{6\text{-H}(B),5\text{-H}(2)}$ = 4.1 Hz, J_{AB} = 11.0 Hz, 2 H, 6-H_2) superimposed by 4.27 (m_c, possibly interpretable as ddd, $J_{1',OH}$ = $J_{1',2'}$ = 8.7 Hz, $J_{1',3}$ = 3.4 Hz, 1 H, 1′-H), 5.49 (ddq, $J_{2',3'}$ = 15.2 Hz, $J_{2',1'}$ = 7.7 Hz, $^4J_{2',4'}$ = 1.6 Hz, 1 H, 2′-H), 5.73 (dqd, $J_{3',2'}$ = 15.1 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 0.9 Hz, 1 H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 1.07 (4-Me) ↔ δ = 1.81–1.91 (4-H, 5-H[2]); δ = 4.23 (6-H^A) ↔ δ = 1.60 (5-H[1]) and δ = 4.33 (6-H^B) ↔ 1.60 (5-H[1]); δ = 4.23 (6-H^A) ↔ δ = 1.81–1.91 (4-H, 5-H[2]) and δ = 4.33 (6-H^B) ↔ 1.81–1.91 (4-H, 5-H[2]) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.78 (C-4′)^A, 20.45 (C-4-Me)^A, 28.25 (C-4)^A, 31.09 (C-5)^A, 53.67 (C-3)^A, 68.34 (C-6)^A, 72.34 (C-1′)^A, 129.69 (C-2′, C-3′)^A, 173.93 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.78 (C-4′) ↔ δ = 1.73 (4′-H_3); δ = 20.45 (C-4-Me) ↔ δ = 1.07 (4-Me); δ = 28.25 (C-4) ↔ δ = 1.81–1.91 (4-H, 5-H[2]); δ = 31.09 (C-5)↔ δ = 1.60 (5-H[1]) and 1.81–1.91 (4-H, 5-H[2]); δ = 53.67 (C-3) ↔ δ = 2.43 (3-H); δ = 68.34 (C-6) ↔ δ = AB-Signal (δ_A = 4.23, δ_B = 4.33, 6-H_2); δ = 72.34 (C-1′) ↔ δ = 4.27 (1′-H); δ = 129.69 (C-2′, C-3′) ↔ δ = 5.49 (2′-H) and 5.73 (3′-H). IR (film): $\tilde{\nu}$ = 3445, 2960, 2920, 2360, 2345, 1710, 1475, 1450, 1405, 1315, 1270, 1220, 1190, 1160, 1090, 1065, 1030, 1005, 970, 770, 650 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_{10}H_{17}O_3$ [M + H]$^+$ 185.11777; found 185.11790 (+0.7 ppm).

***rel*-(3*S*,4*S*)-3-[(*S*,*trans*)-1-Hydroxybut-2-enyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-37)**



Following the **General Procedure B** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 16–22) rendered the product as a colorless oil (139 mg, 75%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 6:0:94:0; *syn*/*anti* 6:94; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* >95:5 [determined by integration of the signals at δ = 2.25 (3-H, *anti*,*trans*-**37**) vs. δ = 2.48 (3-H, *syn*,*trans*-**37**) in the 400 MHz ^{1}H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*cis*-**37** or *anti*,*cis*-**37**]. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.14 (d, $J_{4\text{-Me},4}$ = 6.6 Hz, 3 H, 4-Me), 1.57 [m_c, possibly interpretable as dddd, J_{gem} = 14.4 Hz, $J_{5\text{-H}(1),4}$ = 6.5 Hz, $J_{5\text{-H}(1),6}$ = 6.5 and 3.8 Hz, 1 H, 5-H[1]], 1.74 (m_c, 3 H, 4′-H_3), 1.99 [m_c, possibly interpretable as dddd, J_{gem} = 14.2 Hz, $J_{5\text{-H}(2),4}$ = 6.6 Hz, $J_{5\text{-H}(2),6}$ = 7.7 and 4.2 Hz, 1 H, 5-H[2]], 2.14 [dqdd, $J_{4,3}$ = 8.2 Hz, $J_{4,4\text{-Me}}$ = $J_{4,5\text{-H}(1)}$ = $J_{4,5\text{-H}(2)}$ = 6.6 Hz, 1 H, 4-H]^A, 2.25 (m_c, possibly interpretable as dd, $J_{3,4}$ = 8.2 Hz, $J_{3,1'}$ = 4.4 Hz, 1 H, 3-H), 2.98 (m_c, possibly interpretable as d, $J_{OH,1'}$ = 6.1 Hz, 1 H, OH), 4.22–4.40 (m, 3 H, 6-H_2, 1′-H)^A, 5.68–5.80 (m, 2 H, 2′-H, 3′-H) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 5.68–5.80 (2′-H, 3′-H) ↔ δ = 4.22–4.40 (6-H_2, 1′-H); δ = 1.14 (4-Me) ↔ δ = 2.14 (4-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.74 (C-4′)^A, 21.45 (C-4-Me)^A, 28.17 (C-4)^A, 31.10 (C-5)^A, 53.46 (C-3)^A, 66.86 (C-6)^A, 73.07 (C-1′)^A, 128.76, 131.77 (C-2′, C-3′), 173.68 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.74 (C-4′) ↔ δ = 1.74 (4′-H_3); δ = 21.45 (C-4-Me) ↔ δ = 1.14 (4-Me); δ = 28.17 (C-4) ↔ δ = 2.14 (4-H); δ = 31.10 (C-5) ↔ δ = 1.57 (5-H[1]) and 1.99 (5-H[2]); δ = 53.46 (C-3) ↔ δ = 2.25 (3-H); δ = 66.86 (C-6) ↔ δ = 4.22–4.40 (6-H_2, 1′-H, CH_2 part); δ = 73.07 (C-1′) ↔ δ = 4.22–4.40 (6-H_2, 1′-H, CH_2 part). IR (film): $\tilde{\nu}$ = 3450, 2960, 2875, 2360, 2255, 1920, 1455, 1400, 1265, 1090, 910, 735, 650 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{17}O_3$ [M + H]$^+$ 185.11722; found 185.11725 (+0.1 ppm). $C_{10}H_{16}O_3$ (184.23): calcd. C 65.19, H 8.75; found C 64.93, H 8.93.

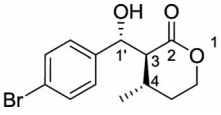
***rel*-(3*S*,4*S*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-38)**



Following the **General Procedure A** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 11–15) rendered the product as a colorless solid (238 mg, 80%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 95:0:5:0; *syn*/*anti* 95:5; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* >95:5 [determined by integration of the signals at δ = 2.64 (3-H *syn*,*trans*-**38**) vs. δ = 2.50 (3-H, *anti*,*trans*-**38**) in the 400 MHz ^{1}H NMR spectrum of the

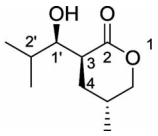
crude product; the NMR contained no signal clearly attributable to *syn*,*cis*-**38** or *anti*,*cis*-**38**], m.p. 87 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.81 (d, $J_{4\text{-Me},4}$ = 6.6 Hz, 3 H, 4-Me), 1.55 [dddd, J_{gem} = 14.0 Hz, $J_{5\text{-H}(1),4}$ = $J_{5\text{-H}(1),6\text{-H}(1)}$ = 10.0 Hz, $J_{5\text{-H}(1),6\text{-H}(2)}$ = 4.0 Hz, 1 H, 5-H^1], 1.83 [dddd, J_{gem} = 14.3 Hz, $J_{5\text{-H}(2),4}$ = $J_{5\text{-H}(2),6\text{-H}(2)}$ = 4.9 Hz, $J_{5\text{-H}(2),6\text{-H}(1)}$ = 2.8 Hz, 1 H, 5-H^2], 1.98 [ddqd, $J_{4,5\text{-H}(1)}$ = 9.8 Hz, $J_{4,3}$ = 8.4 Hz, $J_{4,4\text{-Me}}$ = 6.6 Hz, $J_{4,5\text{-H}(2)}$ = 5.0 Hz, 1 H, 4-H], 2.64 (dd, $J_{3,4}$ = 8.5 Hz, $J_{3,1'}$ = 3.7 Hz, 1 H, 3-H), 3.93 (d, $J_{OH,1'}$ = 7.2 Hz, 1 H, OH), 4.10 [ddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(1),\ 5\text{-H}(1)}$ = 10.2 Hz, $J_{6\text{-H}(1),5\text{-H}(2)}$ = 2.8 Hz, 1 H, 6-H^1], 4.30 [ddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(2),5\text{-H}(2)}$ = 4.7 Hz, $J_{6\text{-H}(2),5\text{-H}(1)}$ = 3.8 Hz, 1 H, 6-H^2], 5.23 (dd, $J_{1',OH}$ = 7.2 Hz, $J_{1',3}$ = 3.6 Hz, 1 H, 1′-H), 7.23 (m_c, 2 H, 2 × *ortho*-H), 7.47 (m_c, 2 H, 2 × *meta*-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.20 (C-4-Me)^A, 27.06 (C-4)^A, 31.44 (C-5)^A, 54.96 (C-3)^A, 68.11 (C-6)^A, 72.93 (C-1′)^A, 121.81, 128.14, 131.70, and 140.28 (6 × Ar-C), 173.75 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 21.20 (C-4-Me) ↔ δ = 0.81 (4-Me); δ = 27.06 (C-4) ↔ δ = 1.98 (4-H); δ = 31.44 (C-5) ↔ δ = 1.55 (5-H^1) and 1.83 (5-H^2); δ = 54.96 (C-3) ↔ δ = 2.64 (3-H); δ = 68.11 (C-6) ↔ δ = 4.10 (6-H^1) and 4.30 (6-H^2); δ = 72.93 (C-1′) ↔ δ = 5.23 (1′-H). IR (film): $\tilde{\nu}$ = 3420, 2990, 2955, 2870, 1705, 1485, 130, 1380, 1360, 1350, 1265, 1220, 1145, 1085, 1070, 770 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02828; found 299.02790 (–1.3 ppm).

***rel*-(3*S*,4*S*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-4-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-38)**



Following the **General Procedure B** the title compound was prepared from β-methyl-δ-lactone (**19**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 12–18) rendered the product as a colorless solid (244 mg, 82%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 3:0:88:9; *syn*/*anti* 3:97; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* 91:9 [determined by integration of the signals at δ = 4.91 (1′-H, *anti*,*cis*-**38**) vs. δ = 4.95 (1′-H, *anti*,*trans*-**38**) vs. δ = 5.24 (1′-H, *syn*,*trans*-**38**) in the 400 MHz ^{1}H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*cis*-**38**], m.p. 72 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (d, $J_{4\text{-Me},4}$ = 6.7 Hz, 3 H, 4-Me), 1.51 [dddd, J_{gem} = 14.3 Hz, $J_{5\text{-H}(1),4}$ = $J_{5\text{-H}(1),6\text{-H}(1)}$ = 6.5 Hz, $J_{5\text{-H}(1),6\text{-H}(2)}$ = 3.2 Hz, 1 H, 5-H^1], 1.89 [dddd, J_{gem} = 14.4 Hz, $J_{5\text{-H}(2),6\text{-H}(2)}$ = 8.1 Hz, $J_{5\text{-H}(2),4}$ = 6.3 Hz, $J_{5\text{-H}(2),6\text{-H}(1)}$ = 3.6 Hz, 1 H, 5-H^2], 1.99 [qddd, $J_{4,3}$ = $J_{4,4\text{-Me}}$ = $J_{4,5\text{-H}(1)}$ = $J_{4,5\text{-H}(2)}$ = 6.8 Hz, 1 H, 4-H], 2.48 (dd, $J_{3,4}$ = 7.5 Hz, $J_{3,1'}$ = 5.7 Hz, 1 H, 3-H), 3.94 (br. s, 1 H, OH), 4.13 [dddd, J_{gem} = 11.2 Hz, $J_{6\text{-H}(1),5\text{-H}(1)}$ = 6.7 Hz, $J_{6\text{-H}(1),5\text{-H}(2)}$ = 3.7 Hz, $J_{6\text{-H}(1),4\text{-H}}$ = 0.4 Hz, 1 H, 6-H^1], 4.27 [ddd, J_{gem} = 11.3 Hz, $J_{6\text{-H}(2),5\text{-H}(2)}$ = 8.1 Hz, $J_{6\text{-H}(2),5\text{-H}(1)}$ = 3.2 Hz, 1 H, 6-H^2], 4.92 (d, $J_{1',3}$ = 5.7 Hz, 1 H, 1′-H), 7.25 (m_c, 2 H, 2 × *ortho*-H), 7.47 (m_c, 2 H, 2 × *meta*-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.37 (C-4-Me)^A, 27.80 (C-4)^A, 30.90 (C-5)^A, 54.41 (C-3)^A, 66.87(C-6), 73.51 (C-1′)^A, 121.76 (C-*para*), 128.34 (2 × C-*ortho*)^A, 131.51 (2 × C-*meta*)^A, 140.56 (C-*ipso*), 173.72 (C-1) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 21.37 (C-4-Me) ↔ δ = 0.88 (4-Me); δ = 27.80 (C-4) ↔ δ = 1.99 (4-H); δ = 30.90 (C-5) ↔ δ = 1.51 (5-H^1) and 1.89 (5-H^2); δ = 54.41 (C-3) ↔ δ = 2.48 (3-H); δ = 66.78 (C-6) ↔ δ = 4.13 (6-H^1) and 4.27 (6-H^2); δ = 73.51 (C-1′) ↔ δ = 4.92 (1′-H); δ = 128.34 (2 × C-*ortho*) ↔ δ = 7.25 (2 × *ortho*-H); δ = 131.51 (2 × C-*meta*) ↔ δ = 7.47 (2 × *meta*-H). IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 2960, 2920, 2850, 1715, 1485, 1400, 1265, 1225, 1160, 1130, 1090, 1070, 1010, 825 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02828; found 299.02860 (+1.1 ppm).

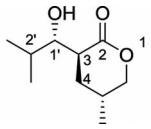
***rel*-(3*S*,5*R*)-3-[(*R*)-1-Hydroxy-2-methylpropyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-39)**



Following the **General Procedure A** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 16–24) rendered the product as a colorless oil (112 mg, 60%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 72:28:0:0; *syn*/*anti* >95:5; *syn*,*trans*/*syn*,*cis* 72:28, *anti*,*trans*/*anti*,*cis* >95:05. [The 300.06 MHz ^{1}H NMR spectrum of the crude product was too contaminated by byproducts to integrate any signals. A short column chromatographic separation (2.0 × 10 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 8–16) was conducted to get rid of most byproducts and a 400.13 MHz ^{1}H NMR spectrum of the product thus obtained was recorded. Integration of the signals at δ = 4.22 (6-H^2, *syn*,*trans*-**39**) vs. δ = 4.31–4.33 (left half of 6-H^2, *syn*,*cis*-**39**) resulted in *syn*/*iso-syn* 72:28. The NMR contained no signal clearly attributable to *anti*,*trans*-**39** or *anti*,*cis*-**39**.] ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (d, $J_{2'\text{-Me},2'}$ = 6Hz, 3 H, 2′-Me)^A, 1.04 (d, $J_{5\text{-Me},5}$ = 6.7 Hz, 3 H, 5-Me)^A superimposed by 1.05 (d, $J_{3',2'}$ = 6.6 Hz, 3 H, 3′-H$_3$)^A, 1.47–1.59 (m_c, 1 H, 4-H^1)^A, 1.68 (dqq, $J_{2',1'}$ = 9.7 Hz, $J_{2',3'}$ = $J_{2',2'\text{-Me}}$ = 6.6 Hz, 1 H, 2′-H), 2.10–2.21 (m, 4-H^2, 5-H)^A, 2.54 (br. s, 1 H, OH), 2.74 [ddd, possibly interpretable as, $J_{3,4\text{-H}(1)}$ = $J_{3,4\text{-H}(2)}$ = 9.3 Hz, $J_{3,1'}$ = 2.3 Hz, 1 H, 3-H], 3.84 (dd, $J_{1',2'}$ = 9.7 Hz, $J_{1',3}$ = 2.3 Hz, 1 H, 1′-H), 3.92 (m_c, possibly interpretable as dd, J_{gem} = 10.8 Hz, $J_{6\text{-H}(1),5}$ = 9.7 Hz, 1 H, 6-H^1], 4.23 (m_c, 1 H, 6-H^2) ppm. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [δ_H(^{1}H) ↔ δ_H(^{1}H)]: δ = 1.68 (2′-H) ↔ δ = 0.86 (2′-Me); δ = 1.68 (2′-H) ↔ δ = 1.05 (3′-H$_3$); δ = 2.74 (3-H) ↔ δ = 1.47–1.59 (4-H^1) and 2.10–2.21 (4-H^2, 5-H); δ = 3.92 (6-H^1) and 4.23 (6-H^2) ↔ δ = 2.10–2.21 (4-H^2, 5-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.16 (C-5-Me)^A, 18.87 (C-2′-Me)^A, 19.77 (C-3′)^A, 24.96 (C-4)^A, 27.94 (C-5)^A, 29.78 (C-2′)^A, 40.34 (C-3)^A, 73.10 (C-6)^A, 75.51 (C-1′)^A, 175.69 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [δ_C(^{13}C) ↔ δ_H(^{1}H)]: δ = 17.16 (C-5-Me) ↔ δ = 1.04 (5-Me); δ = 18.87 (C-2′-Me) ↔ δ = 0.86 (2′-Me); δ = 19.77 (C-3′) ↔ δ = 1.05 (3′-H$_3$); δ = 24.96 (C-4) ↔ δ = 1.47–1.59 (4-H^1) and 2.10–2.21 (4-H^2, 5-H); δ = 27.94 (C-5) ↔ δ = 2.10–2.21 (4-H^2, 5-H); δ = 29.78 (C-2′) ↔ δ = 1.68 (2′-H); δ = 40.34 (C-3) ↔ δ = 2.74 (3-H); δ = 73.10 (C-6) ↔ δ = 3.92 (6-H^1) and 4.23 (6-H^2); δ = 75.51 (C-1′) ↔ δ = 3.84

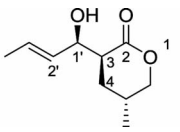
(1′-H). IR (film): ṽ = 3460, 2960, 2875, 1730, 1460, 1385, 1345, 1250, 1210, 1185, 1160, 1095, 1050, 1020 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_{10}H_{16}O_2$ $[M - H_2O]^+$ 168.11503; found 168.11520 (–1.0 ppm).

***rel*-(3*S*,5*R*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-39)**



Following the **General Procedure B** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 19–24) rendered the product as a colorless oil (130 mg, 70%, *syn*,*trans*-**39**/*syn*,*cis*-**39** = 95:5). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 5:0:72:24; *syn*/*anti* ≈ 5:95; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* ≈ 75:25. [The 300.06 MHz ^{1}H NMR spectrum of the crude product was too contaminated by byproducts to integrate any signals. A short column chromatographic separation (2.0 × 10 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 11–21) was conducted to get rid of most byproducts and a 400.13 MHz ^{1}H NMR spectrum of the product thus obtained was recorded. Integration of the signals at δ = 4.21 (6-H^2, *anti*,*trans*-**39**) vs. δ = 4.28–4.30 (right half of 6-H^2, *syn*,*trans*-**39**) vs. δ = 4.30–4.35 (left half of 6-H^2, *syn*,*trans*-**39** + 6-H^2, *anti*,*cis*-**39**) resulted in *syn*/*anti*:*iso*-*anti* 05:71:24. The NMR contained no signal clearly attributable to *syn*,*cis*-**39**.] ^{1}H NMR (400.13 MHz, $CDCl_3$, 95:5 mixture of diastereomers): δ = 0.92 (d, $J_{2'\text{-Me},2'}$ = 6.8 Hz, 3 H, 2′-Me)^A, 1.03 (d, $J_{3',2'}$ = 7.0 Hz, 3 H, 3′-H$_3$)^A, 1.04 (d, $J_{5\text{-Me},5}$ = 6.9 Hz, 3 H, 5-Me)^A, 1.59 [ddd, J_{gem} = 13.6 Hz, $J_{4\text{-H}(1),3}$ = 9.1 Hz, $J_{4\text{-H}(1),5}$ = 7.1 Hz, 1 H, 4-H^1]^A, 1.80 [ddd, J_{gem} = 13.7 Hz, $J_{4\text{-H}(2),3}$ = 11.0 Hz, $J_{4\text{-H}(2),5}$ = 8.4 Hz, 1 H, 4-H^2]^A, 1.85 (qqd, $J_{2',3'}$ = $J_{2',2'\text{-Me}}$ = 6.8 Hz, $J_{2',1'}$ = 3.7 Hz, 1 H, 2′-H)^A, 2.15 (m$_c$, 1 H, 5-H)^A, 2.61 [ddd, $J_{3,4\text{-H}(2)}$ = 10.8 Hz, $J_{3,4\text{-H}(1)}$ = $J_{3,1'}$ = 8.4 Hz, 1 H, 3-H], 3.56 (dd, $J_{1',3}$ = 7.6 Hz, $J_{1',2'}$ = 3.7 Hz, 1 H, 1′-H), 3.62 (br. s, 1 H, OH), 3.93 [dd, J_{gem} = $J_{6\text{-H}(1),5}$ = 10.8 Hz, 1 H, 6-H^1], 4.21 [dd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(2),5}$ = 4.8 Hz, 1 H, 6-H^2]. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 3.56 (1′-H) ↔ δ = 1.85 (2′-H); δ = 1.85 (2′-H) ↔ δ = 0.92 (2′-Me) and 1.03 (3′-H$_3$); δ = 2.61 (3-H) ↔ δ = 1.59 (4-H^1) and 1.80 (4-H^2); δ = 3.93 (6-H^1) ↔ δ = 2.15 (5-H); δ = 4.21 (6-H^2)↔ δ = 2.15 (5-H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.00 (C-2′-Me)^A, 17.16 (C-5-Me)^A, 20.22 (C-3′)^A, 27.53 (C-5)^A, 29.18 (C-2′)^A, 29.28 (C-4)^A, 40.84 (C-3)^A, 72.63 (C-6)^A, 75.60 (C-1′)^A, 176.33 (C-2) ppm. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 15.00 (C-2′-Me) ↔ δ = 0.92 (2′-Me); δ = 17.16 (C-5-Me) ↔ δ = 1.04 (5-Me); δ = 20.22 (C-3′) ↔ δ = 1.03 (3′-H$_3$); δ = 27.53 (C-5) ↔ δ = 2.15 (5-H); δ = 29.18 (C-2′) ↔ δ = 1.85 (2′-H); δ = 29.28 (C-4) ↔ δ = 1.59 (4-H^1) and 1.80 (4-H^2); δ = 40.84 (C-3) ↔ δ = 2.61 (3-H); δ = 72.63 (C-6) ↔ δ = 3.93 (6-H^1) and 4.21 (6-H^2); δ = 75.60 (C-1′) ↔ δ = 3.56 (1′-H). IR (film): ṽ = 3530, 2960, 2360, 1725, 1460, 1400, 12.45, 1205, 1160, 1090, 1050, 1000, 745 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.13287; found 187.13293 (+0.3 ppm).

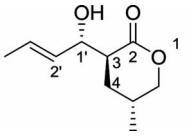
***rel*-(3*S*,5*R*)-3-[(*R*,*trans*)-1-Hydroxybut-2-enyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-40)**



Following the **General Procedure A** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 13–17) rendered the product as a colorless oil (109 mg, 59%, *syn*,*trans*-**40**:*syn*,*cis*-**40** = 66:33). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 68:25:2:5; *syn*/*anti* 93:7; *syn*,*trans*/*syn*,*cis* 73:27, *anti*,*trans*/*anti*,*cis* 23:77 [determined by integration of δ = 0.98 (right peak of 5-Me, *syn*,*cis*-**40**) vs. δ = 0.99 (right peak of 5-Me, *anti*,*cis*-**40**) vs. δ = 1.01 (right peak of 5-Me, *anti*,*trans*-**40**) vs. δ = 1.02 (right peak of 5-Me, *syn*,*trans*-**40**) as well as of δ = 1.00 (left peak of 5-Me, *syn*,*cis*-**40**) vs. δ = 1.01 (left peak of 5-Me, *anti*,*cis*-**40**) vs. δ = 1.03 (left peak of 5-Me, *anti*,*trans*-**40**) vs. δ = 1.04 ppm (left peak of 5-Me, *syn*,*trans*-**40**) in the 400.13 MHz ^{1}H NMR spectrum of the crude product]. ^{1}H NMR (400.13 MHz, $CDCl_3$, 66:33 mixture of diastereomers): δ = 0.98 [d, $J_{5\text{-Me},5}$ = 6.8 Hz, 3 H, 5-Me (*syn*,*cis*-**40**)], 1.01 [d, $J_{5\text{-Me},5}$ = 6.8 Hz, 3 H, 5-Me (*syn*,*trans*-**40**)], 1.45 [ddd, J_{gem} = 13.3 Hz, $J_{4\text{-H}(1),3}$ = 12.4 Hz, $J_{4\text{-H}(1),5}$ = 11.4 Hz, 1 H, 4-H^1 (*syn*,*cis*-**40**)], 1.56 [ddd, J_{gem} = 13.6 Hz, $J_{4\text{-H}(1),3}$ = 9.3 Hz, $J_{4\text{-H}(1),5}$ = 7.6 Hz, 1 H, 4-H^1 (*syn*,*trans*-**40**)], 1.73 [ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.7 Hz, $^5J_{4',1'}$ = 1.0 Hz, 3 H, 4′-H$_3$ (both diastereomers)], 1.88 [dddd, J_{gem} = 13.4 Hz, $J_{4\text{-H}(2),3}$ = 6.9 Hz, $J_{4\text{-H}(2),5}$ = 4.2 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 2.5 Hz, 1 H, 4-H^2 (*syn*,*cis*-**40**)], 1.97 [dddd, J_{gem} = 13.6 Hz, $J_{4\text{-H}(2),3}$ = 9.3 Hz, $J_{4\text{-H}(2),5}$ = 7.4 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 1.2 Hz, 1 H, 4-H^2 (*syn*,*trans*-**40**)], 2.03–2.18 {m, possibly interpretable as 2.03–2.15 [m, 1 H, 5-H (*syn*,*cis*-**40**)] superimposed by 2.11 [dddqd, $J_{5,6\text{-H}(1)}$ = 9.8 Hz, $J_{5,4\text{-H}(1)}$ = $J_{5,4\text{-H}(2)}$ = $J_{5,5\text{-Me}}$ = 7.1 Hz, $J_{5,6\text{-H}(2)}$ = 4.5 Hz, 1 H, 5-H (*syn*,*trans*-**40**)]}, 2.69 [ddd, $J_{3,4\text{-H}(1)}$ = 12.1 Hz, $J_{3,4\text{-H}(2)}$ = 6.9 Hz, $J_{3,1'}$ = 3.4 Hz, 1 H, 3-H (*syn*,*cis*-**40**)], 2.73 [ddd, $J_{3,4\text{-H}(1)}$ = $J_{3,4\text{-H}(2)}$ = 9.3 Hz, $J_{3,1'}$ = 3.2 Hz, 1 H, 3-H (*syn*,*trans*-**40**)], 3.02 [br. d, $J_{OH,1'}$ = 5.9 Hz, 1 H, OH (*syn*,*trans*-**40**)], 3.09 [br. d, $J_{OH,1'}$ = 6.6 Hz, 1 H, OH (*syn*,*cis*-**40**)], 3.85 [dd, J_{gem} = 10.8 Hz, $J_{6\text{-H}(1),5}$ = 10.6 Hz, 1 H, 6-H^1 (*syn*,*cis*-**40**)], 3.91 [dd, J_{gem} = 11.0 Hz, $J_{6\text{-H}(1),5}$ = 9.5 Hz, 1 H, 6-H^1 (*syn*,*trans*-**40**)], 4.21 [ddd, J_{gem} = 11.0 Hz, $J_{6\text{-H}(2),5}$ = 4.4 Hz, $J_{6\text{-H}(2),4\text{-H}(2)}$ = 1.2 Hz, 1 H, 6-H^2 (*syn*,*trans*-**40**)], 4.26 [ddd, J_{gem} = 11.0 Hz, $J_{6\text{-H}(2),5}$ = 4.6 Hz, $J_{6\text{-H}(2),4\text{-H}(2)}$ = 2.4 Hz, 1 H, 6-H^2 (*syn*,*cis*-**40**)], 4.47 [br. m$_c$, 1 H, 1′-H (*syn*,*cis*-**40**)] superimposed by 4.50 [br. m$_c$, 1 H, 1′-H (*syn*,*trans*-**40**)], 5.44–5.52 {m, possibly interpretable as 5.48 [ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 6.9 Hz, $^4J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H (*syn*,*cis*-**40**)] superimposed by 5.49 [ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 6.8 Hz, $^4J_{2',4'}$ = 1.7 Hz, 1 H, 2′-H (*syn*,*trans*-**40**)]}, 5.70–5.80 {m, possibly interpretable as 5.75 [dqd, $J_{3',2'}$ = 15.5 Hz, $J_{3',4'}$ = 6.4 Hz, $^4J_{3',1'}$ = 1.2 Hz, 1 H, 3′-H (*syn*,*cis*-**40**)] superimposed by 5.76 [dqd, $J_{3',2'}$ = 15.4 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 1.3 Hz, 1 H, 3′-H (*syn*,*trans*-**40**)]}. ^{13}C NMR (100.63 MHz, $CDCl_3$, 76:24 mixture of diastereomers): δ = 16.80 [C-5-Me (*syn*,*trans*-**40**)]^A, 16.97 [C-5-Me (*syn*,*cis*-**40**)]^A, 17.80 [C-4′ (both diastereomers)]^A, 27.04 [C-4 (*syn*,*trans*-**40**)]^A, 27.52 [C-5 (*syn*,*trans*-**40**)]^A, 28.37 [C-5 (*syn*,*cis*-**40**)]^A, 29.19 [C-4 (*syn*,*cis*-**40**)]^A, 42.93 [C-3 (*syn*,*trans*-**40**)]^A, 46.50 [C-3 (*syn*,*cis*-**40**)]^A, 71.99 [C-1′ (*syn*,*trans*-**40**)]^A, 72.51 [C-1′ (*syn*,*cis*-**40**)]^A, 73.50 [C-6 (*syn*,*trans*-**40**)]^A, 75.01 [C-6 (*syn*,*cis*-**40**)]^A, 128.74 [C-3′ (*syn*,*trans*-**40**)]^A, 128.89 [C-3′ (*syn*,*cis*-**40**)]^A, 129.61 [C-2′ (*syn*,*trans*-**40**)]^A, 129.80 [C-2′ (*syn*,*cis*-**40**)]^A, 173.21 [C-2 (*syn*,*cis*-**40**)], 174.57 [C-2 (*syn*,*trans*-**40**)]. ^{A}The indicated nuclei – they are non-quaternary –

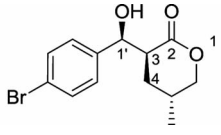
were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.6/400.1 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 16.80 [C-5-Me (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 1.01 [5-Me (*syn*,*trans*-**40**)]; δ = 16.97 [C-5-Me (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 0.98 [5-Me (*syn*,*cis*-**40**)]; δ = 17.80 [C-4′ (both diastereomers)] $\leftrightarrow \delta$ = 1.73 [4′-H_3 (both diastereomers)]; δ = 27.04 [C-4 (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 1.56 [4-H^1 (*syn*,*trans*-**40**)] and 1.97 [4-H^2 (*syn*,*trans*-**40**)]; δ = 27.52 [C-5 (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 2.11 [5-H (*syn*,*trans*-**40**)]; δ = 28.37 [C-5 (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 2.03–2.15 [5-H (*syn*,*cis*-**40**)]; δ = 29.19 [C-4 (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 1.45 [4-H^1 (*syn*,*cis*-**40**)] and 1.88 [4-H^2 (*syn*,*cis*-**40**)]; δ = 42.93 [C-3 (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 2.73 [3-H (*syn*,*trans*-**40**)]; δ = 46.50 [C-3 (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 2.69 [3-H (*syn*,*cis*-**40**)]; δ = 71.99 [C-1′ (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 4.50 [1′-H (*syn*,*trans*-**40**)]; δ = 72.51 [C-1′ (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 4.47 [1′-H (*syn*,*cis*-**40**)]; δ = 73.50 [C-6 (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 3.91 [6-H^1 (*syn*,*trans*-**40**)] and 4.21 [6-H^2 (*syn*,*trans*-**40**)]; δ = 75.01 [C-6 (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 3.85 [6-H^1 (*syn*,*cis*-**40**)] and 4.26 [6-H^2 (*syn*,*cis*-**40**)]; δ = 128.74 [C-3′ (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 5.76 [3′-H (*syn*,*trans*-**40**)]; δ = 128.89 [C-3′ (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 5.75 [3′-H (*syn*,*cis*-**40**)]; δ = 129.61 [C-2′ (*syn*,*trans*-**40**)] $\leftrightarrow \delta$ = 5.49 [2′-H (*syn*,*trans*-**40**)]; δ = 129.80 [C-2′ (*syn*,*cis*-**40**)] $\leftrightarrow \delta$ = 5.48 [2′-H (*syn*,*cis*-**40**)]. IR (film): $\tilde{\nu}$ = 3550, 2965, 1726, 1460, 1400, 1165, 1095, 1045, 970, 915, 745 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.11722; found 185.11717 (–0.3 ppm).

***rel*-(3*S*,5*R*)-3-[(*S*,*trans*)-1-Hydroxybut-2-enyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-40)**



Following the **General Procedure A** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 12–20) rendered the product as a colorless oil (137 mg, 74%, *anti*,*trans*-**40**/*anti*,*cis*-**40** = 75:25). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 7:0:73:20; *syn*/*anti* 7:93; *syn*,*trans*/*syn*,*cis* >95:5, *anti*,*trans*/*anti*,*cis* 78:22. [Integration of the signals at δ = 2.46–2.60 (3-H, *anti*,*trans*-**40** + *anti*,*cis*-**40**) vs. δ = 2.75 (3-H, *syn*,*trans*-**40**) in the 400 MHz ^{1}H NMR spectrum of the crude product resulted in (overall-) *syn*/*anti* 07:93. Integration of the signals at δ = 2.46–2.60 (3-H, *anti*,*trans*-**40** + *anti*,*cis*-**40**) vs. δ = 4.32 (6-H^2, *anti*,*cis*-**40**) resulted in *anti*:*iso*-*anti* 78:22. The NMR contained no signal clearly attributable to *syn*,*cis*-**40**.] ^{1}H NMR (400.13 MHz, $CDCl_3$, 75:25 mixture of diastereomers): δ = 0.99 [d, $J_{5\text{-Me},5}$ = 6.7 Hz, 3 H, 5-Me (*anti*,*cis*-**40**)], 1.00 [d, $J_{5\text{-Me},5}$ = 6.9 Hz, 3 H, 5-Me (*anti*,*trans*-**40**)], 1.15 [ddd, J_{gem} = 13.5 Hz, $J_{4\text{-H}(1),3}$ = 12.7 Hz, $J_{4\text{-H}(1),5}$ = 10.4 Hz, 1 H, 4-H^1 (*anti*,*cis*-**40**)], 1.55 [ddd, J_{gem} = 13.8 Hz, $J_{4\text{-H}(1),3}$ = 9.0 Hz, $J_{4\text{-H}(1),5}$ = 7.3 Hz, 1 H, 4-H^1 (*anti*,*trans*-**40**)], 1.72 [dddd, J_{gem} = 13.8 Hz, $J_{4\text{-H}(2),3}$ = 10.4 Hz, $J_{4\text{-H}(2),5}$ = 8.2 Hz, $J_{4\text{-H}(2),6\text{-H}(2)}$ = 0.9 Hz, 1 H, 4-H^2 (*anti*,*trans*-**40**)] superimposed by 1.71 [dd, $J_{4',3'}$ = 6.3 Hz, $^4J_{4',2'}$ = 1.4 Hz, 3 H, 4′-H_3 (both diastereomers)], 1.97 [dddd, J_{gem} = 13.6 Hz $J_{4\text{-H}(2),3}$ = 6.8 Hz, $J_{4\text{-H}(2),5}$ = 4.8 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 2.1 Hz, 1 H, 4-H^2 (*anti*,*cis*-**40**)], 2.03–2.18 [m, 1 H, 5-H (both diastereomers)], 2.49 [ddd, $J_{3,4\text{-H}(1)}$ = 12.6 Hz, $J_{3,1'}$ = 8.0 Hz, $J_{3,4\text{-H}(2)}$ = 6.9 Hz, 1 H, 3-H (*anti*,*cis*-**40**)], 2.55 [ddd, $J_{3,4\text{-H}(2)}$ = 10.4 Hz, $J_{3,4\text{-H}(1)}$ = 9.0 Hz, $J_{3,1'}$ = 8.0 Hz, 1 H, 3-H (*anti*,*trans*-**40**)], 3.84 [dd, J_{gem} = $J_{6\text{-H}(1),5}$ = 9.9 Hz, 1 H, 6-H^1 (*anti*,*cis*-**40**)], 3.87 [br. s, 1 H, OH (*anti*,*trans*-**40**)] superimposed by 3.90 [dd, J_{gem} = $J_{6\text{-H}(1),5}$ = 10.7 Hz, 1 H, 6-H^1 (*anti*,*trans*-**40**)], 4.14 [br. s, 1 H, OH (*anti*,*cis*-**40**)], 4.19–4.26 [m, 1 H, 1′-H (both diastereomers)] superimposed by 4.20 [ddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(2),5}$ = 4.9 Hz, $^4J_{6\text{-H}(2),4\text{-H}(2)}$ = 0.9 Hz, 1 H, 6-H^2 (*anti*,*trans*-**40**)], 4.31 [ddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(2),5}$ = 4.8 Hz, $J_{6\text{-H}(2),4\text{-H}(2)}$ = 2.1 Hz, 1 H, 6-H^2 (*anti*,*cis*-**40**)], 5.44 [ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 7.7 Hz, $^4J_{2',4'}$ = 1.5 Hz, 1 H, 2′-H (*anti*,*cis*-**40**)] superimposed by 5.45 [ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 7.7 Hz, $^4J_{2',4'}$ = 1.6 Hz, 1 H, 2′-H (*anti*,*trans*-**40**)], 5.75 [dqd, $J_{3',2'}$ = 15.4 Hz, $J_{3',4'}$ = 6.4 Hz, $^4J_{3',1'}$ = 0.7 Hz, 1 H, 3′-H (*anti*,*cis*-**40**)] superimposed by 5.76 [dqd, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 0.8 Hz, 1 H, 3′-H (*anti*,*trans*-**40**)]. ^{13}C NMR (100.62 MHz, $CDCl_3$, 75:25 mixture of diastereomers): δ = 16.95 [C-5-Me (*anti*,*trans*-**40**)]^A, 17.43 [C-5-Me (*anti*,*cis*-**40**)]^A, 17.75 [C-4′ (*anti*,*cis*-**40**)]^A, 17.78 [C-4′ (*anti*,*trans*-**40**)]^A, 27.30 [C-5 (*anti*,*trans*-**40**)]^A, 28.17 [C-5 (*anti*,*cis*-**40**)]^A, 29.26 [C-4 (*anti*,*trans*-**40**)]^A, 30.99 [C-4 (*anti*,*cis*-**40**)]^A, 43.02 [C-3 (*anti*,*trans*-**40**)]^A, 45.81 [C-3 (*anti*,*cis*-**40**)]^A, 72.96 [C-6 (*anti*,*trans*-**40**)]^A, 73.30 [C-1′ (*anti*,*trans*-**40**)]^A, 73.70 [C-1′ (*anti*,*cis*-**40**)]^A, 74.84 [C-6 (*anti*,*cis*-**40**)]^A, 129.80 [C-2′ (*anti*,*trans*-**40**)]^B, 129.88 [C-3′ (*anti*,*trans*-**40**)]^B, 129.92 [C-2′ (*anti*,*cis*-**40**)]^B, 129.97 [C-3′ (*anti*,*cis*-**40**)]^B, 174.45 [C-2 (*anti*,*cis*-**40**)], 175.61 [C-2 (*anti*,*trans*-**40**)]. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 16.95 [C-5-Me (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 1.00 [5-Me (*anti*,*trans*-**40**)]; δ = 17.43 [C-5-Me (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 0.99 [5-Me (*anti*,*cis*-**40**)]; δ = 17.75 [C-4′ (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 1.71 [4′-H_3 (both diastereomers)]; δ = 17.78 [C-4′ (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 1.71 [4′-H_3 (both diastereomers)]; δ = 27.30 [C-5 (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 2.03–2.18 [5-H (both diastereomers)]; δ = 28.17 [C-5 (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 2.03–2.18 [5-H (both diastereomers)]; δ = 29.26 [C-4 (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 1.55 [4-H^1 (*anti*,*trans*-**40**)] and 1.72 [4-H^2 (*anti*,*trans*-**40**)]; δ = 30.99 [C-4 (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 1.15 [4-H^1 (*anti*,*cis*-**40**)] and 1.97 [4-H^2 (*anti*,*cis*-**40**)]; δ = 43.02 [C-3 (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 2.55 [3-H (*anti*,*trans*-**40**)]; δ = 45.81 [C-3 (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 2.49 [3-H (*anti*,*cis*-**40**)]; δ = 72.96 [C-6 (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 3.90 [6-H^1 (*anti*,*trans*-**40**)] and 4.20 [6-H^2 (*anti*,*trans*-**40**)]; δ = 73.30 [C-1′ (*anti*,*trans*-**40**)] $\leftrightarrow \delta$ = 4.19–4.26 [1′-H (both diastereomers)]; δ = 73.70 [C-1′ (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 4.19–4.26 [1′-H (both diastereomers)]; δ = 74.84 [C-6 (*anti*,*cis*-**40**)] $\leftrightarrow \delta$ = 3.84 [6-H^1 (*anti*,*cis*-**40**)] and 4.31 [6-H^2 (*anti*,*cis*-**40**)]; ^{B} Assignments pairwise interchangeable. IR (film): $\tilde{\nu}$ = 3450, 2965, 2935, 2920, 2880, 1725, 1460, 1400, 1250, 1220, 1165, 1120, 1095, 1045, 970 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{17}O_3$ $[M + H]^+$ 185.11722; found 185.11725 (+0.1 ppm).

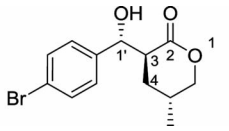
***rel*-(3*S*,5*R*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*trans*-41)**



Following the **General Procedure A** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 17–25) rendered the product as a colorless solid (225 mg, 75%, *syn*,*trans*-**41**:*syn*,*cis*-**41** = 66:33). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 66:31:2:1; *syn*/*anti* 97:3; *syn*,*trans*/*syn*,*cis* 68:32, *anti*,*trans*/*anti*,*cis* 70:30 [determined by integration of the signals at δ = 4.77 (1′-H *anti*,*trans*-**41**) vs. δ = 4.80 (1′-H, *anti*,*cis*-**41**) vs. δ = 5.44 (1′-H, *syn*,*trans*-**41**) vs. δ = 5.48 (1′-H, *syn*,*cis*-**41**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 66 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, 66:33 mixture of diastereomers): δ = 0.91 [d, $J_{5\text{-Me},5}$ = 6.8 Hz, 3 H, 5-Me

(*syn*,*trans*-**41**)] superimposed by 0.92 [d, $J_{5\text{-Me},5}$ = 6.7 Hz, 3 H, 5-Me (*syn*,*cis*-**41**)], 1.14 [m_c, possibly interpretable as ddd, J_{gem} = 13.4 Hz, $J_{4\text{-H}(1),3}$ = 9.3 Hz, $J_{4(1),5}$ = 7.4 Hz, 1 H, 4-H^1 (*syn*,*trans*-**41**)]^A, 1.47–1.53 [m, 2 H, 4-H$_2$ (*syn*,*cis*-**41**)]^A, 1.92–2.16 [m, 5-H (both diastereomers)]^A superimposed by 2.00 [m_c, possibly interpretable as dddd, J_{gem} = 13.4 Hz, $J_{4\text{-H}(2),3}$ = 9.4 Hz, $J_{4\text{-H}(2),5}$ = 7.9 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 1.3 Hz, 1 H, 4-H^2 (*syn*,*trans*-**41**)]^A, 2.77 [m_c, possibly interpretable as ddd, $J_{3,4}$ = 11.0 and 8.2 Hz, $J_{3,1'}$ = 2.8 Hz, 1 H, 3-H (*syn*,*cis*-**41**)], 2.84 [ddd, $J_{3.4\text{-H}(1)}$ = $J_{3,4\text{-H}(2)}$ = 9.4 Hz, $J_{3,1'}$ = 2.7 Hz, 1 H, 3-H (*syn*,*trans*-**41**)], 3.17 [br. s, 1 H, OH (*syn*,*cis*-**41**)] superimposed by 3.22 [br. s, 1 H, OH (*syn*,*trans*-**41**)], 3.85 [m_c, possibly interpretable as dd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(!),5}$ = 10.1 Hz, 1 H, 6-H^1 (*syn*,*cis*-**41**)] superimposed by 3.88 [m_c, possibly interpretable as dd J_{gem} = 11.2 Hz, $J_{6\text{-H}(!),5}$ = 9.5 Hz, 1 H, 6-H^1 (*syn*,*trans*-**41**)], 4.19 [m_c, possibly interpretable as ddd, J_{gem} = 11.0 Hz, $J_{6\text{-H}(2),5}$ = 4.3 Hz, $^4J_{6\text{-H}(2),4\text{-H}(2)}$ = 1.2 Hz, 1 H, 6-H^2 (*syn*,*trans*-**41**)], 4.25 [m_c, possibly interpretable as ddd, J_{gem} = 11.0 Hz, $J_{6\text{-H}(2),5}$ = 4.6 Hz, $^4J_{6\text{-H}(2),4\text{-H}(2)}$ = 1.9 Hz, 1 H, 6-H^2 (*syn*,*cis*-**41**)], 5.42 [d, $J_{1',3}$ = 2.4 Hz, 1 H, 1′-H (*syn*,*trans*-**41**)], 5.48 [d, $J_{1',3}$ = 2.5 Hz, 1 H, 1′-H (*syn*,*cis*-**41**)], 7.23 [m_c, 2 H, 2 × *ortho*-H (both diastereomers)], 7.47 [m_c, 2 H, 2 × *meta*-H (both diastereomers)]. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.77 [3-H (*syn*,*cis*-**41**)] ↔ δ = 1.47–1.53 [4-H$_2$ (*syn*,*cis*-**41**)]; δ = 2.84 [3-H (*syn*,*trans*-**41**)] ↔ δ = 1.14 [4-H^1 (*syn*,*trans*-**41**)] and 2.00 [4-H^2 (*syn*,*trans*-**41**)]; δ = 3.85 [6-H^1 (*syn*,*cis*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]; δ = 3.88 [6-H^1 (*syn*,*trans*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]; δ = 4.19 [6-H^2 (*syn*,*trans*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]; δ = 4.25 [6-H^2 (*syn*,*cis*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]. ^{13}C NMR (100.62 MHz, $CDCl_3$, 66:33 mixture of diastereomers): δ = 16.76 [C-5-Me (*syn*,*trans*-**41**)]^A, 17.04 [C-5-Me (*syn*,*cis*-**41**)]^A, 25.25 [C-4 (*syn*,*trans*-**41**)]^A, 27.16 [C-4 (*syn*,*cis*-**41**)]^A, 27.70 [C-5 (*syn*,*trans*-**41**)]^A, 28.32 [C-5 (*syn*,*cis*-**41**)]^A, 44.37 [C-3 (*syn*,*trans*-**41**)]^A, 48.00 [C-3 (*syn*,*cis*-**41**)]^A, 71.03 [C-1′ (*syn*,*trans*-**41**)]^A, 71.67 [C-1′ (*syn*,*cis*-**41**)]^A, 73.47 [C-6 (*syn*,*trans*-**41**)]^A, 75.05 [C-6 (*syn*,*cis*-**41**)]^A, 121.26 [C-*para* (*syn*,*trans*-**41**)], 121.28 [C-*para* (*syn*,*cis*-**41**)], 127.52 [2 × C-*ortho* (*syn*,*trans*-**41**)]^A, 127.60 [2 × C-*ortho* (*syn*,*cis*-**41**)]^B, 131.52 [2 × C-*meta* (*syn*,*cis*-**41**)]^B, 131.54 [2 × C-*meta* (*syn*,*trans*-**41**)]^A, 139.83 [C-*ipso* (*syn*,*trans*-**41**)], 140.16 [C-*ipso* (*syn*,*cis*-**41**)], 172.93 [C-2 (*syn*,*cis*-**41**)], 174.69 [C-2 (*syn*,*trans*-**41**)]. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 16.76 [C-5-Me (*syn*,*trans*-**41**)] ↔ δ = 0.91 [5-Me (*syn*,*trans*-**41**)]; δ = 17.04 [C-5-Me (*syn*,*cis*-**41**)] ↔ δ = 0.92 [5-Me (*syn*,*cis*-**41**)]; δ = 25.25 [C-4 (*syn*,*trans*-**41**)] ↔ δ = 1.14 [4-H^1 (*syn*,*trans*-**41**)] and 2.00 [4-H^2 (*syn*,*trans*-**41**)]; δ = 27.16 [C-4 (*syn*,*cis*-**41**)] ↔ δ = 1.47–1.53 [4-H$_2$ (*syn*,*cis*-**41**)]; δ = 27.70 [C-5 (*syn*,*trans*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]; δ = 28.32 [C-5 (*syn*,*cis*-**41**)] ↔ δ = 1.92–2.16 [5-H (both diastereomers)]; δ = 44.37 [C-3 (*syn*,*trans*-**41**)] ↔ δ = 2.84 [3-H (*syn*,*trans*-**41**)]; δ = 48.00 [C-3 (*syn*,*cis*-**41**)] ↔ δ = 2.77 [3-H (*syn*,*cis*-**41**)]; δ = 71.03 [C-1′ (*syn*,*trans*-**41**)] ↔ δ = 5.42 [1′-H (*syn*,*trans*-**41**)]; δ = 71.67 [C-1′ (*syn*,*cis*-**41**)] ↔ δ = 5.48 [1′-H (*syn*,*cis*-**41**)]; δ = 73.47 [C-6 (*syn*,*trans*-**41**)] ↔ δ = 3.88 [6-H^1 (*syn*,*trans*-**41**)] and 4.19 [6-H^2 (*syn*,*trans*-**41**)]; δ = 75.05 [C-6 (*syn*,*cis*-**41**)] ↔ δ = 3.85 [6-H^1 (*syn*,*cis*-**41**)] and 4.25 [6-H^2 (*syn*,*cis*-**41**)]; δ = 127.52 [2 × C-*ortho* (*syn*,*trans*-**41**)] ↔ δ = 7.23 [2 × *ortho*-H (both diastereomers)]; δ = 131.54 [2 × C-*meta* (*syn*,*trans*-**41**)] ↔ δ = 7.47 [2 × *meta*-H (both diastereomers)]; ^{B} the indicated nuclei were assigned in analogy to *syn*-**41**. IR (film): $\tilde{\nu}$ = 3440, 2960, 1725, 1490, 1460, 1400, 1345, 1220, 1175, 1165, 1095, 1070, 1050, 1030, 1010 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02773; found 299.02786 (+0.4 ppm).

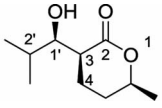
***rel*-(3*S*,5*R*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-5-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*trans*-41)**



Following the **General Procedure B** the title compound was prepared from γ-methyl-δ-lactone (**20**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 19–27) rendered the product as a colorless solid (245 mg, 82%, *anti*,*trans*-**41**/*anti*,*cis*-**41** = 75:25). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 3:4:68:25; *syn*/*anti* 7:93; *syn*,*trans*/*syn*,*cis* 41:59, *anti*,*trans*/*anti*,*cis* 73:27 [determined by integration of the signals at δ = 4.77 (1′-H *anti*,*trans*-**41**) vs. δ = 4.80 (1′-H, *anti*,*cis*-**41**) vs. δ = 5.43 (1′-H, *syn*,*trans*-**41**) vs. δ = 5.48 (1′-H, *syn*,*cis*-**41**) in the 400 MHz ^{1}H NMR spectrum of the crude product], m.p. 60 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, 75:25 mixture of diastereomers): δ = 0.90 [d, $J_{5\text{-Me},5}$ = 6.8 Hz, 3 H, 5-Me (*anti*,*trans*-**41**)] superimposed by 0.91 [d, $J_{5\text{-Me},5}$ = 6.7 Hz, 3 H, 5-Me (*anti*,*cis*-**41**)], 1.05 [m_c, possibly interpretable as ddd, J_{gem} = $J_{4\text{-H}(1),3}$ = 13.2 Hz, $J_{4(1),5}$ = 10.5 Hz, 1 H, 4-H^1 (*anti*,*cis*-**41**)]^A, 1.11 [m_c, possibly interpretable as ddd, J_{gem} = 13.8 Hz, $J_{4\text{-H}(1),3}$ = 9.0 Hz, $J_{4(1),5}$ = 7.2 Hz, 1 H, 4-H^1 (*anti*,*trans*-**41**)]^A, 1.44 [m_c, possibly interpretable as dddd, J_{gem} = 13.5 Hz, $J_{4\text{-H}(2),3}$ = 6.7 Hz, $J_{4\text{-H}(2),5}$ = 4.7 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 2.0 Hz, 1 H, 4-H^2 (*anti*,*cis*-**41**)]^A, 1.59 [m_c, possibly interpretable as dddd, J_{gem} = 13.8 Hz, $J_{4\text{-H}(2),3}$ = 10.8 Hz, $J_{4\text{-H}(2),5}$ = 8.4 Hz, $^4J_{4\text{-H}(2),6\text{-H}(2)}$ = 0.8 Hz, 1 H, 4-H^2 (*anti*,*trans*-**41**)]^A, 1.97–2.14 [m, 1 H, 5-H (both diastereomers)]^A, 2.66 [m_c, possibly interpretable as ddd, $J_{3,4\text{-H}(1)}$ = 12.8 Hz, $J_{3,1'}$ = 8.7 Hz, $J_{3,4\text{-H}(2)}$ = 6.7 Hz, 1 H, 3-H (*anti*,*cis*-**41**)], 2.75 [ddd, $J_{3.4\text{-H}(2)}$ = 10.7 Hz, $J_{3,4\text{-H}(1)}$ = $J_{3,1'}$ = 8.8 Hz, 1 H, 3-H (*anti*,*trans*-**41**)], 3.86 [m_c, possibly interpretable as dd, J_{gem} = 11.2 Hz, $J_{6\text{-H}(1),5}$ = 9.3 Hz, 1 H, 6-H^1 (*anti*,*cis*-**41**)] superimposed by 3.91 [m_c, possibly interpretable as dd J_{gem} = $J_{6\text{-H}(1),5}$ = 10.7 Hz, 1 H, 6-H^1 (*anti*,*trans*-**41**)], 4.21 [m_c, possibly interpretable as ddd, J_{gem} = 11.1 Hz, $J_{6\text{-H}(2),5}$ = 4.8 Hz, $^4J_{6\text{-H}(2),4\text{-H}(2)}$ = 0.9 Hz, 1 H, 6-H^2 (*anti*,*trans*-**41**)], 4.32 [m_c, possibly interpretable as ddd, J_{gem} = 11.2 Hz, $J_{6\text{-H}(2),5}$ = 4.8 Hz, $^4J_{6\text{-H}(2),4\text{-H}(2)}$ = 2.0 Hz, 1 H, 6-H^2 (*anti*,*cis*-**41**)], 4.41 [br. s, 1 H, OH (*anti*,*trans*-**41**)], 4.77 [d, $J_{1',3}$ = 8.7 Hz, 1 H, 1′-H (*anti*,*trans*-**41**)], 4.80 [d, $J_{1',3}$ = 8.5 Hz, 1 H, 1′-H (*anti*,*cis*-**41**)], 4.38 [br. s, 1 H, OH (*anti*,*cis*-**41**)], 7.24 [m_c, 2 H, 2 × *ortho*-H (both diastereomers)], 7.50 [m_c, 2 H, 2 × *meta*-H (both diastereomers)]. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.66 [3-H (*anti*,*cis*-**41**)] ↔ δ = 1.05 [4-H^1 (*anti*,*cis*-**41**)] and 1.44 [4-H^2 (*anti*,*cis*-**41**)]; δ = 2.75 [3-H (*anti*,*trans*-**41**)] ↔ δ = 1.11 [4-H^1 (*anti*,*trans*-**41**)] and 1.59 [4-H^2 (*anti*,*trans*-**41**)]; δ = 3.86 [6-H^1 (*anti*,*cis*-**41**)] and 4.32 [6-H^2 (*anti*,*cis*-**41**)] ↔ δ = 1.97–2.14 [5-H (both diastereomers)]; δ = 3.91 [6-H^1 (*anti*,*trans*-**41**)] and 4.21 [6-H^2 (*anti*,*trans*-**41**)] ↔ δ = 1.97–2.14 [5-H (both diastereomers)]. ^{13}C NMR (100.62 MHz, $CDCl_3$, 75:25 mixture of diastereomers): δ = 16.83 [C-5-Me (*anti*,*trans*-**41**)]^A, 17.33 [C-5-Me (*anti*,*cis*-**41**)]^A, 27.29 [C-5 (*anti*,*trans*-**41**)]^A, 28.18 [C-5 (*anti*,*cis*-**41**)]^A, 29.22 [C-4 (*anti*,*trans*-**41**)]^A, 31.08 [C-4 (*anti*,*cis*-**41**)]^A, 44.36 [C-3 (*anti*,*trans*-**41**)]^A, 47.13 [C-3 (*anti*,*cis*-**41**)]^A, 72.93 [C-6 (*anti*,*trans*-**41**)]^A, 74.28 [C-1′ (*anti*,*trans*-**41**)]^A, 74.70 [C-1′ (*anti*,*cis*-**41**)]^A, 75.00 [C-6 (*an-*

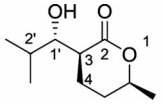
ti,*cis*-**41**)][A], 122.23 [C-*para* (*anti*,*cis*-**41**)], 122.26 [C-*para* (*anti*,*trans*-**41**)], 128.80 [2 × C-*ortho* (*anti*,*trans*-**41**)][A], 128.85 [2 × C-*ortho* (*anti*,*cis*-**41**)][B], 131.76 [2 × C-*meta* (*anti*,*cis*-**41**)][B], 131.80 [2 × C-*meta* (*anti*,*trans*-**41**)][A], 139.16 139.83 [C-*ipso* (*anti*,*trans*-**41**)], 139.34 [C-*ipso* (*anti*,*cis*-**41**)], 174.62 [C-2 (*anti*,*cis*-**41**)], 175.72 [C-2 (*anti*,*trans*-**41**)]. [A]The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 16.83 [C-5-Me (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 0.90 [5-Me (*anti*,*trans*-**41**)]; δ = 17.33 [C-5-Me (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 0.91 [5-Me (*anti*,*cis*-**41**)]; δ = 27.29 [C-5 (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 1.97–2.14 [5-H (both diastereomers)]; δ = 28.18 [C-5 (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 1.97–2.14 [5-H (both diastereomers)]; δ = 29.22 [C-4 (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 1.11 [4-H^1 (*anti*,*trans*-**41**)] and 1.59 [4-H^2 (*anti*,*trans*-**41**)]; δ = 31.08 [C-4 (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 1.05 [4-H^1 (*anti*,*cis*-**41**)] and 1.44 [4-H^2 (*anti*,*cis*-**41**)]; δ = 44.36 [C-3 (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 2.75 [3-H (*anti*,*trans*-**41**)]; δ = 47.13 [C-3 (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 2.66 [3-H (*anti*,*cis*-**41**)]; δ = 72.93 [C-6 (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 3.91 [6-H^1 (*anti*,*trans*-**41**)] and 4.21 [6-H^2 (*anti*,*trans*-**41**)]; δ = 74.28 [C-1′ (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 4.77 [1′-H (*anti*,*trans*-**41**)]; δ = 74.70 [C-1′ (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 4.80 [1′-H (*anti*,*cis*-**41**)]; δ = 75.00 [C-6 (*anti*,*cis*-**41**)] $\leftrightarrow \delta$ = 3.86 [6-H^1 (*anti*,*cis*-**41**)] and 4.32 [6-H^2 (*anti*,*cis*-**41**)]; δ = 128.80 [2 × C-*ortho* (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 7.24 [2 × *ortho*-H (both diastereomers)]; δ = 131.80 [2 × C-*meta* (*anti*,*trans*-**41**)] $\leftrightarrow \delta$ = 7.50 [2 × *meta*-H (both diastereomers)]. IR (film): $\tilde{\nu}$ = 3450, 2960, 1720, 1485, 1460, 1400, 1345, 1165, 1095, 1070, 1045, 1010, 915, 835, 745 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.02773; found 299.02774 (±0.0 ppm).

***rel*-(3*S*,6*S*)-3-[(*R*)-1-Hydroxy-2-methylpropyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*cis*-42)**



Following the **General Procedure A** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 20–26) rendered the main diastereomer as a colorless oil (140 mg, 75%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 14:85:0:1; *syn*/*anti* 99:1; *syn*,*trans*/*syn*,*cis* 14:86, *anti*,*trans*/*anti*,*cis* <5:95. [The 300 MHz ^1H NMR spectrum of the crude product was too contaminated by byproducts to integrate any signals. A short column chromatographic separation (2.0 × 10 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 11–24) was conducted to get rid of most byproducts and a 400 MHz ^1H NMR spectrum of the product thus obtained was recorded. Integration of the signals at δ = 3.54 (1′-H_3, *anti*,*cis*-**42**) vs. δ = 3.83 (1′-H, *syn*,*cis*-**42**) vs. δ = 3.96 (1′-H, *syn*,*trans*-**42**) resulted in *syn*/*anti* 99:01 and *syn*/*iso*-*syn* 86:13. The NMR contained no signal clearly attributable to *anti*,*trans*-**42**.] ^1H NMR (400.13 MHz, $CDCl_3$): δ = 0.86 (d, $J_{2'\text{-Me},2'}$ = 6.8 Hz, 3 H, 2′-Me), 1.05 (d, $J_{3',2'}$ = 6.5 Hz, 3 H, 3′-H_3), 1.37 (d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me), 1.57–1.68 (m, 1 H, 5-H^1)[A] superimposed by 1.68 (dqq, $J_{2',1'}$ = 9.7 Hz, $J_{2',2'\text{-Me}} = J_{2',3'}$ = 6.6 Hz, 1 H, 2′-H)[A], 1.85–2.03 (m, 3 H, 4-H_2, 5-H^2)[A], 2.63–2.71 (m, 2 H, 3-H, OH)[A], 3.83 (m_c, possibly interpretable as dd, $J_{1',2'}$ = 9.8 Hz, $J_{1',3}$ = 2.0 Hz, 1 H, 1′-H)[A], 4.46 (m_c, possibly interpretable as dqd, $J_{6,5}$ = 10.6 and 2.6 Hz, $J_{6,6\text{-Me}}$ = 6.3 Hz, 1 H, 6-H)[A]. [A]The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 0.86 (2′-Me) $\leftrightarrow \delta$ = 1.68 (2′-H) and δ = 1.05 (3′-H_3) $\leftrightarrow \delta$ = 1.68 (2′-H); δ = 1.68 (2′-H) $\leftrightarrow \delta$ = 3.83 (1′-H); δ = 3.83 (1′-H) $\leftrightarrow \delta$ = 2.63–2.71 (3-H); δ = 2.63–2.71 (3-H) $\leftrightarrow \delta$ = 1.85–2.03 (m, 4-H_2, 5-H^2); δ = 1.37 (6-Me) $\leftrightarrow \delta$ = 4.46 (6-H); δ = 4.46 (6-H) $\leftrightarrow \delta$ = 1.57–1.68 (5-H^1); δ = 4.46 (6-H) $\leftrightarrow \delta$ = 1.85–2.03 (m, 4-H_2, 5-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.39 (C-4)[A], 18.83 (C-2′-Me)[A], 19.85 (C-3′)[A], 20.89 (C-6-Me)[A], 28.98 (C-5)[A], 29.72 (C-2′)[A], 41.06 (C-3)[A], 74.75 (C-6)[A], 75.02 (C-1′)[A], 176.18 (C-2) ppm. [A]The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 15.39 (C-4) $\leftrightarrow \delta$ = 1.85–2.03 (4-H_2, 5-H^2); δ = 18.83 (C-2′-Me) $\leftrightarrow \delta$ = 0.86 (2′-Me); δ = 19.85 (C-3′) $\leftrightarrow \delta$ = 1.05 (3′-H_3); δ = 20.89 (C-6-Me) $\leftrightarrow \delta$ = 1.37 (6-Me); δ = 28.98 (C-5) $\leftrightarrow \delta$ = 1.57–1.68 (5-H^1) and 1.85–2.03 (4-H_2, 5-H^2); δ = 29.72 (C-2′) $\leftrightarrow \delta$ = 1.68 (2′-H); δ = 41.06 (C-3) $\leftrightarrow \delta$ = 2.63–2.71 (3-H); δ = 74.75 (C-6) $\leftrightarrow \delta$ = 4.46 (6-H); δ = 75.02 (C-1′) $\leftrightarrow \delta$ = 3.83 (1′-H). IR (film): $\tilde{\nu}$ = 3480, 2980, 2875, 2360, 2250, 1720, 1470, 1385, 1200, 1130, 1075, 910, 735, 650 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.13287; found 187.13292 (+0.3 ppm). $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.26, H 9.78.

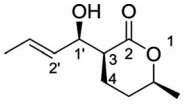
***rel*-(3*S*,6*S*)-3-[(*S*)-1-Hydroxy-2-methylpropyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*cis*-42)**



Following the **General Procedure B** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and isobutyraldehyde (**22**, 144 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 18–24) rendered the main diastereomer as a colorless oil (115 mg, 62%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 0:6:23:71; *syn*/*anti* 6:94; *syn*,*trans*/*syn*,*cis* <5:95, *anti*,*trans*/*anti*,*cis* 24:76 [determined by integration of the signals at δ = 2.44 (3-H, *anti*,*trans*-**42**) vs. δ = 2.51–2.61 (3-H, *anti*,*cis*-**42**) vs. δ = 2.63–2.71 (3-H, *syn*,*cis*-**42**) in the 400 MHz ^1H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*trans*-**42**]. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 0.92 (d, $J_{2'\text{-Me},2'}$ = 6.8 Hz, 3 H, 2′-Me)[A], 1.03 (d, $J_{3',2'}$ = 7.3 Hz, 3 H, 3′-H_3)[A], 1.37 (d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me), 1.52–1.69 (m, 2 H, 4-H^1, 5-H^1)[A], 1.85 (qqd, $J_{2',3'} = J_{2',2\text{-Me}}$ = 6.8 Hz, $J_{2',1'}$ = 3.8 Hz, 1 H, 2′-H), 1.94–2.06 (m, 2 H, 4-H^2, 5-H^2)[A], 2.51–2.61 (m, 1 H, 3-H)[A], 3.56 (m_c, possibly interpretable as dd, $J_{1',3}$ = 7.6 Hz, $J_{1',2'}$ = 3.7 Hz, 1 H, 1′-H)[A], 3.66 (br. s, 1 H, OH), 4.43–4.53 (m, 1 H, 6-H)[A]. [A]The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 1.86 (2′-H) $\leftrightarrow \delta$ = 0.92 (2′-Me); δ = 1.85 (2′-H) $\leftrightarrow \delta$ = 1.03 (3′-H_3); δ = 1.85 (2′-H) $\leftrightarrow \delta$ = 3.56 (1′-H); δ = 3.56 (1′-H) $\leftrightarrow \delta$ = 2.51–2.61 (3-H); δ = 2.51–2.61 (3-H) $\leftrightarrow \delta$ = 1.52–1.69 (4-H^1, 5-H^1); δ = 2.51–2.61 (3-H) $\leftrightarrow \delta$ = 1.94–2.06 (4-H^2, 5-H^2); δ = 1.37 (6-Me) $\leftrightarrow \delta$ = 4.43–4.53 (6-H); δ = 4.43–4.53 (6-H) $\leftrightarrow \delta$ = 1.52–1.69 (4-H^1, 5-H^1); δ = 4.43–4.53 (6-H) $\leftrightarrow \delta$ = 1.94–2.06 (4-H^2, 5-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.02 (C-2′-Me)[A], 20.00 (C-4)[B], 20.20 (C-3′)[A], 20.73 (C-6-Me)[A], 28.61 (C-5)[B], 29.19 (C-2′)[A], 41.60 (C-3)[A], 74.28 (C-6)[A], 75.52 (C-1′)[A], 176.66 (C-2) ppm. [A]The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 15.02 (C-2′-Me) $\leftrightarrow \delta$ = 0.92 (2′-Me); δ = 20.20 (C-

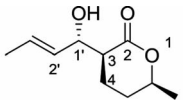
3′) ↔ δ = 1.03 (3′-H_3); δ = 20.73 (C-6-Me) ↔ δ = 1.37 (6-Me); δ = 29.19 (C-2′) ↔ δ = 1.86 (2′-H); δ = 41.60 (C-3) ↔ δ = 2.51–2.61 (3-H); δ = 74.28 (C-6) ↔ δ = 4.43–4.53 (6-H); δ = 75.52 (C-1′) ↔ δ = 1.56 (1′-H); [B] these nuclei produce identical crosspeaks in the C,H-COSY spectrum, because their respective protons have identical chemical shifts. They were assigned by their chemical shifts. IR (film): ṽ = 3530, 2980, 2875, 2360, 2245, 1720, 1465, 1390, 1130, 1170, 915, 735 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{10}H_{19}O_3$ $[M + H]^+$ 187.13287; found 187.13290 (+0.2 ppm). $C_{10}H_{18}O_3$ (186.25): calcd. C 64.49, H 9.74; found C 64.32, H 9.73.

***rel*-(3*S*,6*S*)-3-[(*R*,*trans*)-1-Hydroxybut-2-enyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*cis*-43)**



Following the **General Procedure A** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 17–22) rendered the product as a colorless oil (131 mg, 71%, *syn*,*cis*-**43**:*syn*,*trans*-**43** = 90:10). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 27:73:0:0; *syn*/*anti* >95:5; *syn*,*trans*/*syn*,*cis* 27:73, *anti*,*trans*/*anti*,*cis* <5:95 [integration of the signals at δ = 4.53 (1′-H, *syn*,*cis*-**43**) vs. δ = 5.46–5.56 (2′-H, *syn*,*cis*-**43** + *syn*,*trans*-**43**) as well as δ = 3.04 (OH, *syn*,*cis*-**43**) vs. δ = 3.16 (OH, *syn*,*trans*-**43**) in the 400 MHz ^1H NMR spectrum of the crude product resulted in *syn*/*iso*-*syn* 73:27; the NMR contained no signal clearly attributable to *anti*,*cis*-**43** or *anti*,*trans*-**43**]. ^1H NMR (400.13 MHz, $CDCl_3$, contains 10% *syn*,*trans*-**43** with signals at δ = 1.34 and 3.20): δ = 1.34 (d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me), 1.54–1.65 (m, 1 H, 5-H^1)[A], 1.69 (m_c, possibly interpretable as ddd, $J_{4',3'}$ = 6.5 Hz, $^4J_{4',2'}$ = 1.5 Hz, $^5J_{4',1'}$ = 0.9 Hz, 3 H, 4′-H_3), 1.76–1.97 (m, 3 H, 4-H_2, 5-H^2)[A], 2.64 (m_c, possibly interpretable as ddd, $J_{3,4}$ = 10.3 and 8.5 Hz, $J_{3,1'}$ = 2.9 Hz, 1 H, 3-H), 3.06 (d, $J_{OH,1'}$ = 5.8 Hz, 1 H, OH) 4.28 (m_c, possibly interpretable as dqd, $J_{6,5}$ = 9.6 and 3.2 Hz, $J_{6,6\text{-Me}}$ = 6.4 Hz, 1 H, 6-H), 4.50 (br. m_c, possibly interpretable as br. dd, $J_{1',2'}$ = 7.7 Hz, $J_{1',OH}$ = 6.0 Hz, 1 H, 1′-H), 5.49 (ddq, $J_{2',3'}$ = 15.1 Hz, $J_{2',1'}$ = 6.9 Hz, $^4J_{2',4'}$ = 1.6 Hz, 1 H, 2′-H), 5.74 (dqd, $J_{3',2'}$ = 15.2 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 1.2 Hz, 1 H, 3′-H) ppm. [A]The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.28 (6-H) ↔ δ = 1.54–1.65 (5-H^1); δ = 4.28 (6-H) ↔ δ = 1.76–1.97 (4-H_2, 5-H^2); δ = 2.64 (3-H) ↔ δ = 1.76–1.97 (4-H_2, 5-H^2). ^{13}C NMR (100.62 MHz, $CDCl_3$, 90:10 mixture of diastereomers): δ = 17.51 [C-4 (*syn*,*cis*-**43**)][A], 17.77 [C-4′ (both diastereomers)][A,B], 20.93 [C-6-Me (*syn*,*cis*-**43**)][A], 21.10 [C-4 (*syn*,*trans*-**43**)][B], 21.93 [C-6-Me (*syn*,*trans*-**43**)][B], 28.65 [C-5 (*syn*,*cis*-**43**)][A], 30.37 [C-5 (*syn*,*trans*-**43**)][B], 43.80 [C-3 (*syn*,*cis*-**43**)][A], 46.47 [C-3 (*syn*,*trans*-**43**)][B], 71.50 [C-1′ (*syn*,*cis*-**43**)][A], 72.92 [C-6 (*syn*,*trans*-**43**)][B], 75.08 [C-6 (*syn*,*cis*-**43**)][A], 78.01 [C-1′ (*syn*,*trans*-**43**)][B], 128.57 [C-3′ (*syn*,*cis*-**43**)][A], 128.91 [C-3′ (*syn*,*trans*-**43**)][B], 129.65 [C-2′ (*syn*,*cis*-**43**)][A], 129.94 [C-2′ (*syn*,*trans*-**43**)][B], 173.34 [C-2 (*syn*,*trans*-**43**)][B], 175.07 [C-2 (*syn*,*cis*-**43**)]. [A]The indicated nuclei – they are non-quaternary – belong to *syn*,*cis*-**43** and were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 17.51 (C-4) ↔ δ = 1.76–1.97 (4-H_2, 5-H^2); δ = 17.77 (C-4′) ↔ δ = 1.69 (4′-H_3); δ = 20.93 (C-6-Me) ↔ δ = 1.34 (6-Me); δ = 28.65 (C-5) ↔ δ = 1.54–1.65 (5-H^1) and 1.76–1.97 (4-H_2, 5-H^2); δ = 43.80 (C-3) ↔ δ = 2.64 (3-H); δ = 71.50 (C-1′) ↔ δ = 4.50 (1′-H); δ = 75.08 (C-6) ↔ δ = 4.28 (6-H); δ = 128.57 (C-3′) ↔ δ = 5.74 (3′-H); δ = 129.65 (C-2′) ↔ δ = 5.49 (2′-H); [B]The indicated nuclei belong to *syn*,*trans*-**43** and were assigned in analogy with the corresponding nuclei in *syn*,*cis*-**43**. IR (film): ṽ = 3450, 2935, 1720, 1450, 1385, 1245, 1200, 1080, 970, 770, 700, 640 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_9H_{16}O_2$ $[M - H_2O]^+$ 166.09938; found 166.09920 (δ = –1.1 ppm).

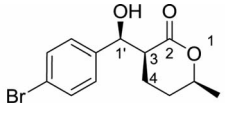
***rel*-(3*S*,6*S*)-3-[(*R*,*trans*)-1-Hydroxybut-2-enyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*cis*-43)**



Following the **General Procedure B** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and crotonaldehyde (**23**, 140 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 18–24) rendered the product as a colorless oil (134 mg, 73%, *anti*,*cis*-**43**/*anti*,*trans*-**43** 77:23). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 0:6:24:71; *syn*/*anti* 6:94; *syn*,*trans*/*syn*,*cis* <5:95, *anti*,*trans*/*anti*,*cis* 25:75 [determined by integration of the signals at δ = 4.20 (1′-H, *anti*,*cis*-**43**) vs. δ = 4.27 (1′-H, *anti*,*trans*-**43**) vs. δ = 4.52 (1′-H, *syn*,*cis*-**43**) in the 400 MHz ^1H NMR spectrum of the crude product; the NMR contained no signal clearly attributable to *syn*,*trans*-**43**]. ^1H NMR (400.13 MHz, $CDCl_3$, 77:23 mixture of diastereomers): δ = 1.37 [d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me (*anti*,*cis*-**43**)] superimposed by 1.39 [d, $J_{6\text{-Me},6}$ = 6.3 Hz, 3 H, 6-Me (*anti*,*trans*-**43**)], 1.45–1.64 [m, 2 H, 4-H^1 (both diastereomers), 5-H^1 (both diastereomers)][A], 1.71–1.74 [m, 3 H, 4′-H_3 (both diastereomers)], 1.89–2.02 [m, 2 H, 4-H^2 (both diastereomers), 5-H^2 (both diastereomers)][A], 2.38–2.53 {m, possibly interpretable as δ = 2.42 [ddd, $J_{3,4}$ = 12.0 und 6.6 Hz, $J_{3,1'}$ = 8.2 Hz, 1 H, 3-H(*anti*,*trans*-**43**)], δ = 2.49 [ddd, $J_{3,4}$ = 11.0 und 8.2 Hz, $J_{3,1'}$ = 8.2 Hz, 1 H, 3-H (*anti*,*cis*-**43**)]}, 3.95 [br. s, 1 H, OH (*anti*,*cis*-**43**)][A], 4.20 [br. dd, $J_{1',3}$ = $J_{1',2'}$ = 7.9 Hz, 1 H, 1′-H (*anti*,*cis*-**43**)], 4.27 [br. dd, $J_{1',2'}$ = $J_{1',3'}$ = 8.1 Hz, 1 H, 1′-H (*anti*,*trans*-**43**)], 4.32 [br. s, 1 H, OH (*anti*,*trans*-**43**)], 4.39–4.50 [m, 1 H, 6-H (both diastereomers)], 5.41–5.52 {m, possibly interpretable as δ = 5.45 [ddq, $J_{2',3'}$ = 15.1 Hz, $J_{2',1'}$ = 7.7 Hz, $^4J_{2',4'}$ = 1.6 Hz, 1 H, 2′-H (*anti*,*trans*-**43**)], δ = 5.48 [ddq, $J_{2',3'}$ = 15.3 Hz, $J_{2',1'}$ = 7.8 Hz, $^4J_{2',4'}$ = 1.6 Hz, 2′-H (*anti*,*cis*-**43**)][A]}, 5.72–5.83 {m, possibly interpretable as δ = 5.77 [dqd, $J_{3',2'}$ = 15.2 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 0.8 Hz, 1 H, 3′-H (*anti*,*trans*-**43**)], δ = 5.78 [dqd, $J_{3',2'}$ = 15.3 Hz, $J_{3',4'}$ = 6.5 Hz, $^4J_{3',1'}$ = 0.9 Hz, 1 H, 3′-H (*anti*,*cis*-**43**)]}. [A]The indicated protons – they all belong to *anti*,*cis*-**43** – were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 4.20 (1′-H) ↔ δ = 5.41–5.52 (2′-H); δ = 4.20 (1′-H) ↔ δ = 3.95 (OH); δ = 4.20 (1′-H) ↔ δ = 2.38–2.53 (3-H); δ = 2.38–2.53 (3-H) ↔ δ = 1.45–1.64 (4-H^1, 5-H^1); δ = 2.38–2.53 (3-H) ↔ δ = 1.89–2.02 (4-H^2, 5-H^2); δ = 4.39–4.60 (6-H) ↔ δ = 1.45–1.64 (4-H^1, 5-H^1); δ = 4.39–4.60 (6-H) ↔ δ = 1.89–2.02 (4-H^2, 5-H^2). ^{13}C NMR (100.62 MHz, $CDCl_3$, 77:23 mixture of diastereomers): δ = 17.80 [C-4′ (*anti*,*trans*-**43**)][A], 17.83 [C-4′ (*anti*,*cis*-**43**)][A], 20.30 [C-4* (*anti*,*cis*-**43**)][A], 20.85 [C-6-Me (*anti*,*cis*-**43**)][A], 22.06 [C-6-Me (*anti*,*trans*-**43**)][A], 23.12 [C-4 (*anti*,*trans*-**43**)**][A], 28.47 [C-5* (*anti*,*cis*-**43**)][A], 30.41 [C-5 (*anti*,*trans*-**43**)**][A], 43.94 [C-3 (*anti*,*cis*-**43**)][A], 46.05 [C-3 (*anti*,*trans*-**43**)][A], 73.33 [C-1′ (*anti*,*cis*-**43**)][A], 74.04 [C-1′ (*anti*,*trans*-**43**)][A], 74.69 [C-6 (*anti*,*cis*-**43**)][A], 78.57 [C-6 (*anti*,*trans*-**43**)][A], 129.87, 129.89 [C-2′, C-3′ (*anti*,*cis*-**43**)][B], 129.99, 130.18 [C-2′, C-3′ (*anti*,*trans*-**43**)][B], 174.42 [C-2 (*anti*,*trans*-**43**)], 176.17 [C-2 (*anti*,*cis*-**43**)]. [A] the indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum

["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 17.80 [C-4′(*anti*,*trans*-**43**)] ↔ δ = 1.71–1.74 [4′-H_3 (both diastereomers)]; δ = 17.83 [C-4′ (*anti*,*cis*-**43**)] ↔ δ = 1.71–1.74 [4′-H_3 (both diastereomers)]; δ = 20.30 [C-4* (*anti*,*cis*-**43**)] ↔ δ = 1.45–1.64 [4-H^1 (both diastereomers), 5-H^1 (both diastereomers)] and 1.89–2.02 [4-H^2 (both diastereomers), 5-H^2 (both diastereomers)]; δ = 20.85 [C-6-Me (*anti*,*cis*-**43**)] ↔ δ = 1.37 [6-Me (*anti*,*cis*-**43**)]; δ = 22.06 [C-6-Me (*anti*,*trans*-**43**)] ↔ δ = 1.39 [6-Me (*anti*,*trans*-**43**)]; δ = 23.12 [C-4 (*anti*,*trans*-**43**)**] ↔ δ = 1.45–1.64 [4-H^1 (both diastereomers), 5-H^1 (both diastereomers)] and 1.89–2.02 [4-H^2 (both diastereomers), 5-H^2 (both diastereomers)]; δ = 28.47 [C-5* (*anti*,*cis*-**43**)] ↔ δ = 1.45–1.64 [4-H^1 (both diastereomers), 5-H^1 (both diastereomers)] and 1.89–2.02 [4-H^2 (both diastereomers), 5-H^2 (both diastereomers)]; δ = 30.41 [C-5 (*anti*,*trans*-**43**)**] ↔ δ = 1.45–1.64 [4-H^1 (both diastereomers), 5-H^1 (both diastereomers)] and 1.89–2.02 [4-H^2 (both diastereomers), 5-H^2 (both diastereomers)]; δ = 43.94 [C-3 (*anti*,*cis*-**43**)] ↔ δ = 2.38–2.53 [3-H (both diastereomers)]; δ = 46.05 [C-3 (*anti*,*trans*-**43**)] ↔ δ = 2.38–2.53 [3-H (both diastereomers)]; δ = 73.33 [C-1′ (*anti*,*cis*-**43**)] ↔ δ = 4.20 [1′-H (*anti*,*cis*-**43**)]; δ = 74.04 [C-1′ (*anti*,*trans*-**43**)] ↔ δ = 4.27 [1′-H (*anti*,*trans*-**43**)]; δ = 74.69 [C-6 (*anti*,*cis*-**43**)] ↔ δ = 4.39–4.50 [6-H (both diastereomers)]; δ = 78.57 [C-6 (*anti*,*trans*-**43**)] ↔ δ = 4.39–4.50 [6-H (both diastereomers)]. [B] Designation pairwise interchangeable. IR (film): $\tilde{\nu}$ = 3450, 2935, 1720, 1450, 1385, 1245, 1200, 1080, 970, 770, 700, 640 cm^{-1}. HRMS (CI, NH_3): calcd. for $C_{10}H_{17}O_3$ [M + H]$^+$ 185.11777; found 185.11820 (+2.3 ppm).

***rel*-(3*S*,6*S*)-3-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*syn*,*cis*-44)**

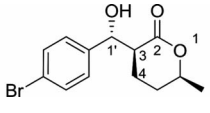


Following the **General Procedure A** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 10–14) rendered the product as a colorless solid (155 mg, 52%). Two further fractions were collected, containing a mixture of both diastereomers (15–16, 36.2 mg, 12%) and *syn*,*trans*-**44** (17–22, 52.1 mg, 17%; overall yield: 81%). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 26:72:1:1; *syn*/*anti* 98:2; *syn*,*trans*/*syn*,*cis* 27:73, *anti*,*trans*/*anti*,*cis* 37:63 [determined by integration of the signals at δ = 4.79 (1′-H *anti*,*cis*-**44**) vs. δ = 4.82 (1′-H, *anti*,*trans*-**44**) vs. δ = 5.44 (1′-H, *syn*,*cis*-**44**) vs. δ = 5.49 (1′-H, *syn*,*trans*-**44**) in the 400 MHz ^{1}H NMR spectrum of the crude product].

Analytical Data for *syn*,*cis*-44: M.p. 84 °C. ^{1}H NMR (400.13 MHz, $CDCl_3$, contains 6% *syn*,*trans*-**44**): δ = 1.34 (d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me), 1.47–1.64 (m, 2 H, 4-H^1, 5-H^1)[A], 1.80–1.92 (m, 2 H, 4-H^2 5-H^2)[A], 2.76 (m_c, possibly interpretable as ddd, $J_{3,4}$ = 10.7 and 8.4 Hz, $J_{3,1'}$ = 2.5 Hz, 1 H, 3-H), 3.18 (d, $J_{OH,1'}$ = 4.0 Hz, 1 H, OH), 4.42 (m_c, possibly interpretable as dqd, $J_{6,5}$ = 9.8 and 3.3 Hz, $J_{6,6\text{-Me}}$ = 6.5 Hz, 1 H, 6-H), 5.43 (br. dd, $J_{1',OH}$ = 3.5 Hz, $J_{1',3}$ = 3.1 Hz, 1 H, 1′-H), 7.23 (m, 2 H, 2 × *ortho*-H), 7.48 (m, 2 H, 2 × *meta*-H) ppm. [A]The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.76 (3-H) ↔ δ = 1.47–1.64 (4-H^1, 5-H^1) and 1.80–1.92 (4-H^2 5-H^2); δ = 4.42 (6-H) ↔ δ = 1.47–1.64 (4-H^1, 5-H^1) and 1.80–1.92 (4-H^2 5-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.84 (C-4)[A], 20.86 (C-6-Me)[B], 28.70 (C-5)[A], 45.21 (C-3)[B], 70.45 (C-1′)[B], 75.07 (C-6)[B], 121.26 (C-*para*), 127.53 (2 × C-*ortho*)[B], 131.53 (2 × C-*meta*)[B], 139.78 (C-*ipso*), 175.24 (C-1) ppm. [A]Assignments interchangeable. [B]The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.63/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 20.86 (C-6-Me) ↔ δ = 1.34 (6-Me); δ = 45.21 (C-3) ↔ δ = 2.76 (3-H); δ = 70.45 (C-1′) ↔ δ = 5.43 (1′-H); δ = 75.07 (C-6) ↔ δ = 4.42 (6-H); δ = 127.53 (2 × C-*ortho*) ↔ δ = 7.23 (2 × *ortho*-H); δ = 131.53 (2 × C-*meta*) ↔ δ = 7.48 (2 × *meta*-H). IR (film): $\tilde{\nu}$ = 3450, 2975, 2935, 1720, 1490, 1390, 1365, 1295, 1205, 1185, 1115, 1095, 1070, 1050, 1010, 960, 835, 820, 770 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ [M + H]$^+$ 299.02773; found 299.02777 (+0.1 ppm).

Analytical Data for *syn*,*trans*-44: ^{1}H NMR (400.13 MHz, $CDCl_3$, contains 6% *syn*,*cis*-**44**): δ = 1.35 (d, $J_{6\text{-Me},6}$ = 6.3 Hz, 3 H, 6-Me), 1.40–1.54 (m, 2 H, 4-H^1, 5-H^1)[A], 1.73–1.92 (m, 2 H, 4-H^2, 5-H^2)[A], 2.72 (m_c, possibly interpretable as ddd, $J_{3,4}$ = 12.1 and 6.7 Hz, $J_{3,1'}$ = 3.0 Hz, 1 H, 3-H), 2.97 (d, $J_{OH,1'}$ = 5.6 Hz, 1 H, OH), 4.38 (m_c, possibly interpretable as dqd, $J_{6,5}$ = 11.2 and 3.0 Hz, $J_{6,6\text{-Me}}$ = 6.3 Hz, 1 H, 6-H), 5.49 (br. dd, $J_{1',OH}$ = 5.4 Hz, $J_{1',3}$ = 3.0 Hz, 1 H, 1′-H), 7.23 (m, 2 H, 2 × *ortho*-H), 7.43 (m, 2 H, 2 × *meta*-H) ppm. [A]The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.72 (3-H) ↔ δ = 1.40–1.54 (4-H^1, 5-H^1) and 1.73–1.92 (4-H^2, 5-H^2); δ = 4.38 (6-H) ↔ δ = 1.40–1.54 (4-H^1, 5-H^1) and 1.73–1.92 (4-H^2, 5-H^2) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 19.45 (C-4)[A], 22.00 (C-6-Me)[B], 30.46 (C-5)[A], 48.17 (C-3)[B], 72.25 (C-1′)[B], 78.33 (C-6)[B], 121.41 (C-*para*), 127.70 (2 × C-*ortho*)[B], 131.59 (2 × C-*meta*)[B], 140.24 (C-*ipso*), 172.80 (C-1) ppm. [A]Assignments interchangeable. [B]The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 22.00 (C-6-Me) ↔ δ = 1.35 (6-Me); δ = 48.17 (C-3) ↔ δ = 2.72 (3-H); δ = 72.25 (C-1′) ↔ δ = 5.49 (1′-H); δ = 78.33 (C-6) ↔ δ = 4.38 (6-H); δ = 127.70 (2 × C-*ortho*) ↔ δ = 7.23 (2 × *ortho*-H); δ = 131.59 (2 × C-*meta*) ↔ δ = 7.43 (2 × *meta*-H). IR (film): $\tilde{\nu}$ = 3425, 2975, 2935, 2920, 1710, 1485, 1390, 1365, 1265, 1240, 1215, 1185, 1140, 1090, 1070, 1010, 945, 915, 840, 740 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{15}O_3BrNa$ [M + Na]$^+$ 321.00968; found 321.00983 (+0.5 ppm).

***rel*-(3*S*,6*S*)-3-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (*anti*,*cis*-44)**



Following the **General Procedure B** the title compound was prepared from δ-methyl-δ-lactone (**21**, 114 mg, 1.00 mmol) and 4-bromobenzaldehyde (**24**, 370 mg, 2.00 mmol, 2.0 equiv.). Purification by flash chromatography[25] (2.0 × 15 cm, 15 mL, *c*-C_6H_{12}/EtOAc 3:1 to 1:1, 8–13) rendered the product as a colorless oil (248 mg, 83%, *anti*,*cis*-**44**/*anti*,*trans*-**44** 77:23). *syn*,*trans*/*syn*,*cis*/*anti*,*trans*/*anti*,*cis* 0:6:23:71; *syn*/*anti* 6:94; *syn*,*trans*/*syn*,*cis* >5:95, *anti*,*trans*/*anti*,*cis* 24:76 [determined by integration of the signals at δ = 2.68 (3-H, *anti*,*cis*-**44**) vs. δ = 2.77 (3-H, *syn*,*cis*-**44**) vs. δ = 2.57 (3-H, *anti*,*trans*-**44**) in the 400 MHz ^{1}H NMR spectrum of the

crude product; the spectrum contained no signal clearly attributable to *syn*,*trans*-**44**]. ^{1}H NMR (400.13 MHz, $CDCl_3$, 77:23 mixture of diastereomers): δ = 1.33–1.60 [m, 3 H, 4-H_2, 5-H^1 (both diastereomers)]^A superimposed by 1.35 [d, $J_{6\text{-Me},6}$ = 6.2 Hz, 3 H, 6-Me (*anti*,*cis*-**44**)] superimposed by 1.36 [d, $J_{6\text{-Me},6}$ = 5.8 Hz, 3 H, 6-Me (*anti*,*trans*-**44**)], 1.79–1.91 [m, 1 H, 5-H^2 (both diastereomers)]^A, 2.56 [m_c, possibly interpretable as ddd, $J_{3,4}$ = 11.3 and 7.6 Hz, $J_{3,1'}$ = 8.8 Hz, 1 H, 3-H (*anti*,*trans*-**44**)], 2.67 [m_c, possibly interpretable as ddd, $J_{3,4}$ = 11.3 and 8.6 Hz, $J_{3,1'}$ = 8.6 Hz, 1 H, 3-H (*anti*,*cis*-**44**)], 4.35–4.49 [m, 2 H, 6-H (both diastereomers), OH (*anti*,*cis*-**44**)], 4.75 [d, $J_{1',3}$ = 8.7 Hz, 1 H, 1′-H (*anti*,*cis*-**44**)], 4.82 [d, $J_{1',3}$ = 8.8 Hz, 1 H, 1′-H (*anti*,*trans*-**44**)], 5.03 [br. s, 1 H, OH, (*anti*,*trans*-**44**)], 7.24 [m_c, 2 H, 2 × *ortho*-H (both diastereomers)], 7.45–7.50 [m, 2 H, 2 × *meta*-H (both diastereomers)]. ^{A}The indicated protons were distinguished in a DQF-COSY spectrum ["H,H-COSY spectrum" (400.13 MHz, $CDCl_3$)] by their crosspeaks with protons that previously had been assigned unequivocally [$\delta_H(^1H) \leftrightarrow \delta_H(^1H)$]: δ = 2.56 [3-H (*anti*,*trans*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)]; δ = 2.67 [3-H (*anti*,*cis*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)]; δ = 4.35–4.49 [6-H (both diastereomers), OH (*anti*,*cis*-**44**)] ↔ δ = 1.79–1.91 [5-H^2 (both diastereomers)]. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 20.25 [C-4 (*anti*,*cis*-**44**)]^A, 20.75 [C-6-Me (*anti*,*cis*-**44**)]^A, 22.00 [C-6-Me (*anti*,*trans*-**44**)]^A, 23.20 [C-4 (*anti*,*trans*-**44**)]^A, 28.24 [C-5 (*anti*,*cis*-**44**)]^A, 30.47 [C-5 (*anti*,*trans*-**44**)]^A, 45.37 [C-3 (*anti*,*cis*-**44**)]^A, 47.37 [C-3 (*anti*,*trans*-**44**)]^A, 74.28 [C-1′ (*anti*,*cis*-**44**)]^A, 74.67 [C-6 (*anti*,*cis*-**44**)]^A, 74.85 [C-1′ (*anti*,*trans*-**44**)]^A, 78.89 [C-6 (*anti*,*trans*-**44**)]^A, 122.18 [C-*para* (both diastereomers)], 128.77 [2 × C-*ortho* (*anti*,*cis*-**44**)]^A, 128.85 [2 × C-*ortho* (*anti*,*trans*-**44**)]^A, 131.72 [2 × C-*meta* (both diastereomers)]^A, 139.31 [C-*ipso* (*anti*,*cis*-**44**)], 139.56 [C-*ipso* (*anti*,*trans*-**44**)], 174.43 [C-2 (*anti*,*trans*-**44**)], 176.10 [C-2 (*anti*,*cis*-**44**)]. ^{A}The indicated nuclei – they are non-quaternary – were identified in an edHSQC spectrum ["short-range C,H-COSY spectrum" (100.62/400.13 MHz, $CDCl_3$)] by their crosspeaks with directly bonded protons (these had previously been assigned unequivocally) [$\delta_C(^{13}C) \leftrightarrow \delta_H(^1H)$]: δ = 20.25 [C-4 (*anti*,*cis*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)]; δ = 20.75 [C-6-Me (*anti*,*cis*-**44**)] ↔ δ = 1.35 [6-Me (*anti*,*cis*-**44**)]; δ = 22.00 [C-6-Me (*anti*,*trans*-**44**)] ↔ δ = 1.36 [6-Me (*anti*,*trans*-**44**)]; δ = 23.20 [C-4 (*anti*,*trans*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)]; δ = 28.24 [C-5 (*anti*,*cis*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)] and 1.79–1.91 [5-H^2 (both diastereomers)]; δ = 30.47 [C-5 (*anti*,*trans*-**44**)] ↔ δ = 1.33–1.60 [4-H_2, 5-H^1 (both diastereomers)] and 1.79–1.91 [5-H^2 (both diastereomers)]; δ = 45.37 [C-3 (*anti*,*cis*-**44**)] ↔ δ = 2.67 [3-H (*anti*,*cis*-**44**)]; δ = 47.37 [C-3 (*anti*,*trans*-**44**)] ↔ δ = 2.56 [3-H (*anti*,*trans*-**44**)]; δ = 74.28 [C-1′ (*anti*,*cis*-**44**)] ↔ δ = 4.75 [1′-H (*anti*,*cis*-**44**)]; δ = 74.67 [C-6 (*anti*,*cis*-**44**)] ↔ δ = 4.35–4.49 [6-H (both diastereomers), OH (*anti*,*cis*-**44**)]; δ = 74.85 [C-1′ (*anti*,*trans*-**44**)] ↔ δ = 4.82 [1′-H (*anti*,*trans*-**44**)]; δ = 78.89 [C-6 (*anti*,*trans*-**44**)] ↔ δ = 4.35–4.49 [6-H (both diastereomers), OH (*anti*,*cis*-**44**)]; δ = 128.77 [2 × C-*ortho* (*anti*,*cis*-**44**)] ↔ δ = 7.24 [2 × *ortho*-H (both diastereomers)]; δ = 128.85 [2 × C-*ortho* (*anti*,*trans*-**44**)] ↔ δ = 7.24 [2 × *ortho*-H (both diastereomers)]; δ = 131.72 [2 × C-*meta* (both diastereomers)] ↔ δ = 7.45–7.50 [2 × *meta*-H (both diastereomers)]. IR ($CHCl_3$): $\tilde{\nu}$ = 3450, 2975, 2935, 1715, 1490, 1390, 1210, 1190, 1120, 1090, 1070, 1010, 945, 835, 740 cm^{-1}. HRMS (pos. APCI, MeOH): calcd. for $C_{13}H_{16}O_3Br$ $[M + H]^+$ 299.02773; found 299.02777 (+0.1 ppm).

Acknowledgments

The authors thank the Studienstiftung des Deutschen Volkes for a Ph. D. fellowship to F. W. They also thank Rita M. DaSilva-Freitas for tireless technical assistance.

[1] Recent reviews: a) M. Kalesse, M. Cordes, G. Symkenberg, H.-H. Lu, *Nat. Prod. Rep.* **2014**, *31*, 563–594; b) J. Mlynarski, S. Bas, *Chem. Soc. Rev.* **2014**, *43*, 577–587; c) I. Shiina, *Chem. Rec.* **2014**, *14*, 144–183; d) R. Mahrwald (Ed.), *Modern Methods in Stereoselective Aldol Reactions*, Wiley-VCH, Weinheim, Germany, **2013**; e) T. Kitanosono, S. Kobayashi, *Adv. Synth. Catal.* **2013**, *355*, 3095–3118; f) R. L. Sutar, N. N. Joshi, *Tetrahedron: Asymmetry* **2013**, *24*, 1345–1363; g) M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2013**, *24*, 1149–1188; h) S. B. J. Kan, K. K. H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108; *Angew. Chem.* **2013**, *125*, 9267–9279; i) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086–9096; *Angew. Chem.* **2013**, *125*, 9256–9266; j) S. Kotani, M. Sugiura, M. Nakajima, *Chem. Rec.* **2013**, *13*, 362–370; The Mukaiyama Aldol Reaction: 40 Years of Continuous Development: k) J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118; *Angew. Chem.* **2013**, *125*, 9280–9289; l) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 4541–4580; m) L. C. Dias, E. C. de Lucca Jr., M. A. B. Ferreira, E. C. Polo, *J. Braz. Chem. Soc.* **2012**, *23*, 2137–2158.

[2] Examples of aldol additions of lithium enolates of δ-lactones that proceeded without stereocontrol (c, d, e, g, h, i, j) or were not characterized stereochemically (a, b, f): a) K. Narasaka, T. Sakakura, T. Uchimaru, D. Guédin-Vuong, *J. Am. Chem. Soc.* **1986**, *106*, 2954–2961 (stereoselectivity not specified); b) H. Niwa, Y. Miyachi, Y. Uosaki, K. Yamada, *Tetrahedron Lett.* **1986**, *27*, 4601–4604 (stereoselectivity not specified); c) M. Shiozaki, Y. Kobayashi, T. Hata, Y. Furukawa, *Tetrahedron* **1991**, *47*, 2785–2800 (mixture of four diastereomers); d) J. D. White, J. C. Amedio Jr., S. Gut, S. Ohira, L. R. Jayasinghe, *J. Org. Chem.* **1992**, *57*, 2270–2284 (mixture of unspecified number of diastereomers); e) R. Schneider, P. Gérardin, B. Loubinoux, *J. Org. Chem.* **1995**, *60*, 6397–6401 (*syn*/*anti* 54:46); f) A. Padwa, C. K. Eidell, J. D. Ginn, M. S. McClure, *J. Org. Chem.* **2002**, *67*, 1595–1606 (stereoselectivity not specified); g) S. V. Ley, D. J. Dixon, R. T. Guy, F. Rodríguez, T. D. Sheppard, *Org. Biomol. Chem.* **2005**, *3*, 4095–4107 (*syn*/*anti* 71:29 to 76:24); h) P. Tang, B. Yu, *Eur. J. Org. Chem.* **2009**, 259–269 (diastereomeric mixture); i) A. M. Stewart, K. Meier, B. Schulz, M. Steinert, B. B. Snider, *J. Org. Chem.* **2010**, *75*, 6057–6060 (*syn*/*anti* ≈ 66:34); j) D. Petrović, R. Brückner, *Org. Lett.* **2011**, *13*, 6524–6527 (*syn*/*anti* ≈ 50:50).

[3] For an aldol addition of the lithium enolate of a cyclononene-fused δ-lactone that proceeded with 100% *syn* selectivity, see: C. Hamel, E. V. Prusov, J. Gertsch, W. B. Schweizer, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 10081–10085; *Angew. Chem.* **2008**, *120*, 10235–10239.

[4] Aldol additions of dibutylboron enolates of δ-lactones: The aldol addition described in ref.[4d] was effected based on prior experience in our group with a closely related *anti*-selective reaction: a) S. Anklam, *Dissertation*, University of Freiburg, Germany, **2003**, 17–19, 65; b) H. Ito, T. Momose, M. Konishi, E. Yamada, K. Watanabe, K. Iguchi, *Tetrahedron* **2006**, *62*, 10425–10433 (highly *anti*-selective); c) S. P. Cakir, S. Stokes, A. Sygula, K. T. Mead, *J. Org. Chem.* **2009**, *74*, 7529–7532 (only *anti* isomer); d) S. B. Kamptmann, R. Brückner, *Eur. J. Org. Chem.* **2013**, 6584–6600 (perfectly *anti*-selective).

[5] An aldol addition of the dibutylzinc enolate of a trisubstituted δ-lactone to benzaldehyde delivered a single yet unassigned diastereomer: F. Marion, S. Calvet, J.-C. Marié, C. Courillon, M. Malacria, *Eur. J. Org. Chem.* **2006**, 453–462.

[6] For aldol additions of the trichlorotitanium(IV) enolate of a δ-lactone, which proceeded with *ds* = 50:50 to 67:33, see: Q. Su, J. L. Wood, *Tetrahedron Lett.* **2010**, *51*, 4237–4239.

[7] For aldol additions of an (*R*)-MeO-BIPHEP-complexed silver(I) enolate of the α-methylsulfanylated δ-lactone, which proceeded with >95:5 *anti* selectivity (in the nomenclature of the sulfur-free analogue) and with 99% *ee*, see: S. Takechi, S. Ya-

suda, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 4218–4222; *Angew. Chem.* **2012**, *124*, 4294–4298.

[8] For aldol additions of copper(I)-containing magnesium enolates of monosubstituted δ-lactones, which proceeded with up to a 85:15 *syn*/*anti* preference, see: J. Csizmadiová, M. Mečiarová, A. Almássy, B. Horváth, R. Šebesta, *J. Organomet. Chem.* **2013**, *737*, 47–52.

[9] a) The aldol addition described in ref.[9b] was effected based on prior experience in our group with a closely related reaction: S. Müller, *Dissertation*, University of Freiburg, **2008**, 65. 78–87, 98–101; b) The aldol addition of a dichloro(cyclopentadienyl)-titanium(IV) enolate of a disubstituted δ-lactone proceeded completely *syn*-selectively, see: P. Walleser, R. Brückner, *Eur. J. Org. Chem.* **2014**, 3210–3224.

[10] For aldol additions of dialkylboron enolates of α-unsubstituted β-oxa-δ-lactones (i.e., of 3-unsubstituted 1,4-dioxan-2-ones), see: a) M. B. Andrus, B. B. V. S. Sekhar, E. L. Meredith, N. K. Dalley, *Org. Lett.* **2000**, *2*, 3035–3037 (*anti*-selective; ratio of the *anti* diastereomers: 4:1 to >20:1); b) M. B. Andrus, E. L. Meredith, B. B. V. S. Sekhar, *Org. Lett.* **2001**, *3*, 259–262 (*anti*-selective; ratio of the *anti* diastereomers: 15:1); c) M. B. Andrus, K. G. Mendenhall, E. L. Meredith, B. B. V. S. Sekhar, *Tetrahedron Lett.* **2002**, *43*, 1789–1792 (*anti*-selective; ratio of the *anti* diastereomers: 2:1 to 12:1); d) M. B. Andrus, E. L. Meredith, B. L. Simmons, B. B. V. S. Sekhar, E. J. Hicken, *Org. Lett.* **2002**, *4*, 3549–3552(*anti*-selective; ratio of the *anti* diastereomers: 10:1); e) M. B. Andrus, E. L. Meredith, E. J. Hicken, B. L. Simmons, R. R. Glancey, W. Ma, *J. Org. Chem.* **2003**, *68*, 8162–8169 (*anti*-selective; ratio of the *anti* diastereomers: 10:1); f) M. Kapur, A. Khartulyari, M. E. Maier, *Org. Lett.* **2006**, *8*, 1629–1632 (*anti*-selective; ratio of the *anti* diastereomers: 9:1 to 10:1); g) X.-T. Zhou, L. Lu, D. P. Furkert, C. E. Wells, R. G. Carter, *Angew. Chem. Int. Ed.* **2006**, *45*, 7622–7626; *Angew. Chem.* **2006**, *118*, 7784–7788 (*anti*-selective; ratio of the *anti* diastereomers: >10:1); h) A. S. Khartulyari, M. Kapur, M. E. Maier, *Org. Lett.* **2006**, *8*, 5833–5836 (*anti*-selective; ratio of the *anti* diastereomers: 9:1); i) C. M. Burnett, R. M. Williams, *Tetrahedron Lett.* **2009**, *50*, 5449–5451 (*syn*/*anti* 1:1); j) M. B. Andrus, Y. Wong, J. Liu, K. Beebe, L. M. Neckers, *Tetrahedron Lett.* **2009**, *50*, 6705–6708 (*anti*-selective; ratio of the *anti* diastereomers: 8:1 to 9:1).

[11] Astonishingly, the most selective aldol additions of the lithium enolate of an α-unsubstituted β-oxa-δ-lactone (i.e., of a 3-unsubstituted 1,4-dioxan-2-one) gave the *anti* product exclusively, see: a) S. V. Ley, D. J. Dixon, R. T. Guy, M. A. Palomero, A. Polara, F. Rodríguez, T. D. Sheppard, *Org. Biomol. Chem.* **2004**, *2*, 3618–3627; b) For analogous diastereoselective aldol additions to ketones, see: D. J. Dixon, A. Guarna, S. V. Ley, A. Polara, F. Rodríguez, *Synthesis* **2002**, 1973–1978.

[12] Aldol additions of the potassium enolates of α-substituted analogues (i.e., of 3-substituted 1,4-dioxan-2-ones) of the β-oxa-δ-lactone mentioned in ref.[11a] exhibited perfect *anti* selectivities.

[13] For aldol additions of boron enolates of β-aza-δ-lactones (i.e., of morpholin-2-ones), see: a) D. S. Reno, B. T. Lotz, M. J. Miller, *Tetrahedron Lett.* **1990**, *31*, 827–830 (predominantly *anti*-selective; ratio of diastereomers: 5:1 and 17:3:1; the minor diastereomers were not identified); b) R. M. Williams, M. N. Im, J. Cao, *J. Am. Chem. Soc.* **1991**, *113*, 6976–6981 (*anti*-selective; ratio of the *anti* diastereomers: 15:1 to 25:1); c) R. M. Williams, C. Yuan, *J. Org. Chem.* **1992**, *57*, 6519–6527 (*anti*-selective; ratio of the *anti* diastereomers not given, but "excellent" selectivity); d) J. D. Scott, T. N. Tippie, R. M. Williams, *Tetrahedron Lett.* **1998**, *39*, 3659–3662 (*anti*-selective). e) D. E. DeMong, R. M. Williams, *Tetrahedron Lett.* **2001**, *42*, 183–185 (predominantly *anti*-selective; ratio of diastereomers 8:1; the minor diastereomers were not identified).

[14] We are unaware of aldol additions of dialkylboron enolates of β-thia-δ-lactones (i.e., of 1,4-oxathian-2-ones).

[15] Early aldol additions of metal enolates of unsubstituted cyclohexanone: a) D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111 [*anti*/*syn* 67:33 for the addition of the dibutylboron enolate of cyclohexanone to benzaldehyde and >96:4 for the addition of the cyclopentyl(*tert*-hexyl)boron enolate]; b) M. T. Reetz, R. Peter, *Tetrahedron Lett.* **1981**, *22*, 4691–4694 [up to *syn*/*anti* 97:3 for additions of the tris(diethylamino)titanium(IV) enolate of cyclohexanone]; c) R. W. Hoffmann, K. Ditrich, S. Froech, D. Cremer, *Tetrahedron* **1985**, *41*, 5517–5524 (*syn*/*anti* 92:8 for the addition of the dimethoxyboron enolate of cyclohexanone to benzaldehyde); d) M. Hirama, T. Noda, S. Îto, *J. Org. Chem.* **1988**, *53*, 706–708 [*anti*/*syn* 100:0 for the addition of the lithium enolate of cyclohexanone to (*Z*)-5-(*p*-methoxybenzyloxy)-2-methylpent-2-enal]; e) M. Hirama, T. Noda, S. Takeishi, S. Îto, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645–2646 (*anti*/*syn* up to 84:16 for the addition of the lithium enolate of cyclohexanone to benzaldehyde and up to 97:3 for the addition to isobutanal).

[16] For aldol additions of the "thermodynamic" dibutylboron (→ *anti*/*syn* up to 99.5:0.5) and triisopropoxytitanium(IV) enolates of α-methylcyclohexanone (→ *anti*/*syn* 95:5), see: S. Yamago, D. Machii, E. Nakamura, *J. Org. Chem.* **1991**, *56*, 2098–2106.

[17] There seem to be no aldol additions of metal enolates of γ-oxacyclohexanones (i.e., of 4-pyranones) even if organocatalytic aldol additions of γ-oxacyclohexanone abound.

[18] For aldol additions of the lithium enolate of a γ-azacyclohexanone (i.e., of 4-piperidone), see: M. Majewski, D. M. Gleave, *Tetrahedron Lett.* **1989**, *30*, 5681–5684 (*anti*/*syn* 84:16).

[19] For aldol additions of various metal enolates of γ-thiacyclohexanones (i.e., of 4-thianones), see: a) T. Hayashi, *Tetrahedron Lett.* **1991**, *32*, 5369–5372 [lithium enolates generated with LDA: *anti*/*syn* 70:30 to 98:2; 1,3-dioxa-2-borolan enolate: *anti*/*syn* 95:5 triisopropoxytitanium(IV) enolate: *anti*/*syn* 99:1]; b) D. E. Ward, C. C. Man, C. Guo, *Tetrahedron Lett.* **1997**, *38*, 2201–2202 (lithium enolate generated with LDA: *anti*/*syn* 71:29; amine-free lithium enolate: *anti*/*syn* 88:12); c) D. E. Ward, C. Guo, P. K. Sasmal, C. C. Man, M. Sales, *Org. Lett.* **2000**, *2*, 1325–1328 [various chiral titanium(IV) enolates were combined with chiral aldehydes; *syn*/*anti* selectivity was determined by the substrates]; d) D. E. Ward, M. Sales, C. C. Man, J. Shen, P. K. Sasmal, C. Guo, *J. Org. Chem.* **2002**, *67*, 1618–1629 (dialkylboron enolates → *anti*/*syn* up to 94:6; trichlorotitanium(IV) enolates → *syn*/*anti* 78:22); e) D. E. Ward, G. E. Beye, M. Sales, I. Q. Alarcon, H. M. Gillis, V. Jheengut, *J. Org. Chem.* **2007**, *72*, 1667–1674 [various chiral titanium(IV) enolates were combined with chral aldehydes; *syn*/*anti* selectivity was determined by the substrates]; f) V. Jheengut, D. E. Ward, *J. Org. Chem.* **2007**, *72*, 7805–7808 [chiral titanium(IV) enolate combined with a chral aldehyde: *syn*/*anti* 41:59]; g) G. E. Beye, J. M. Goodman, D. E. Ward, *Org. Lett.* **2009**, *11*, 1373–1376 (chiral aldehydes were combined with chiral enolates: dicyclohexylboron enolates: *anti*/*syn* 90:10 to 100:0); h) D. E. Ward, F. Becerril-Jimenez, M. M. Zahedi, *J. Org. Chem.* **2009**, *74*, 4447–4454 [dialkylboron enolates: *anti*/*syn* 83:17 to 95:5; trichlorotitanium(IV) enolates: *syn*/*anti* 50:50 to >95:5]; i) G. E. Beye, D. E. Ward, *J. Am. Chem. Soc.* **2010**, *132*, 7210–7215 [a chiral aldehyde was combined with a chiral trichlorotitanium(IV) enolate: *syn*/*anti* 95:5]; j) D. E. Ward, A. Kazemeini, *J. Org. Chem.* **2012**, *77*, 10789–10803 [chiral aldehydes were combined with chiral enolates: dicyclohexylboron enolates: *anti*/*syn* 90:10 to >95:5; triisopropoxytitanium(IV) enolates: *syn*/*anti* 25:75 to 93:7].

[20] For aldol additions of various metal enolates of dihydroxyacetone acetonide and substituted dihydroxyacetone acetonides, see: a) M. Hirama, T. Noda, S. Ito, C. Kabuto, *J. Org. Chem.* **1988**, *53*, 706–708 (an achiral aldehyde was combined with a "kinetic", chiral lithium enolate; selectivity was predominantly *anti*, but not specified further); b) D. Enders, O. F. Prokopenko, G. Raabe, J. Runsink, *Synthesis* **1996**, 1095–1100 (achiral aldehydes were combined with "kinetic", chiral dicyclohexylboron enolates: *anti*/*syn* 98:2 to >99:1); c) M. Majewski, P. Nowak, *Synlett* **1999**, 1447–1449 (dicyclohexylboron

enolate: *anti*/*syn* 96:4; lithium enolates: *anti*/*syn* 65:35 to 100:0); d) M. Majewski, P. Nowak, *J. Org. Chem.* **2000**, *65*, 5152–5160 (diakylboron enolates: *anti*/*syn* 53:47 to 96:4, depending on the alkyl groups and the workup; lithium enolate: *anti*/*syn* 65:35); e) D. Enders, S. J. Ince, *Synthesis* **2002**, 619–624 (achiral aldehydes were combined with "kinetic", chiral dicyclohexylboron enolates: *anti*/*syn* 98:2); f) D. Enders, S. J. Ince, M. Bonnekessel, J. Runsink, G. Raabe, *Synlett* **2002**, 962–966 (achiral aldehydes were combined with "kinetic", chiral dicyclohexylboron enolates *anti*-selectively); g) D. Enders, J. Barbion, *Chem. Eur. J.* **2008**, *14*, 2842–2849 (an achiral aldehyde was combined with a "kinetic", chiral dicyclohexylboron enolate: *anti*/*syn* ≥99:1); h) I. Niewczas, M. Majewski, *Eur. J. Org. Chem.* **2009**, 33–37 (achiral aldehyde + "kinetic", chiral dicyclohexylboron enolate: *anti*/*syn* 99:1; achiral aldehydes + chiral and achiral lithium enolates: *anti*/*syn* 91:9 to 100:0); i) N. Palyam, I. Niewczas, M. Majewski, *Synlett* **2012**, *23*, 2367–2370 [an achiral aldehyde was combined with a chiral lithium enolate *anti*-selectively (two *anti* diastereomers)]; j) S. D. Halperin, R. Britton, *Org. Biomol. Chem.* **2013**, *11*, 1702–1705 (a chiral aldehyde was combined with an achiral lithium enolate. Selectivity was predominantly *anti* and "excellent", but not specified further).

[21] Such $CpCl_2Ti^{IV}$ enolates – albeit cyclic – have a certain resemblance to (acyclic) ester enolates that contain the Cp(diacetoneglucofuranosyl)Ti^{IV} group (diacetoneglucofuranosyl = 1:2,5:6-di-*O*-isopropylidene-D-α-glucofuranos-3-yl). The latter is the Duthaler–Hafner auxiliary (R. O. Duthaler, A. Hafner, M. Riedike, *Pure Appl. Chem.* **1990**, *62*, 631–642).

[22] This methylation has been reported repeatedly, by, for example: a) J. L. Herrmann, R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.* **1973**, 711–712; b) M. Kuehne, US Patent 4841045 A **1989**; c) J. J. Wolff, G. Frenking, K. Harms, *Chem. Ber.* **1991**, *124*, 551–561; d) M. Oikawa, H. Oikawa, A. Ichihara, *Tetrahedron* **1995**, *51*, 6237–6254; e) B. W. Boal, A. W. Schammel, N. K. Garg, *Org. Lett.* **2009**, *11*, 3458–3461; f) A. W. Schammel, B. W. Boal, L. Zu, T. Mesganaw, N. K. Garg, *Tetrahedron* **2010**, *66*, 4687–4695.

[23] Usually (see ref.[22a,22c–22f]) this methylation has seemed to require the addition of HMPA. However, this additive might complicate workup procedures and leave trace amounts of residue in the product (ref.[22c]). Therefore we opted for a procedure without HMPA (ref.[22b]) even if this lowers the yield.

[24] D. J. Phillips, A. E. Graham, *Synlett* **2008**, 649–652.

[25] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[26] a) For a review on TEMPO oxidations, see: A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153–1174; b) for TEMPO oxidations of lactols furnishing lactones, see: C. U. Grünanger, B. Breit, *Angew. Chem. Int. Ed.* **2010**, *49*, 967–970; *Angew. Chem.* **2010**, *122*, 979–982; c) for a TEMPO oxidation of pentane-1,5-diol giving δ-valerolactone in 61% yield, see: T. Miyazawa, T. Endo, *J. Org. Chem.* **1985**, *50*, 3930–3931.

[27] J. M. Aurrecoechea, B. López, A. Fernández, A. Arrieta, F. P. Cossío, *J. Org. Chem.* **1997**, *62*, 1125–1135.

[28] These conditions resemble those of Sharpless' asymmetric dihydroxylations with AD-mix α (K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, X.-L. Zhang, *J. Org. Chem.* **1992**, *57*, 2768–2771). Unusually, stereocontrol – potentially comprising both enantio- and diastereocontrol – was of no interest in our work. We simply made recourse to this procedure after attempted racemic dihydroxylations in the presence of citric acid ("second cycle dihydroxylation"; P. Dupau, R. Epple, T. A. Allen, V. V. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421–433) of the unsaturated alcohol **27** had failed (to the extent that **27** had been recovered quantitatively).

[29] When trying to oxidize a secondary hydroxy group that was part of a vicinal diol we found that one equivalent of $PhI(OAc)_2$ was enough to effect quantitative glycol cleavage (F. Weber, R. Brückner, *Eur. J. Org. Chem.* **2015**, 2428–2449). Here we needed a second equivalent of $PhI(OAc)_2$ combined with a catalytic amount of TEMPO for obtaining the lactone and not ending one oxidation level lower (i.e., at the lactol).

[30] The conversion of lactone **19** was calculated after determining the integrals over the ^{1}H NMR signals at δ = 2.62–2.73 (two α-protons of **19**) versus δ = 7.64–7.77 (four aromatic protons of aldehyde **24**).

[31] a) For detailed compilation see Table SI-1 in the Supporting Information; b) cf. also footnote 39.

[32] A highly *anti*-selective (*anti*/*syn* 95:5) aldol addition of the triisopropoxytitanium(IV) enolate of α-methylcyclohexanone was described in ref.[16] (cf. also the bottom line of Scheme 2). This is the same *sense* of simple diastereocontrol as in analogous aldol additions of the dibutylboron enolate of the same α-methylcyclohexanone (→ *anti*/*syn* up to 99.5:0.5; cf. the bottom line of Scheme 2 again).[16]

[33] We obtained pure specimens of the aldol adducts *syn*-**33**–**35** by flash chromatography (on silica gel):[25] aldol adduct *syn*-**33** eluted slightly faster than *anti*-**33** and resulted pure from the early fractions. Aldol adduct *syn*-**34** eluted slightly before *anti*-**34**. The 50:50 mixture of the aldol adducts *syn*- and *anti*-**35** furnished pure *anti*-**35** in 32% yield followed by pure *syn*-**35** in 44% yield. The 400 MHz ^{1}H NMR spectra of these *syn*-aldols (*syn*-**34**: 300 MHz) supplemented the previously obtained 400 MHz ^{1}H NMR spectroscopic data of the isomeric *anti*-aldols such that an independent indication for the configurational homologies, which we assume, emerged.

[34] Isolation, through purification by flash chromatography,[25] of binary mixtures of the major *cis* and the major *trans* aldol adduct from these seven aldol additions was not self-evident. This is because the corresponding crude aldol mixtures were binary only in one case (→ **43**, boron route) but contained a small amount of a third diastereomer in four instances (→ **40**, **43**, **44**, boron route; → **43**, titanium route) and small amounts both of a third and a fourth diastereomer in two cases (→ **41**, boron and titanium route) ppm. Accordingly, six of these seven purifications by flash chromatography[25] depleted the third and fourth diastereomer sufficiently for being no longer recognizable ^{1}H-NMR-spectroscopically.

[35] The 1′-H resonances in $CDCl_3$ of *anti*,*trans*-**38** (δ = 4.95 ppm, d, *J* = 5.7; 88 mol-%) and *syn*,*trans*-**38** (δ = 5.24 ppm, m_c, 3 mol-%) were accompanied by another m_c at δ = 4.91 ppm (9 mol-%). We attributed it to the aldol *anti*,*cis*-**38** rather than *syn*,*cis*-**38** because of its chemical shift.

[36] The aldol *syn*,*trans*-**41** was the major constituent in a 67:33 mixture with the isomer *syn*,*cis*-**41**. This mixture was obtained by flash chromatography[25] from a 66:31:2:1 mixture of *syn*,*trans*-**41**, *syn*,*cis*-**41**, *anti*,*trans*-**41**, and *anti*,*cis*-**41**, which had resulted from the titanium-mediated addition of γ-methyl-δ-lactone (**20**) to *para*-bromobenzaldehyde (**24**; Table 2, Entry 6, at right). For (re)crystallizing the mentioned 67:33 mixture of *syn*,*trans*-**41** and *syn*,*cis*-**41** from Et_2O, almost all solvent had to have evaporated (over the course of two weeks) before crystals appeared. As a consequence we obtained two different crops of crystals. They had different habiti: what appeared more abundant and would be identified as *syn*,*trans*-**41** by X-ray analysis (cf. Figure 2, line 4, right) occurred as long, thin, flattened needles. What appeared less abundant was in essence a single platelet-like crystal. We performed X-ray diffraction on this particular crystal and interpreted the result as the scattering of a single crystal, which was composed of the diastereomers *syn*,*trans*-**41** and *syn*,*cis*-**41** in a 1:2 ratio. The dissection of this analysis' original crystal structure (cf. Supporting Information) into superimposing scatterings from the diastereomers *syn*,*trans*-**41** and *syn*,*cis*-**41** is shown in Figure 3.

[37] At the time of the single-crystal structure analyses of *syn*,*trans*-**41** and *anti*,*trans*-**41** we had assumed, but not verified, that the crystals represented the respective major diastereomer of the respective aldol adduct mixture. In order to make sure in retrospect, we sampled one spatula tip of representative small crys-

tals from each of the two final crops of solids, from which, at the time, we had gathered the X-ray single-crystal specimens of *syn*,*trans*-**41** and *anti*,*trans*-**41**, respectively. These "final crops of solids" had each been obtained by a series of consecutive crystallizations; the X-rayed *syn*,*trans*-**41** stemmed from what had originally been a 67:33 mixture of *syn*,*trans*-**41** and *syn*,*cis*-**41**, whereas the X-rayed *anti*,*trans*-**41** originated from what had originally been a 75:25 mixture of *anti*,*trans*-**41** and *anti*,*cis*-**41**. After grinding of these samples XRD diffractograms of the resulting powders were recorded. They showed nothing but reflections from *syn*,*trans*-**41** and *anti*,*trans*-**41**, respectively (details: Supporting Information). These findings, in conjunction with the corresponding ^{1}H NMR spectra, confirmed that our corresponding single-crystal structure analyses had affected the *major* diastereomer produced by the mentioned serial crystallizations of the mentioned aldol adduct mixtures.

[38] The aldol *anti*,*trans*-**41** was the major constituent in a 75:25 mixture with the isomer *anti*,*cis*-**41**. This mixture was obtained by flash chromatography[25] from a 68:25:4:3 mixture of *anti*,*trans*-**41**, *anti*,*cis*-**41**, *syn*,*cis*-**41**, and *syn*,*trans*-**41**, which had resulted from the titanium-mediated addition of γ-methyl-δ-lactone (**20**) to *para*-bromobenzaldehyde (**24**; Table 2, Entry 6, at left). For recrystallizing the mentioned 75:25 mixture from Et_2O, the solvent was slowly evaporated (over 7 days) until the product crystallized. Care was taken to stop this procedure when the first crystals appeared, such that the major component *anti*,*trans*-**41** exclusively would crystallize.

[39] Altogether, Table 2 documents the identification of nine *syn*,*anti*-isomeric *trans*-aldols (compounds **36**–**44**) and six *syn*,*anti*-isomeric *cis*-aldols (compounds **39**–**44**). In each *syn*, *anti* pair the 400 MHz ^{1}H NMR resonance of 3-H is deshielded in the *syn* isomer (in $CDCl_3$); for a detailed compilation see Table SI-1 in the Supporting Information. The identical deshielding of 3-H was noticed in the *syn* versus *anti* isomers of the aldols **30**–**32** (Table 1).[31a]

[40] In order to establish the configurations of our products we first envisioned a purely ^{1}H NMR-based assignment. Its foundation would have been the analysis of vicinal ^{1}H,^{1}H coupling constants: interpreted with the aid of the Karplus equation, they might have allowed the dihedral angle of the respective ^{1}H-C-C-^{1}H moieties to be assessed. Analyzing the dihedral angles in all endocyclic ^{1}H-C-C-^{1}H moieties might have revealed the conformation and configuration of the lactone ring itself. Analyzing the dihedral angle in the hemicyclic ^{1}H-C$^\alpha$-C(OH)-^{1}H moiety might have established the *syn* or *anti* correlation [this might have been less straightforward than it appears at first sight, because the mentioned moiety might have a different conformation in the adducts **36**–**38** of β-methyl-δ-lactone (**19**) than in the adducts **39**–**44** of γ-methyl- (**20**) and δ-methyl-δ-lactone (**21**)]. However, this approach failed. As a consequence we performed a computational conformational analysis of dimethylated δ-lactones to model our aldol adducts (F. Weber, R. Brückner, *Chem. Eur. J.* **2013**, *19*, 1288–1302). The hope was that that would deliver clearly preferred conformations of our possible products. In that case we just would have had to fit the dihedral angles of our ^{1}H NMR analysis to the lactone structures obtained by our calculations. It turned out, however, that δ-lactones in general are conformationally insufficiently biased towards representing a single stereostructure. This insight led us to our search for extensive crystallographic information (Figure 2) as a basis for our structural assignments.

[41] The crystallographic data of the aldol adduct *syn*-**32** are contained in CCDC-1061978.

[42] The crystallographic data of the aldol adduct *anti*-**32** are contained in CCDC-1061979.

[43] The crystallographic data of the aldol adduct *anti*-**35** are contained in CCDC-1061980.

[44] The crystallographic data of the aldol adduct *syn*,*trans*-**38** are contained in CCDC-1061981.

[45] The crystallographic data of the aldol adduct *syn*,*trans*-**41** are contained in CCDC-1400059.

[46] The crystallographic data of the aldol adduct *anti*,*trans*-**41** are contained in CCDC-1400060.

[47] The crystallographic data of the aldol adduct *syn*,*cis*-**44** are contained in CCDC-1061983.

[48] The crystallographic data of the aldol adduct *anti*,*trans*-**36** are contained in CCDC-1061982.

[49] The crystallographic data of the aldol adduct *anti*,*cis*-**45** are contained in CCDC-1061984.

[50] The crystallographic data of a co-crystal of the aldol adducts *syn*,*cis*-**41** and *syn*,*trans*-**41** are contained in CCDC-1400061.

[51] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *78*, 1920–1923.

[52] The weakness of this interpretation is the absence of an explanation for why boat-like Zimmerman–Traxler analogous transition states should be favored over chair-like transition states. Accordingly, different ways of interpreting our respective results should not be excluded. For instance, chlorotitanium(IV)-containing enolates are known to be able to – or at least suspected of being able to – aldol-add via acyclic (i.e., non-Zimmerman–Traxler) transition states. The best-known examples are Heathcock's $TiCl_4$-mediated formations of non-Evans *syn*-aldols from dibutylboron enolates of acyloxazolidinones, $TiCl_4$, and aldehydes. It was suggested that they proceed via an acyclic transition state: M. A. Walker, C. H. Heathcock, *J. Org. Chem.* **1991**, *56*, 5747–5750. Cyclic transition states, yet of bimetallic enolates – specifically with $2\times Ti^{IV}$ – were suggested for aldol additions, see: J. Zambrana, F. Urpí, C. Luján, *J. Org. Chem.* **2011**, *76*, 8575–8587.

[53] The meaning of a "half-chair" conformation in the present context is defined in footnote [a] of Figure 5.

[54] The meaning of a "half-boat" conformation in the present context is defined in footnote [b] of Figure 5.

[55] "Half-chair" conformations of α,β-substituted δ-lactone enolates were drawn in K. Tomioka, H. Kawasaki, K. Yasuda, K. Koga, *J. Am. Chem. Soc.* **1988**, *110*, 3597–3601 for rationalizing the diastereoselectivity of α-alkylations.

[56] B. E. Love, E. G. Jones, *J. Org. Chem.* **1999**, *64*, 3755–3756.

[57] The melting points are neither corrected nor uncorrected, because these terms refer to total immersion thermometers. In our laboratory, like in most modern laboratories, only partial immersion thermometers are used, which per definition need no correction for immersion depth, as they are intended to be only partially immersed, see: G. V. D. Tiers, *J. Chem. Educ.* **1990**, *67*, 258–259.

[58] The supplementary crystallographic data for this paper can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: August 31, 2015
Published Online: November 13, 2015

