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Stereoselective Synthesis of Alcohols, XIX[1]

The Sense of Asymmetric Induction on Addition to α-Chiral Aldehydes

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On addition of (*E*)-crotylboronates to aldehydes with an α-methyl branch the expected Cram-products are formed predominantly. On addition of the (*Z*)-crotylboronates to the same aldehydes the anti-Cram-products are formed in preference. Hence, the sense of 1,2-asymmetric induction depends also on the nature of the achiral reagent. The reasons for and the conditions leading to such a phenomenon are discussed.

Stereoselektive Synthese von Alkoholen, XIX[1]

Die Richtung der asymmetrischen Induktion bei der Addition an α-chirale Aldehyde

Bei der Addition von (*E*)-Crotylboronsäureestern an α-methylverzweigte Aldehyde entsteht überwiegend das erwartete Cram-Produkt. Bei der Addition von (*Z*)-Crotylboronsäureestern an dieselben Aldehyde resultieren bevorzugt die anti-Cram-Diastereomeren. Die Richtung der 1,2-asymmetrischen Induktion ist also auch von der Natur des achiralen Reagenz abhängig. Die Ursache für dieses Phänomen und die Bedingungen, unter denen es auftreten kann, werden diskutiert.

Nowadays much attention is given to the synthesis of natural products of propiogenic origin, for which denticulatin (**1**)[2] may serve as an example. A biomimetic strategy for the synthesis of such compounds amounts to repetitive joining of C_3-building blocks. Using aldol[3] or aldol analogous[4] reactions **2**→**3** + **4** for this purpose, in each carbon-carbon bond forming step up to two new centers of chirality are formed at C-2 and C-3 of **3** or **4**. Their relative configuration can be controlled by a variety of methods[3,4]. The major problem of stereocontrol concerns the selectivity between **3** and **4**, which differ in the relative configuration of the newly formed stereocenter at C-3 with respect to the existent stereocenter at C-4, originally present in the aldehyde **2**. The ratio of **3**/**4** depends primarily on the extent of asymmetric induction that originates from the chiral center in the aldehyde **2**. Of course, by using chiral enolates[3], or chiral allylboronates[5] one has been able to improve on an insufficient asymmetric induction. With highly efficient chiral enolate[6] or allylboronate[7] reagents it was even possible to override the asymmetric induction from a chiral aldehyde[8]. Unfortunately this has not been successful in all cases.

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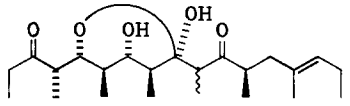
While these efforts are curative measures to compensate for an insufficient 1,2-asymmetric induction, it might be profitable to learn more about the factors determining the extent and sense of asymmetric induction[9].



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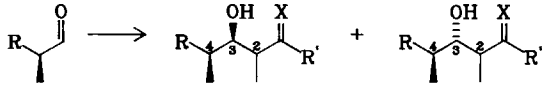
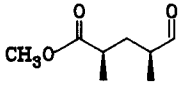


2 3 4

It is generally accepted that on addition of an achiral reagent to an α-chiral aldehyde, it is the chiral center of the aldehyde that determines the sense of the asymmetric induction[10]. In particular on addition to aldehydes of structure **2** the "Cram"-product **3** is preferentially formed over the "anti-Cram"-product **4**[3].



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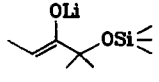
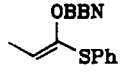
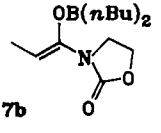
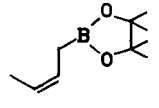
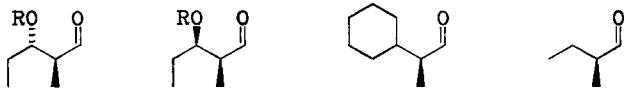
	Cram		anti-Cram	
 6	46	:	54	11)
 7a	46	:	54	11)
 7b	36	:	64	12)
 8	40	:	60	5)

An exception to this Cram-preference has first been noted on addition to the aldehyde **5**[11]. While, on addition of the enolate **6** this could be ascribed[13] to some sort of chelation control[14], this could clearly not be the cause on addition of the boron reagents **7** or **8**. This picture is quite typical: the anti-Cram-preference noted

on addition to aldehydes such as **9**[11,15], **10**[11] and congeners is not restricted to lithium- and zirconium-enolates. It has similarly been recorded on addition of boron-enolates[11]. Moreover the aldehydes **11** and **12** offer no chance for any chelation control, yet an anti-Cram-preference was noted on addition of a lithium (*Z*)-enolate[11] or of the (*Z*)-crotylboronate **8**[5]. Even more disturbing is the fact that the regular Cram-preference prevailed on addition of the corresponding (*E*)-crotylboronate **25** to the same aldehyde **12**[5].



9 **10** **11** **12**

No wonder that these data led to the statement[11] "that the behaviour of the aldehydes is inexplicable by any model available at present". We therefore embarked on a more general study of crotylboronate addition to the aldehydes **16** and **20**, considered as representatives for polypropionate building blocks. This investigation complements the above mentioned studies[11] of *Masamune*.

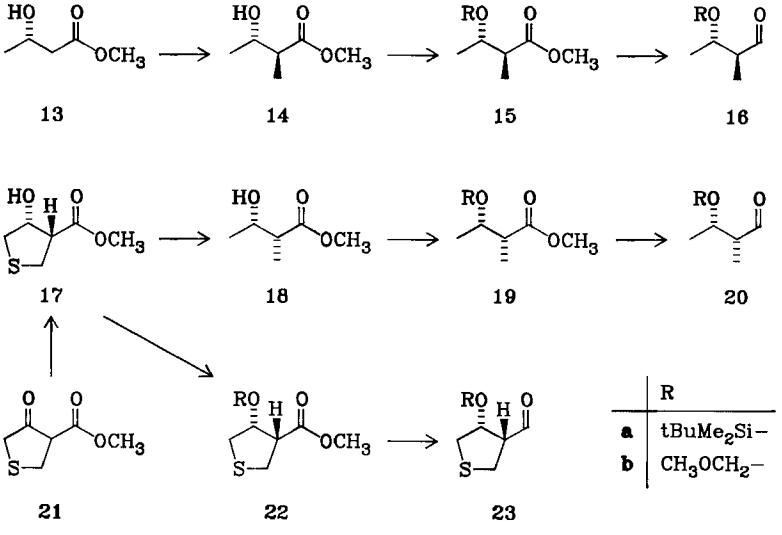
Syntheses of the Aldehydes

The diastereoselectivity in question can be evaluated using the racemic aldehydes **16** and **20**. However, in view of potentially improving the diastereoselectivity by double stereodifferentiation[5] access to optically active aldehydes was sought.

In the anti-series **16**, there exists a well established[15,16] route to the ester **15a**, starting from the yeast reduction of ethyl acetoacetate[17], followed by Frater alkylation[18]. Accordingly we reduced methyl acetoacetate to the (*S*)-β-hydroxybutyrate **13** of 85–91% o. p. Reaction of **13** with lithium diisopropylamide using short metallation times followed by methyl iodide gave the ester **14** consistently with an *anti*/*syn*-ratio of 95:5. This ester **14** was converted to the *tert*-butyldimethylsilyl (**15a**) and methoxymethyl (**15b**) derivatives by standard techniques. Their direct reduction to the aldehydes **16** with DIBAH required careful optimization eventually yielding **16a**[16] and **16b** in 90% yield, 95% diastereomeric purity and 80% optical purity.

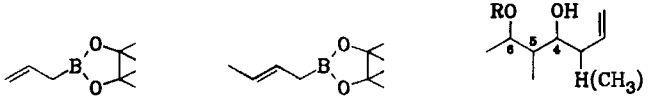
Access to the *syn*-aldehydes **20** was more laborious, since yeast reduction of ethyl α-methylacetoacetate led to **18** of only 85% diastereomeric purity[19]. Moreover, attempts to invert the configuration of **14** by a deprotonation/reprotonation sequence[20] met with no success[21]. Thus, we resorted to the yeast reduction of a cyclic β-ketoester as a reliable route to *syn*-configurated α-branched β-hydroxyesters[22]. We were pleased that reduction of **21**[23] led to 60% of **17** which was submitted to Raney-Ni desulfurization forming 50–72% of **18** of 93–97% diastereomeric purity. The relative and absolute configuration of **18** was established by comparison with authentic material[19,24]. The enantiomeric excess of **18** was determined to be 80–85% by comparing the ^{19}F NMR spectra of the MTPA-

esters of **18** and of racemic **18**[24]. Further conversion of **18** into the protected aldehydes **20** posed no problems. In addition, **21** was converted by a similar set of steps into **23a**.



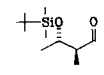
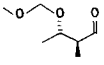
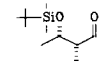
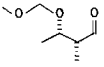
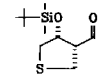
Addition of Crotyl- and Allylboronates to the Aldehydes

The aldehydes **16** and **20** were reacted with the neat allylboronates **8**[25], **24**[26] and **25**[25] for three days. This resulted in a 95% conversion into the homoallyl alcohols **26**, the mixture of which was purified by v.p.c. The structures of the main components of **26** were assigned either on the basis of the ^{1}H NMR spectra of cyclic derivatives or empirically using the ^{13}C NMR spectra[27].



The ratios of the diastereomers were determined either by capillary g. c. or by ^{13}C NMR spectroscopy[28]. Next to the presence of one or two major products, capillary g. c. revealed the formation of up to 7% of one to three other diastereomers. There are several sources of these side products: The starting aldehydes had a diastereomeric purity of only 95% and partial epimerisation of **16** and **20** during the reaction is not completely excluded. The *E*/*Z*-purity of the crotylboronates varied between 90 and 95%. Assignment of these trace components to specific diastereomers of **26** was not pursued, rather the ratio of the two most prominent products is given in Table 1.

Table 1. Diastereoselectivity on addition of allylboronates to α-chiral aldehydes; given is the 4/5 *syn* (Cram): 4/5 *anti* (anti-Cram) ratio in the products, cf. **26**; $\Delta\Delta G$-values in kcal

Aldehyde		Allyl **24**	$\Delta\Delta G_1^{\ddagger}$	(*E*)-Crotyl **25**	$\Delta\Delta G_2^{\ddagger}$	(*Z*)-Crotyl **8**	$\Delta\Delta G_3^{\ddagger}$	W $\Delta\Delta G_2^{\ddagger} - \Delta\Delta G_1^{\ddagger}$	$\Delta\Delta G_1^{\ddagger} - \Delta\Delta G_3^{\ddagger}$
	**16a**	49:51[a]	0.02	95:5[a]	1.71	9:91[a]	−1.35	1.7	1.3
	**16b**	61:39[a]	0.26	89:11[b]	1.21	22:78[b]	−0.74	0.9	1.0
	**20a**	79:21[a]	0.77	98:2[a]	2.26	40:60[a]	−0.23	1.5	1.0
	**20b**	79:21[b]	0.77	94:6[a]	1.60	41:59[a]	−0.21	0.8	1.0
	**23a**	73:27[b]	0.6	90:10[b]	1.28	(68:32)[a,c]		0.7	
	**12**	(62:38)[b,c][5]	0.28	83:17[b]	0.92	30:70[a]	−0.49	0.6	0.8

[a] Determined by capillary g.c. — [b] Determined by ^{13}C NMR spectroscopy. — [c] Structural assignment uncertain.

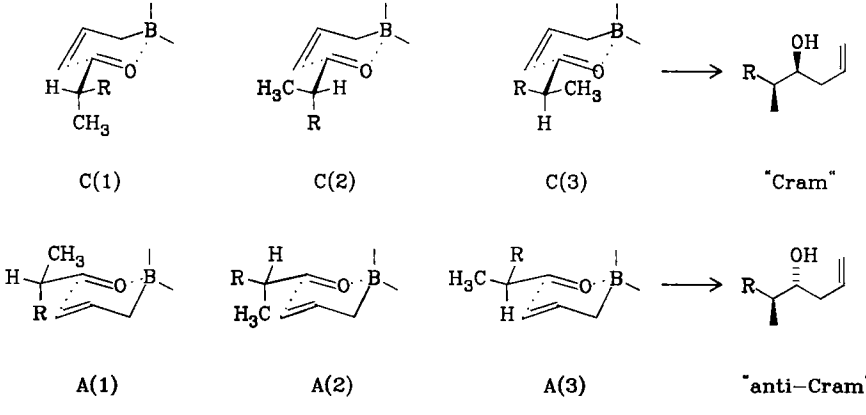
Included in the table are the diastereomer ratios observed on similar addition of **8**, **24**, and **25** to the aldehydes **12**[29] and **23a**. The structures of the products derived from the reaction of **24** with **23a** were secured by conversion to the cyclic carbonate and inspection of the ^1H NMR coupling constants[27]. The products of addition of **8** and **25** to **23a** were not rigorously assigned: Similarities in the ^{13}C NMR spectra to those of the corresponding diastereomers of **26** suggest the assignment given in Table 1. However, the general similarities in the diastereoselectivities of **20a** and **23a** would suggest that in the case of the reaction of **23a** with the (*Z*)-crotylboronate **8** this assignment ought to be reversed. Since this is not a central issue of this paper, we did not clarify this point further. While the structures of the adducts of **8** and **25** to **12** are known[5], the structures of the adducts resulting on addition of **24** to **12** are not secured. In keeping with the other results of this study we assume that Cram-preference prevailed.

Discussion

Consider first the diastereoselectivities on reaction of the simple allylboronate **24** with the various aldehydes. This shows, that a change in the protecting group in the aldehyde, e. g. from *tert*-butyldimethylsilyl to methoxymethyl, has only a

minor effect on the diastereoselectivity. This applies probably also to a change from the open chain aldehyde **20a** to its cyclic analogue **23a**. Moreover, the relative configuration of the β-alkoxy group in the aldehydes **16** versus **20** has not a major influence[30]. Stereoselection is predominantly determined by the configuration of the α-center in the aldehyde, the methyl branch. Remarkable changes in diastereoselectivity results when the achiral reagent is changed from the allyl- to the (*E*)-crotyl- on to the (*Z*)-crotylboronates. With the allylboronate **24** almost all aldehydes show a – small – selectivity in favour of the 4/5-*syn*-product, following Cram's rule. On addition of the (*E*)-crotylboronates **25**, a much more pronounced Cram-preference resulted: Indeed, the (*E*)-crotylboronates reach a useful level of diastereoselection. On reaction with the (*Z*)-crotylboronate **8**, however, the 4/5 *anti*-product is favoured. This anti-Cram-preference corresponds to the one observed on addition of (*Z*)-enolborinates to the related aldehydes **9** and **10**[11] (see page 3967). It becomes obvious that this anti-Cram-preference is not peculiar to the aldehyde, but to the reagent! Our first observation to this point[31] was clearly not an isolated case, but is representative of a general phenomenon.

These uniform trends must reflect uniform features in the diastereomeric transition states. The cyclic transition states for allylboronate additions should be fairly rigid. Similarly the bond from the carbonyl group to the chiral α-carbon of the aldehydes should have high rotational barriers in the transition states[32]. It is therefore meaningful to discuss fixed (staggered) rotamers about this bond.



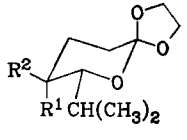
In the above schema are depicted the transition states C(1 – 3) for the formation of the Cram-product, and the transition states A (1 – 3) for the formation of the anti-Cram-product. On addition of the allylboronate **24** to an α-chiral aldehyde **2** the structures (1) to (3) differ in their torsional arrangement of the side chain to the aldehyde group, for R = CH_3 the arrangements of the A- and the C-series would be enantiomorphic.

An analysis as to which are the most favourable transition states leading to the Cram- or anti-Cram-product, respectively, can be based on the experiments described above: When the addition of the (*Z*)-crotylboronate leads to more anti-

Cram-product, the (*Z*)-methyl group must destabilize the otherwise favoured Cram-transition state. This would apply to the transition states C(1) and C(2). When the addition of the (*E*)-crotylboronate leads to more Cram-product, the (*E*)-methyl group must destabilize the most favourable transition state of the A-series, this would apply to A(2) or A(3). If the transition states (2) were to be the favoured ones in both of the reactions leading to the anti-Cram- and the Cram-product, no marked effect on the geometry of the crotylboronates should have been noticed. As discussed further below, the transition states (2) are probably of no importance. We rather deduce that the transition state C(1) is the predominant one leading to the Cram-product and the transition state A(3) is the predominant one leading to the anti-Cram-product.

Could this have been predicted? With respect to the reactions of the simple allylboronate **24** molecular mechanics calculations with the SYBEL program on the transition state model **27a** show[33] that the conformations corresponding to the arrangements (1), (2), and (3) do not differ in energy by more than 0.1 kcal. Hence the slight Cram-preference observed on addition of **24** to the α-chiral aldehydes is not due to nonbonded interactions, but must have some stereoelectronic origin. This makes sense, since with "long bonds" in the transition states delocalisation becomes of prime importance and nonbonded interactions across long bonds are only in their beginning stage. If the transition states are stabilized by interaction of the forming bonds with antiperiplanar arranged σ-bonds (antiperiplanar effect[32,34]), such stabilization should be better on interaction with C–C-, than with C–H-bonds. This would render the transition states (2) of higher energy and hence of lower importance.

Moreover, stabilization by a C–R-bond should be slightly better, than that by a C–CH_3-group[34]. This would render C(1) better than C(3), and A(3) better than A(1). On this level of approximation it is not apparent, why A(3) should be (slightly) less stable than C(1), to account for the slight Cram-preference.



27

	R^1	R^2
a	H	H
b	H	CH_3
c	CH_3	H

On the other hand, these differences become indeed pronounced on introduction of an extra methyl group on the allylboronate. For instance calculations on the model **27b** for the addition of (*E*)-crotylboronates now show that the arrangement (1) is more stable by 1.7 kcal than the arrangement (3). Hence the normal Cram-preference, as expressed by $\Delta\Delta G_1^{\neq}$ is augmented by a term $W = \alpha \cdot 1.7$ kcal, where $0 < \alpha < 1$, since the nonbonded interactions are not as large in the transition state as in the model **27b**.

Turning to the addition of a (*Z*)-crotylboronate, calculations on the model **27c** similarly reveal the arrangement (3) to be more stable than (1) by 1.4 kcal. The

ordinary Cram-preference $\Delta\Delta G_1^{\neq}$ is hence diminished by a term $W = \alpha \cdot 1.4$ kcal, setting the nonbonded interaction terms of the additional methyl group W equal in both series, by default of more accurate information. The diastereoselectivity on addition of the allylboronate **24**, $\Delta\Delta G_1^{\neq}$, that of the (*E*)-crotylboronate **25** $\Delta\Delta G_2^{\neq}$, and that of the (*Z*)-crotylboronate **8**, $\Delta\Delta G_3^{\neq}$, should be related by the following equations:

$$\Delta\Delta G_2^{\neq} = \Delta\Delta G_1^{\neq} + W$$
$$\Delta\Delta G_3^{\neq} = \Delta\Delta G_1^{\neq} - W$$

In Table 1 values for W were derived from the experimentally observed selectivities. They fell into the magnitude expected ($\alpha \approx 0.6$) from the model calculations on **27**. The derived values range surprisingly constant around 0.8 to 1.0 kcal. The few higher numerical W-values in the table were derived from reactions displaying high selectivities, where the inaccuracies in the analytical determination of the isomer ratio render the W-value only approximate. The W-values derived from the addition to **12** and **23a** are slightly lower. This may reflect a somewhat less crowded transition state. The data are, however, too approximate to draw any conclusions to this point. Rather it is surprising, how consistent the theoretical interpretation is with the experimental results.

Conclusions

We have found a series of reactions, in which the sense of asymmetric induction that originates from an α-chiral aldehyde does not depend solely on the nature of the aldehyde, but also on the structure of the achiral reagent. This situation can arise when nonbonded interactions in the transition states corresponding to the term W above, are larger than the stereoelectronic preference for asymmetric induction, $\Delta\Delta G_1^{\neq}$. Such situations may arise preferentially in addition reactions with a late and hence tight transition state. This would apply to the addition of allylboronates to aldehydes. The observed anti-Cram-preference on addition of (*Z*)-enolates to α-chiral aldehydes may therefore result, if nonbonded interactions outwin the stereoelectronic preferences in a late transition state. This makes it plausible that an anti-Cram-preference is not necessarily observed in all addition reactions of (*Z*)-enolates[3].

The fortuitous situation that the nonbonded interactions are larger than the stereoelectronic preferences in the addition of crotylboronates to α-chiral aldehydes allowed us for the first time to experimentally probe the conformations that lead to the asymmetric induction. It turns out that the favoured transition state C(1) and A(3) correspond to the best and second best prediction of the Felkin-Anh model[34]. We caution that this may be fortuitous, because the Felkin-Anh model pertains to the addition of a charged nucleophile to an α-chiral aldehyde, a reaction in which substantial charge is delocalized. We feel that allylboronate additions do not qualify as such a process.

We would like to thank the *Deutsche Forschungsgemeinschaft* for extensive support of this study. We are particularly grateful to Drs. *G. Barnickel* and *H. Bruns* of the *E. Merck AG* for performing the molecular mechanics calculations.

Experimental Part

All temperatures quoted are non corrected. – ^{1}H NMR spectra: Bruker WH-400; Jeol FX-100. ^{13}C NMR spectra: Jeol FX-100, Varian CFT-20 and XL-100. – Preparative gas chromatography: Aerograph A-90-P-3, 1.5 m × 0.6 cm column with 5% SE-30 on chromosorb G, AW-DMCS (60–80 mesh), 130 ml He/min; similarly with 5% apiezon M or with 5% QF-1. – Analytical gas chromatography: Perkin-Elmer F-900, 45 m × 0.25 mm steel capillary column with Ucon , or 40 m × 0.3 mm glas capillary column with SE-52. – Optical rotations: Perkin-Elmer polarimeter 141.

1. *Methyl (2S,3S)-3-Hydroxy-2-methylbutanoate* (**14**): A solution of lithium diisopropylamide was prepared at 0°C from 20.24 g (0.2 mol) of diisopropylamine in 100 ml of dry THF and 4.03 g (0.2 mol) of *n*-butyllithium as solution in hexane. Upon addition of 10.3 g (87 mmol) of methyl (3*S*)-3-hydroxybutanoate to the precooled (–50°C) reagent metallation occurred exothermically. After 10 min at –50°C, a solution of 14.2 g (100 mmol) of methyl iodide in 30 ml of HMPT was added dropwise. The solution was allowed to reach room temperature and was subsequently refluxed for 45 min. The total mixture was stirred into 400 ml of saturated aqueous NH_4Cl-solution. The aqueous phase was extracted 5 times with 100 ml of ether each. The combined organic phases were dried over Na_2SO_4. Removal of the solvent i. vac. left a liquid which was chromatographed with ether/petroleum ether (1:1) on silica gel. The eluate was concentrated and distilled to give 4.6–5.7 g (40–50%) of **14** of b. p. 76°C/10 Torr. The diastereomeric purity was determined by g. c. to be 95:5. A sample was purified by preparative g. c. (apiezon, 100°C): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 2.4 (m, 1H), 2.45 (s, 1H), 3.6 (s, 3H), 4.1 (m, 1H). – ^{13}C NMR ($CDCl_3$): δ = 13.8, 20.5, 46.9, 51.6, 69.2, 176.1. – $[\alpha]_D^{20}$ = +28.7 (*c* = 1.68, methanol).

$C_6H_{12}O_3$ (132.3) Calc. C 54.53 H 9.15 Found C 54.40 H 9.28

2. *Methyl (2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylbutanoate* (**15a**): To 50 ml of DMF was added 4.00 g (30.3 mmol) of methyl (2*S*,3*S*)-3-hydroxy-2-methylbutanoate (**14**), 4.56 g (30.3 mmol) of *tert*-butylchlorodimethylsilane, and 4.65 g (68.4 mmol) of imidazole. After stirring for 24 h at room temperature the mixture was extracted 5 times with 50 ml of petroleum ether (40–60°C) each. The combined extracts were washed free of imidazole by a saturated solution of NaCl which was 1 N in HCl. The organic phase was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After removal of the solvent the residue was bulb to bulb distilled at 10 Torr from a bath of 120°C to give 5.68 g (76%) of **15a**. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.8 (s, 9H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.1 (d, *J* = 6.1 Hz, 3H), 2.47 (m, 1H), 3.64 (s, 3H), 3.97 (m, 1H). – ^{13}C NMR ($CDCl_3$): δ = –5.1, –4.3, 12.7, 17.9, 20.6, 25.7, 48.1, 51.3, 70.2, 175.5. The diastereoselectivity was determined from the ^{13}C NMR spectrum to 95:5. $[\alpha]_D^{18}$ = +37.1 (*c* = 1.43, $CDCl_3$).

$C_{12}H_{26}O_3Si$ (246.4) Calc. C 58.49 H 10.64 Found C 58.58 H 10.78

3. *(2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylbutanal* (**16a**): To a solution of 0.84 g (3.5 mmol) of methyl (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylbutanoate (**15a**) in 50 ml of dry ether was added under nitrogen at –100°C 1.00 g (7 mmol) of diisobutylaluminium hydride. After 45 min at this temperature the reaction was quenched into 200 ml of saturated NaCl solution which was 1 N in HCl. The aqueous phase was extracted 5 times with 50 ml of ether each. The combined organic extracts were dried over Na_2SO_4. The solvents were removed and the residue bulb to bulb distilled at 0.01 Torr: 0.70 g (92%) of **16a** as a colourless liquid. A small sample was purified by g. c. (SE 30, 110°C): Analytical g. c. (Ucon, 130°C) revealed the diastereomeric purity to be 97:3. – ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 0.05 (s, 3H), 0.0 (s, 3H), 0.85 (s, 9H), 1.08 (d, J = 7.3 Hz, 3H), 1.23 (d, J = 6.6 Hz, 3H), 2.36 (m, 1H), 4.0 (m, 1H), 9.7 (d, J = 2.7 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = −5.3, −4.6, 10.2, 17.6, 21.3, 25.4, 53.3, 69.5, 203.9. $[\alpha]_D^{19}$ = +39 (c = 1.57, $CDCl_3$).

$C_{11}H_{24}O_2Si$ (216.4) Calc. C 61.05 H 11.18 Found C 60.95 H 11.26

4. *Methyl (2S,3S)-3-(Methoxymethyloxy)-2-methylbutanoate* (**15b**): To a solution of 2.20 g (16.6 mmol) of methyl (2*S*,3*S*)-3-hydroxy-2-methylbutanoate (**14**) in 50 ml of CH_2Cl_2 were added 6.19 g (41.5 mmol) of *N*,*N*-diethylaniline and 2.0 g (24 mmol) of chloromethoxymethane. After 6 days at room temperature the reaction was washed 5 times with 30 ml each of a saturated aqueous NaCl-solution which was 1 N in HCl. The organic phase was washed with $NaHCO_3$-solution and dried over Na_2SO_4. The solution was concentrated to 1/3 of its volume and filtered with CH_2Cl_2 over 30 g of silica gel to give 2.3 g (80%) of **15b**. A small sample was purified by g. c. (SE 30, 100°C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (d, J = 7.1 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 2.6 (m, 1H), 3.3 (s, 3H), 3.7 (s, 3H), 3.9 (m, 1H), 4.6 (AB-system, J = 6.8 Hz, 2H). – ^{13}C NMR ($CDCl_3$): δ = 12.5, 17.1, 45.8, 51.5, 55.4, 74.7, 95.3, 175.1. – $[\alpha]_D^{20}$ = +21.3 (c = 2.76, $CDCl_3$).

$C_8H_{16}O_4$ (176.2) Calc. C 54.53 H 9.15 Found C 54.39 H 9.31

5. *(2S,3S)-3-(Methoxymethyloxy)-2-methylbutanal* (**16b**): 1.56 g (8.85 mmol) of methyl (2*S*,3*S*)-3-(methoxymethyloxy)-2-methylbutanoate (**15b**) were reduced as described under 3. The reaction was terminated after 24 min to give 0.92 g (69%) of **16b**. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, J = 7.1 Hz, 3H), 1.19 (d, J = 6.3 Hz, 3H), 2.5 (m, 1H), 3.32 (s, 3H), 3.95 (m, 1H), 4.56 and 4.68 (AB-system, J = 7 Hz, 2H), 9.69 (d, J = 2.4 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = 10.1, 17.6, 51.9, 55.6, 73.5, 95.1, 204.0. – $[\alpha]_D^{20}$ = +42 (c = 1.05, $CDCl_3$).

$C_7H_{14}O_3$ (146.2) Calc. C 57.51 H 9.65 Found C 57.55 H 9.64

6. *Methyl (3R,4R)-4-Hydroxytetrahydrothiophene-3-carboxylate* (**17**): A fermentation was started with 500 g of sucrose, 250 g of yeast in 3 l of distilled water. 50.0 g (0.31 mol) of methyl 4-oxotetrahydrothiophene-3-carboxylate (**21**) were added in small portions over 12 h. The progress of the reaction was followed by working up an aliquot and checking by ^{1}H NMR. Complete reduction was reached after 7 days. After centrifuging the supernatant liquid was continuously extracted with ether for 48 h. The aqueous phase was saturated with NaCl and extracted 5 times with 100 ml of ether each. The combined organic phases were dried over Na_2SO_4, concentrated and distilled i. vac.: 21.8 g (43%) of b. p. 96°C/0.05 Torr, A small sample was purified by g. c. (Apiezon M, 130–150°C). $[\alpha]_D^{21}$ = +8.83 (c = 8.94, $CHCl_3$). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.9–3.2 (m, 6H), 3.7 (s, 3H), 4.76 (m, 1H). – ^{13}C NMR ($CDCl_3$): δ = 28.9, 38.3, 51.9, 53.0, 74.5, 171.6.

$C_6H_{10}O_3S$ (162.2) Calc. C 44.43 H 6.21 S 19.77 Found C 44.64 H 6.18 S 19.46

7. *Methyl (2R,3S)-3-Hydroxy-2-methylbutanoate* (**18**): To a solution of 3.00 g (19 mmol) of methyl (3*R*,4*R*)-4-hydroxytetrahydrothiophene-3-carboxylate (**17**) in 50 ml of dry methanol was added under nitrogen a suspension of 31 g of neutral Raney-nickel in 100 ml of methanol. After 4 h under reflux the nickel was placed into an extractor and continously extracted 2 d with hot methanol. After removal of the solvent distillation at 73°C/10 Torr gave 1.32 g (60%) of **18**. Analytical g. c. (Ucon, 90°C) revealed the diastereomeric purity to be 95:5. $[\alpha]_D^{20}$ = −12 (c = 5.0, methanol). – ^{1}H NMR (100 MHz, $CDCl_3$): δ = 1.14 (d, J = 6.5 Hz, 3H), 1.15 (d, J = 7.2 Hz, 3H), 2.35–2.53 (m, 1H), 2.7 (broad s, 1H), 3.67 (s, 3H), 3.94–4.0 (m, 1H). – ^{13}C NMR ($CDCl_3$): δ = 11.1, 19.8, 45.4, 51.7, 67.9, 176.2.

$C_6H_{12}O_3$ (132.2) Calc. C 54.53 H 9.15 Found C 54.50 H 9.24

80 mg (0.6 mmol) of the above product were added to a solution of 15 mg (0.64 mmol) of (+)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride in 1.2 ml of pyridine. After ca. 12 h at room temperature 2.5 ml of water and 40 ml of ether were added. The pyridine was removed from the organic phase by washing with 2 N HCl. Subsequently the organic phase was washed with $NaHCO_3$-solution and dried over Na_2SO_4. After removal of the solvent the residue was taken up in $CDCl_3$. The ^{19}F NMR spectrum revealed the enantiomeric purity to be 80–85%. A control experiment was carried out with racemic **18**.

8. *Methyl (2R,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylbutanoate* (**19a**): 3.00 g (22.7 mmol) of methyl (2*R*,3*S*)-3-hydroxy-2-methylbutanoate (**18**) were reacted as described under 2. to give 3.78 g (68%) of **19a** of b. p. 99–102°C/10 Torr. $[\alpha]_D^{15} = +9.8$ (c = 0.74, ethanol). – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.13 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 7 Hz, 3H), 2.4 (m, 1H), 3.65 (s, 3H), 4.07 (m, 1H). – ^{13}C NMR ($CDCl_3$): δ = −5.1, −4.4, 11.8, 17.9, 21.8, 25.7, 47.4, 51.3, 69.4, 175.3.

$C_{12}H_{26}O_3Si$ (246.4) Calc. C 58.49 H 10.64 Found C 58.61 H 10.80

9. *(2R,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylbutanal* (**20a**): A solution of 2.50 g (10.5 mmol) of methyl (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylbutanoate (**19a**) in 50 ml of dry ether was cooled to −100°C. Then 2.16 g (15.2 mmol) of diisobutylaluminium hydride were added under vigorous stirring. The reaction was terminated after 40 min by quenching into 250 ml of 1 N HCl. Upon stirring for 10 min the phases separated. The aqueous phase was extracted 5 times with 50 ml of ether each. The combined organic phases were washed with $NaHCO_3$-solution and dried over $MgSO_4$. After removal of the solvent the residue was bulb to bulb distilled at 0.01 Torr: 2.00 g (91%) of **20a**. The diastereomeric purity was determined to 95:5 by analytical g. c. (SE-52, 130°C). A small sample was purified by preparative g. c. (QF-1, 120–130°C). $[\alpha]_D^{20} = +8.6$ (c = 5.68, $CDCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 1.05 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H), 2.35 (m, 1H), 4.25 (m, 1H), 9.75 (d, J = 1.2 Hz, 1H). – ^{13}C NMR ($CDCl_3$): δ = −5.0, −4.3, 8.1, 17.9, 21.1, 25.7, 53.4, 68.2, 205.2.

$C_{11}H_{24}O_2Si$ (216.4) Calc. C 61.05 H 11.18 Found C 60.9 H 11.2

10. *Methyl (2R,3S)-3-(Methoxymethyloxy)-2-methylbutanoate* (**19b**): 2.20 g (16.6 mmol) of methyl (2*R*,3*S*)-3-hydroxy-2-methylbutanoate (**18**) were reacted as described under 4. to give 2.4 g (82%) of **19b** of b. p. 78–80°C/13 Torr. The diastereomeric purity was determined by analytical g. c. (Ucon, 120°C) to be 96:4. A small sample was purified by preparative g. c. (SE-30, 130°C). $[\alpha]_D^{20} = +5.5$ (c = 2.89, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, J = 7 Hz, 6H), 2.5 (m, 1H), 3.3 (s, 3H), 3.7 (s, 3H), 3.9 (m, 1H), 4.6 (AB-system, J = 6.8 Hz, 2H). – ^{13}C NMR ($CDCl_3$): δ = 12.1, 18.2, 45.6, 51.6, 55.5, 74.2, 95.4, 174.9.

$C_8H_{16}O_4$ (176.2) Calc. C 54.53 H 9.15 Found C 54.61 H 9.24

11. *(2R,3S)-3-(Methoxymethyloxy)-2-methylbutanal* (**20b**): 2.00 g (11.4 mmol) of methyl (2*R*,3*S*)-3-(methoxymethyloxy)-2-methylbutanoate (**19b**) were reduced as described under 5. The reaction was terminated after 30 min to give 1.20 g (72%) of **20b** after bulb to bulb distillation at 0.01 Torr. The diastereomeric purity was determined by analytical g. c. (Ucon, 110°C) to be 95:5. A small sample was purified by preparative g. c. (SE-30, 80°C). $[\alpha]_D^{20} = -15$ (c = 1.36, $CDCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, J = 7.0 Hz, 3H), 1.2 (d, J = 6.4 Hz, 3H), 2.5 (m, 1H), 3.3 (s, 3H), 4.2 (m, 1H), 4.65 (AB-system, J = 7.0 Hz, 2H), 9.8 (d, J = 1.0 Hz, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 8.1, 17.5, 51.6, 55.4, 72.5, 95.1, 204.1.

12. *Methyl (3R,4R)-4-(tert-Butyldimethylsilyloxy)tetrahydrothiophene-3-carboxylate* (**22a**): 1.52 g (10 mmol) of methyl (3*R*,4*R*)-4-hydroxytetrahydrothiophene-3-carboxylate (**17**) were reacted as described under 2. to give 1.6 g (65%) of **22a** of b. p. 97°C/0.01 Torr. A

small sample was purified by preparative g. c. (SE-30, 120°C). $[\alpha]_D^{23} = +49.9$ ($c = 0.595$, $CDCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H), 0.07 (s, 3H), 0.84 (s, 9H), 2.78 (dd, $J = 12.8$ and 1.5 Hz, 1H), 2.9 (m, 2H), 3.1 (dd, $J = 11.3$ and 3.9 Hz, 1H), 3.3 (t, $J = 13$ Hz, 1H), 3.68 (s, 3H), 4.8 (m, 1H). – ^{13}C NMR ($CDCl_3$): $\delta = -5.4, -4.8, 17.7, 25.4, 29.0, 39.0, 51.5, 54.9, 75.7, 170.5$.

$C_{12}H_{24}O_3SSi$ (276.4) Calc. C 52.13 H 8.75 S 11.59 Found C 52.28 H 8.49 S 11.74

13. *(3R,4R)-4-(tert-Butyldimethylsilyloxy)tetrahydrothiophene-3-carbaldehyde* (**23a**): 1.5 g (5 mmol) of methyl (3*R*,4*R*)-4-(*tert*-butyldimethylsilyloxy)tetrahydrothiophene-3-carboxylate (**22a**) were reduced as described under 3. Great care was taken that the reaction mixture could be effectively stirred. Sometimes it had to be removed for 10 to 20 seconds from the cooling bath for that purpose. The reaction was terminated after 55 min yielding 1.00 g (79%) of **23a** after bulb to bulb distillation at 0.01 Torr. $[\alpha]_D^{20} = -9.6$ ($c = 1.83$, $CDCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.06$ (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 2.77 (dd, $J = 14.5$ and 3.1 Hz, 1H), 2.87 (m, 2H), 3.05 (dd, $J = 15.7$ and 4.4 Hz, 1H), 3.3 (m, 1H), 4.9 (m, 1H), 9.8 (d, $J = 1.4$ Hz, 1H). – ^{13}C-NMR ($CDCl_3$): $\delta = -5.1, -4.6, 17.9, 25.6, 27.5, 39.0, 60.4, 75.9, 200.6$. – The diastereomeric purity was determined from the ^{13}C NMR spectrum to be 95:5.

$C_{11}H_{22}O_2SSi$ (246.4) Calc. C 53.61 H 8.99 S 13.01 Found C 53.39 H 9.17 S 13.11

Table 2. Analytical data for the homoallyl alcohols obtained

	Formula (Mol. mass)		Analysis C	H	S
(4*RS*,5*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-5-methyl-1-hepten-4-ol	$C_{14}H_{30}O_2Si$ (258.5)	Calc.	65.06	11.69	
		Found	64.95	11.49	
(4*RS*,5*S*,6*S*)-		Found	65.16	11.77	
(4*RS*,5*R*,6*S*)-6-(Methoxymethyloxy)-5-methyl-1-hepten-4-ol	$C_{10}H_{20}O_3$ (188.3)	Calc.	63.79	10.71	
		Found	63.40	10.68	
(4*RS*,5*S*,6*S*)-		Found	63.73	10.77	
(3*S*,4*R*,1′*RS*)-4-(*tert*-Butyldimethylsilyloxy)-3-(1′-hydroxy-3′-butenyl)tetrahydrothiophene	$C_{14}H_{28}O_2SSi$ (288.5)	Calc.	58.28	9.78	11.11
		Found	58.41	9.76	11.27
(3*RS*,4*RS*,5*R*,6*S*)-6-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyl-1-hepten-4-ol	$C_{15}H_{32}O_2Si$ (272.5)	Calc.	66.12	11.84	
		Found	65.92	11.79	
(3*RS*,4*RS*,5*S*,6*S*)-		Found	65.94	11.69	
(3*RS*,4*SR*,5*R*,6*S*)-		Found	66.00	11.72	
(3*RS*,4*SR*,5*S*,6*S*)-		Found	66.01	11.81	
(3*S*,4*R*,1′*RS*,2′*RS*)-4-(*tert*-Butyldimethylsilyloxy)-3-(1′-hydroxy-2′-methyl-3′-butenyl)tetrahydrothiophene	$C_{15}H_{30}O_2SSi$ (302.5)	Calc.	59.55	9.99	10.59
		Found	59.57	10.10	
(3*S*,4*R*,1′*RS*,2′*SR*)-		Found	59.61	10.08	10.76
(3*RS*,4*RS*,5*R*,6*S*)-6-(Methoxymethyloxy)-3,5-dimethyl-1-hepten-4-ol	$C_{11}H_{22}O_3$ (202.3)	Calc.	65.31	10.96	
		Found	65.35	10.95	
(3*RS*,4*RS*,5*S*,6*S*)-		Found	65.56	11.09	
(3*RS*,4*SR*,5*R*,6*S*)-		Found	65.35	10.95	
(3*RS*,4*SR*,5*S*,6*S*)-		Found	65.13	10.90	

14. *Typical Procedure for the Addition of Allyl- or Crotylboronates to Aldehydes: 6-(tert-Butyldimethylsilyloxy)-5-methyl-1-hepten-4-ol:* 170 mg (0.78 mmol) of (2*S*,3*S*)-3-(*tert*-butyl-

dimethylsilyloxy)-2-methylbutanal (**16a**) and 132 mg (0.78 mmol) of 4,4,5,5-tetramethyl-2-(2-propenyl)-1,3,2-dioxaborolane (**24**) were stirred for 3 d. After adding 30 ml of petroleum-ether (40–60°C) and 117.2 mg (0.78 mmol) of triethanolamine, the mixture was stirred for 2 h. The solvent was removed and the residue was filtered with CH_2Cl_2 over 15 g of silica gel. The eluates were concentrated and purified by preparative g. c. (SE-30, 180°C) to give 164 mg (81%) of product. Analytical data see Table 2.

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