Stereoselective Synthesis of Alcohols, XXVIII[1]

Stereocontrol of Addition of Chiral (*E*)-(α-Chlorocrotyl)boronates to Chiral Aldehydes

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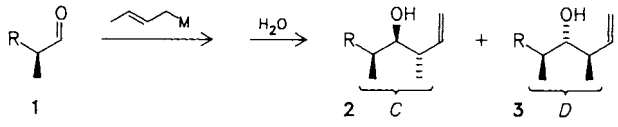
On reaction of the chiral (*E*)-(α-chlorocrotyl)boronates **5** with chiral aldehydes **1**, the diastereoselectivity depends on whether the asymmetric induction of the reagent and the substrate cooperate (matched pair) or whether they are opposed (mismatched pair). In the first situation, very high diastereoselectivity in favor of the products **2** with the stereotriade *C* was realized. In the second case, reagent control of stereoselectivity in favor of the products **3** with the stereotriade *D* was possible only if the asymmetric induction of the aldehyde **1** corresponded to a $\Delta\Delta G^{\neq}$ of ≤ 1 kcal.

Stereoselektive Synthese von Alkoholen, XXVIII[1]. – Stereosteuerung bei der Addition chiraler (*E*)-(α-Chlorcrotyl)-boronsäureester an chirale Aldehyde

Bei der Reaktion chiraler (*E*)-α-(Chlorcrotyl)boronsäureester **5** mit chiralen Aldehyden **1** hängt die Diastereoselektivität davon ab, ob die asymmetrische Induktion des Reagenz und die des Substrats gleichsinnig (matched pair) oder entgegengesetzt (mismatched pair) wirken. Im ersteren Fall konnten sehr hohe Diastereoselektivitäten zugunsten des Produktes **2** mit der Stereotriade *C* erreicht werden. Im zweiten Fall gelang die Steuerung der Diastereoselektivität durch das Reagenz zugunsten des Produktes **3** mit der Stereotriade *D* dann, wenn die asymmetrische Induktion des Aldehyds **1** einem $\Delta\Delta G^{\neq}$-Wert von ≤ 1 kcal entsprach.

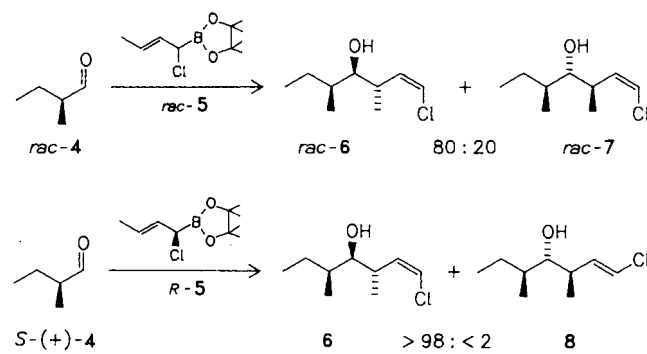
The challenge inherent in the synthesis of macrolide or polyether antibiotics derives from the long sequences of contiguous stereocenters. Efficient strategies require that the new stereocenters should be generated simultaneously with the construction of the carbon backbone of the target molecule. Among the stereoselective carbon–carbon bond forming reactions, the addition of enolates or of allylic metal compounds to aldehydes are most popular in the synthesis of polyketide-derived natural products[2]. Typical substrates for such chain extensions are the aldehydes **1**. Since these are chiral, two diastereomeric products e.g. **2** or **3** may be formed, the ratio of which is determined by the asymmetric induction of the aldehyde. Frequently, the selectivity in favor of the Cram isomer **2** is not sufficient.



Hence, the insufficient asymmetric induction of the substrate has to be supplemented by that of a chiral reagent (double stereodifferentiation)[5]. In order to obtain the other diastereomer **3**, the reagent has to override the asymmetric induction of the substrate (reagent control of diastereoselectivity)[5]. Truely useful reagents should, therefore, not only result in good simple diastereoselection[3,4], but should possess also high inherent asymmetric induction. Recent reviews[2,5] show that rather few reagents fulfill these requirements. We, therefore, became interested in studying and improving α-chiral allylboronates[6] as reagents for stereoselective carbon–carbon bond formation. Along these lines we described recently the optically active α-(chlorocrotyl)-boronates **5**, which displayed asymmetric inductions of ca. 97:3 on addition to achiral aldehydes[1].

Here we would like to report on the stereoselectivities, which can be achieved on addition of these reagents to chiral aldehydes. Some results of this study have been communicated in preliminary form[7].

As a first example we studied the addition of the (*E*)-(α-chlorocrotyl)boronate **5** to (*S*)-α-methylbutyraldehyde **4**[8], because the identity of the resulting adducts **6** and **7** has already been established[1]. Likewise, the diastereofacial bias of the aldehyde **4** was known to be 80:20 from the reaction of the racemic aldehyde **4** with the racemic (*E*)-crotylboronate **5**[1].



On reaction of (*S*)-**4** with the (*R*)-(*E*)-(α-chlorocrotyl)boronate **5** the asymmetric inductions of both the substrate

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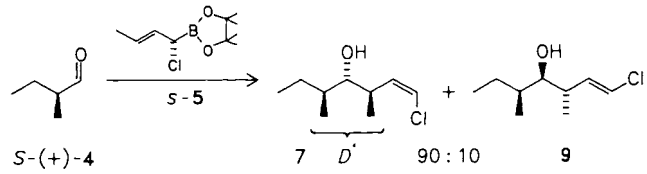
and the reagent cooperate (matched pair[5]) to yield in a highly diastereoselective reaction the product **6**.

None of the anti Cram product **8** could be detected. The more challenging case is the reaction of (*S*)-**4** with the enantiomeric reagent, (*S*)-**5**, in which the asymmetric inductions of both partners are opposed (mismatched pair[5]). It turned out that the asymmetric induction of the reagent **5** was high enough to override the asymmetric induction of the substrate by a margin of 9:1.



The minor isomer **9** is the product of substrate control of diastereoselectivity which in this case causes a noticeable part of the reaction to proceed via a transition state with an equatorially disposed chlorine atom eventually giving the diastereomer **9** with an *E*-double bond. The stereocenters in the major product **7** correspond to the stereotriade of type *D'*[2], which is generally the most difficult one to generate. While this can be achieved by means of the chiral reagent **5**, a closer scrutiny of the selectivities involved shows that the reagent **5** is still far from being optimal: In Figure 1 the individual selectivities of the reagent and of the substrate aldehyde are depicted in terms of $\Delta\Delta G^{\neq}$, the energy differerences between the competing attacks on the diastereotopic faces of the reagent and substrate, respectively. In the matched pair, the selectivities can be multiplied, i.e. the $\Delta\Delta G^{\neq}$ values can be added to result in an overall selectivity

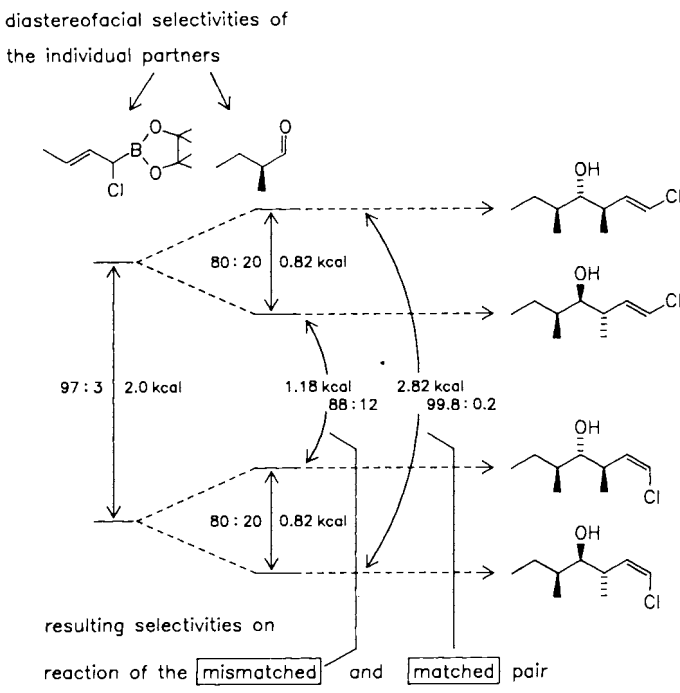
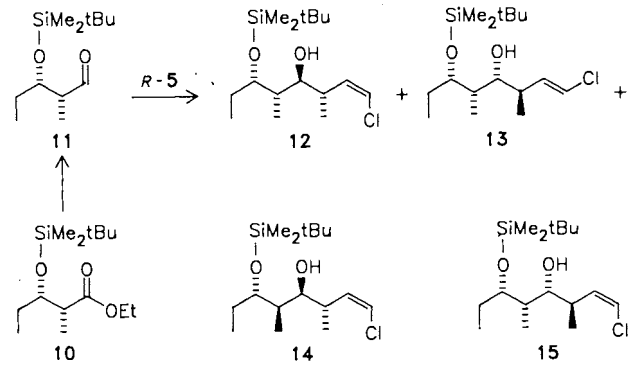


Figure 1. Free Energy differences responsible for diastereoselection during reaction of the *E*-(α-Chlorocrotyl)boronate **5** with aldehydes

of $\Delta\Delta G^{\neq} = 2.82$ kcal, corresponding to a calculated selectivity of 99.8%. In the mismatched pair, the selectivities must be divided, i.e. the $\Delta\Delta G^{\neq}$ values have to be substracted. The difference of 1.18 kcal corresponds to an overall selectivity of 88:12, cf. the experimental value of 90:10. It becomes obvious that the reagent **5** will not be powerful enough to exert reagent control of diastereoselectivity on reaction with chiral aldehydes, which have an opposing asymmetric induction of $\Delta\Delta G^{\neq} \geq 1$ kcal.

In order to evaluate the limits of the reagent **5**, we investigated the diastereoselectivity in mismatched combinations with other chiral aldehydes. Thus, the aldehyde **11**[9] was prepared from the ester **10**[10] with more than 95% ee by reduction with DIBAH.

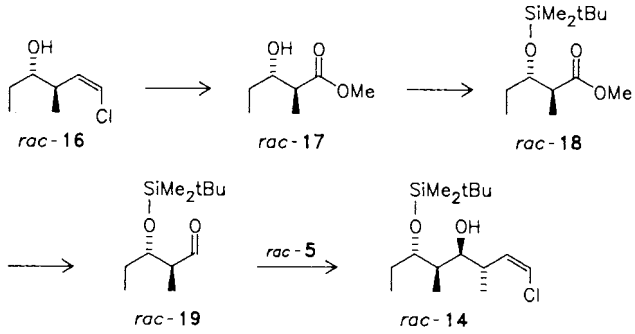


On reaction with *R*-(**5**) (mismatched combination), three isomeric adducts **12**, **13**, **14** could be isolated in 53% yield after chromatography in a 77:19:4 ratio. Since the major isomer had a *Z*-double bond, it should be the product of reagent control of diastereoselectivity and should have the structure **12**. To further substantiate the structural assignment of **12**, another epimer **15** was generated by treating the aldehyde **11** with an excess of racemic **5**. In this case the matched pair [**11** + (*S*)-**5**] reacts much faster than the mismatched combination [**11** + (*R*)-**5**]. Thus, by kinetic resolution the diastereomer **15** was obtained, the ^{13}C-NMR spectra of which differed characteristically from those of **12** and **14**.

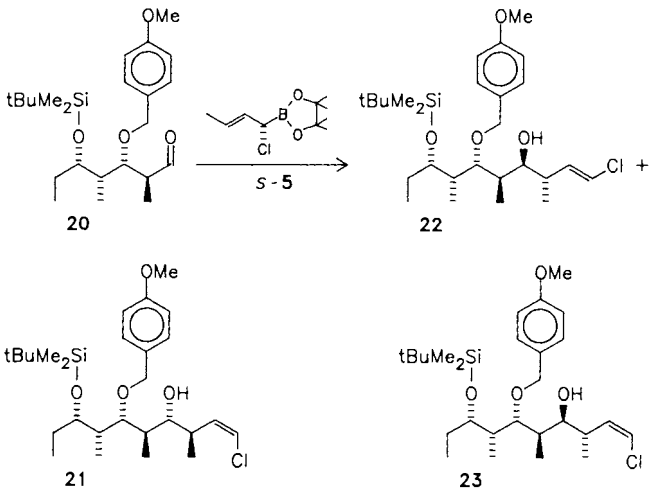
The second-abundant isomer formed in the reaction of **11** with (*R*)-**5** had an *E*-double bond. It, therefore, should be the product with the structure **13**, the configuration of which is dictated by the asymmetric induction of the aldehyde. The minor constituent also had a *Z*-double bond and hence was an epimer of the main product **12**. We surmised that it originated from an epimerisation of the starting aldehyde **11** to **19**, which could then react with (*R*)-**5** in a matched-pair combination to give **14**. To secure this point and the assignments made above, the racemate of the product **14** was prepared by an independent sequence.

For this purpose the homoallyl alcohol **16**[11] was ozonized to give the ester **17**, which after protection and DIBAH reduction furnished the racemic aldehyde **19**. Its reaction with the racemic (α-chlorocrotyl)boronate **5** was rather sluggish and gave 69% of the adduct **14**. No signals of another isomer were seen in the NMR spectra of the crude material.

The ^{13}C-NMR spectrum of the racemic **14** was identical with that of the minor product obtained in the reaction of **11** with (*R*)-**5** described above.



The aldehyde **19** should have a high (reinforced) Cram preference when reacting with an (*E*)-crotylboronate[11] such as **5**. In consequence, the reaction of the two racemates proceeded under high mutual kinetic resolution to give the Cram product **14**. Similarly, the reaction of the aldehyde **11** with the (*E*)-crotylboronate should proceed under reinforced[11] Cram selectivity, equivalent to a high substrate-based asymmetric induction. This is in turn the reason for the low diastereoselectivity of 80:20 in the mismatched combination of **11** with (*R*)-**5**. Hence, in this case the asymmetric induction of the reagent ($\Delta\Delta G^{\neq}$ = 2.0 kcal) is only barely sufficient to override that of the aldehyde ($\Delta\Delta G^{\neq}$ = 1.2 kcal). It is obvious that with aldehydes having an even stronger asymmetric induction, reagent control of diastereoselectivity using **5** would no longer be possible. This was observed in the case of the reaction of aldehyde **20** with (*S*)-**5**.

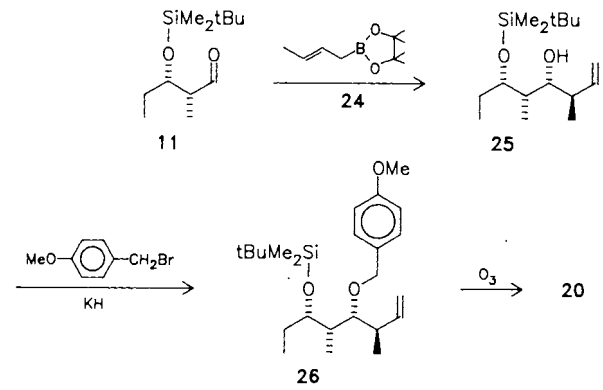


In this mismatched combination reagent control of diastereoselectivity should lead to the diastereomer **21**, substrate control of diastereoselectivity should give the diastereomer **22**. In the latter case the asymmetric induction of the substrate would again force the crotylboronate to react via a transition state with an equatorially disposed chlorine atom[1]. This is reflected in the configuration of the newly formed double bond and results in the diagnostic feature that **22** has an *E*-, whereas **21** has a *Z*-double bond. When the aldehyde **20** was treated with (*S*)-**5** for 60 h at room temperature only **22** was obtained in 56% yield. The crude product probably contained some **21**, but likely not more than 5%. Hence, in the case of **20**, the substrate-based asymmetric induction surpassed that of the reagent by at least a $\Delta\Delta G^{\neq}$ of 1 kcal.

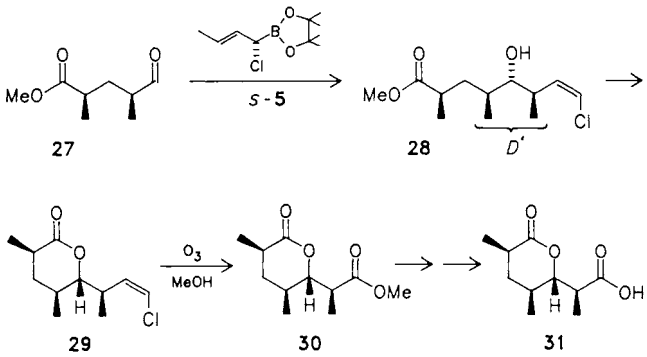
The structural assignment to **22** rests on the configuration of the double bond being *E* (vicinal coupling in the ^1H-NMR spectrum of the olefinic protons of 13 Hz). The relative configuration of the new stereocenters is assigned by inference from the reaction of the aldehyde **4** with (*S*)-**5** described above.

In order to obtain another isomer of **22** for inspecting differences in the NMR-spectra, the aldehyde **20** was treated with racemic **5**. Now one enantiomer of **5**, corresponding to the matched pair, reacted rapidly with **20** to give the product **23** with a *Z*-double bond. The remaining aldehyde was recovered.

The starting aldehyde **20** had been prepared by chain extension of the aldehyde **11**. In order to arrive at the alcohol **25** with an *anti* configuration at the two new stereocenters, an (*E*)-crotylboronate had to be used. This in turn reinforced[11] the Cram selectivity of the substrate aldehyde **11** such that even using the achiral (*E*)-crotylboronate **24** the alcohol **25** was obtained in high yield with a 95:5 selectivity.



The subsequent steps, protection of the newly generated hydroxyl function and ozonolytic cleavage of the double bond proceeded readily to give the aldehyde **20**. The homologation of **11** to **20** illustrates a general approach to a linear synthesis of polyketide natural products. In an optimal case such as the conversion of **11** into **20**, three steps are needed for the creation of two new stereogenic centers. The success of this approach depends ultimately on the ability to control the configuration of the new stereocenters. The data reported in this paper show that the asymmetric induction of the chiral (*E*)-(α-chlorocrotyl)boronate **5** is more than sufficient to achieve this in situations of double stereodifferentiation (matched pairs). However, the efficiency of **5** is only marginal in cases of reagent control of diastereoselectivity (mismatched combinations). To delineate the limits of the reagents **5** further, we tested it with still another chiral aldehyde **27**[8].



The combination of **27** with (*S*)-**5** is a mismatched one, which should give rise to the stereotriade *D'*[2]. Reaction of **27** with the crotylboronate **5** proceeded smoothly. After saponification of the ester **28**, lactonisation produced a single stereoisomer of the lactone **29** in 52% yield. Inspection of the crude reaction products indicated the reaction to be highly stereoselective. That the stereostructure of the product **28** corresponded to the stereotriade *D'* was secured by conversion of **28** into the known[12] 2-*epi*-Prelog-Djerassi lactone **30**.

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Experimental

All temperatures quoted are not corrected. – ^{1}H-NMR: Bruker WH 400. – ^{13}C-NMR: Varian XL 100, CFT 20 and Bruker WH 400. – Preparative gas chromatography: Varian Aerograph A-90-P3 using a 1.5 × 0.6-cm column with "A" 5% apiezon, or "B" 5% SE 30 on chromosorb G, AW, DMCS, 60–80 mesh, 200 ml He/min. – Rotations: Perkin-Elmer Polarimeter 141.

1) *(1Z,3S,4R,5S)-1-Chloro-3,5-dimethyl-1-hepten-4-ol* (**6**): 1.60 g (7.4 mmol) of crude (*R*)-2-[(*E*)-1-chloro-2-butenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*R*)-**5**[13] [containing ca. 30% of 2-(3-chloro-1-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane] and 0.65 g (7.5 mmol) of (*S*)-2-methylbutanal (**4**)[8] were treated in 5 ml of petroleum ether (b.p. 40–60°C) as described in ref.[1] to give 0.73 g (56%) of **6**. Its ^{1}H-NMR and ^{13}C-NMR spectra matched those described in ref.[1] and showed the product to be diastereomerically pure (≥98%).

2) *(1Z,3R,4S,5S)-1-Chloro-3,5-dimethyl-1-hepten-4-ol* (**7**): 1.20 g (5.5 mmol) of crude (*S*)-**5**[13] (purity ca. 70%) and 0.50 g (5.8 mmol) of (*S*)-2-methylbutanal (**4**)[8] were treated in 5 ml of toluene as described in ref.[1]. The products were chromatographed over 45 g of silica gel (Kieselgel 60, E. Merck) with petroleum ether (b.p. 40–60°C)/ether, 7:3, to give 0.43 g (44%) of **7**, which was identified by its ^{1}H-NMR and ^{13}C-NMR spectra[1]. The material contained ca. 10% of **6** (presumably *ent*-**6**) due to partial racemisation of the aldehyde **4**. Further elution gave 40 mg (4%) of *(1E,3S,4R,5S)-1-chloro-3,5-dimethyl-1-hepten-4-ol* (**9**) identified by its ^{1}H-NMR and ^{13}C-NMR spectra[1].

3) *(2R,3S)-3-(tert-Butyldimethylsilyloxy)-2-methylpentanal* (**11**): To a solution of 3.50 g (13.4 mmol) of ethyl (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentanoate (**10**)[14] in 50 ml of anhydrous ether was added over 5 min at −95 to −105°C 2.35 g (15.7 mmol) of 90% DIBAH (Schering) under stirring. Sometimes, the flask had to be removed briefly from the cooling bath to ensure efficient stirring. After 55 min, the contents were poured into 380 ml of 1 N aqueous hydrochloric acid and extracted 5 times with 120 ml each of ether. The extracts were washed with 150 ml of saturated $NaHCO_3$ solution, dried with $MgSO_4$ and concentrated to give 3.00 g (97%) of **11**, which according to the ^{1}H-NMR spectrum was pure enough for further use. Distillation gave 2.50 g (81%) of **11**, b.p. 48°C/0.50 Torr. – $[\alpha]_D^{20}$ = −49.6 (*c* = 11.43, $CHCl_3$). – ^{1}H-NMR (400 MHz, $CDCl_3$): δ = −0.02 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 0.87 (t, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 1.49–1.55 (m, 2H), 2.45 (qdd, *J* = 7.0, 3.5 and 1.1 Hz, 1H), 4.02 (td, *J* = 7.0 and 3.5 Hz, 1H), 9.76 (d, *J* = 1.1 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = −4.7, −4.3, 7.6, 10.0, 18.0, 25.7, 27.4, 50.8, 73.4, 205.3.

$C_{12}H_{26}O_2Si$ (230.4) Calcd. C 62.55 H 11.37
Found C 62.03 H 11.65

4) *(1Z,3S,4S,5S,6S)-6-(tert-Butyldimethylsilyloxy)-1-chloro-3,5-dimethyl-1-octen-4-ol* (**12**): 0.45 g (2.1 mmol) of crude (*R*)-**5** (purity ca. 70%) and 0.30 g (1.3 mmol) of the aldehyde **11** were dissolved in 1.8 ml of toluene and kept for 8 h at 4 kbar. Workup as described in ref.[1] and chromatography over 45 g of silica gel with petroleum ether (b.p. 40–60°C)/ether, 4:1, gave 170 mg (41%) of **12**, 40 mg (10%) of **13**, and 10 mg (2%) of **14**.

12: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.09 (s, 3H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.56 (m, 2H), 1.71 (ddq, *J* = 10.0, 7.0 and 3.0 Hz, 1H), 2.86 (m, 1H), 3.61 (m, 2H), 4.44 (s, broad, 1H), 5.93 (dd, *J* = 9.6 and 7.1 Hz, 1H), 6.05 (d, *J* = 7.1 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.8, −4.5, 11.4, 13.7, 17.0, 17.9, 23.8, 25.7, 35.2, 41.2, 77.0, 80.2, 117.5, 132.7.

$C_{16}H_{33}ClO_2Si$ (321.0) Calcd. C 59.87 H 10.37
Found C 59.92 H 10.31

(1E,3R,4R,5S,6S)-6-(tert-Butyldimethylsilyloxy)-1-chloro-3,5-dimethyl-1-octen-4-ol (**13**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.72 (m, 2H), 1.89 (m, 1H), 2.36 (q, broad, *J* = 7.1 Hz, 1H), 2.45 (d, *J* = 2.6 Hz, 1H), 3.46 (ddd, *J* = 7.4, 2.8 and 2.6 Hz, 1H), 3.70 (ddd, *J* = 9.1, 7.4 and 3.4 Hz, 1H), 5.95 (dd, *J* = 13.3 and 7.6 Hz, 1H), 6.00 (d, *J* = 13.3 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6, −3.8, 6.2, 9.7, 17.0, 18.0, 25.9, 27.3, 36.9, 39.7, 77.5, 78.0, 117.3, 136.6.

$C_{16}H_{33}ClO_2Si$ (321.0) Calcd. C 59.87 H 10.37
Found C 60.07 H 10.14

(1Z,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-1-chloro-3,5-dimethyl-1-octen-4-ol (**14**) showed the same ^{1}H-NMR and ^{13}C-NMR spectra as described under 8).

5) *Methyl (2R*,3R*)-3-Hydroxy-2-methylpentanoate* (*rac*-**17**): To a solution of 2.50 g (16.8 mmol) of (3*R**,4*R**,5*E*)-6-chloro-4-methyl-5-hexen-3-ol (*rac*-**16**)[1] in 17 ml of methanol was introduced at −78°C a stream of ozone until the blue colour persisted. Excess of ozone was removed with a stream of nitrogen. Upon warming to room temperature, a slightly exothermic reaction ensued. After 3 h at 60°C, the solvent was removed i.vac. The residue was taken up in 30 ml of ether and washed once with 5 ml of a 10% aqueous $NaHCO_3$ solution and once with 10 ml of water. The organic phases were dried with $MgSO_4$ and concentrated to give 1.54 g (63%) of crude **17** which was used as such for the next transformation. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.42 (m, 1H), 1.55 (m, 1H), 2.52 (m, 2H), 3.58 (m, 1H), 3.68 (s, 3H).

6) *Methyl (2R*,3R*)-3-(tert-Butyldimethylsilyloxy)-2-methylpentanoate* (**18**): 1.82 g (12.4 mmol) of methyl (2*S**,3*S**)-3-hydroxy-2-methylpentanoate (**17**) in 10 ml of *N,N*-dimethylformamide and 1.93 g (14.9 mmol) of diisopropylethylamine, and 2.62 g (17.4 mmol) of *tert*-butylchlorodimethylsilane were allowed to react for 16 h at room temperature. After quenching with 25 ml of 2 N aqueous hydrochloric acid, the mixture was extracted 3 times with 20 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated i.vac. The residue was chromatographed over 120 g of silica gel with petroleum ether (b.p. 40–60 °C)/ether, 9:1, to give 2.26 g (70%) of crude **18**, which was used as such. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.86 (t, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 1.47 (m, 2H), 2.63 (m, 1H), 3.64 (s, 3H), 3.89 (m, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.0, −4.6, 8.2, 12.1, 17.9, 25.7, 44.8, 51.3, 74.2, 175.4 (one signal obscured).

7) *(2R*,3R*)-3-(tert-Butyldimethylsilyloxy)-2-methylpentanal* (**19**): 1.84 g (7.1 mmol) of the ester **18** was reduced as described under 3) to give 1.52 g (93%) of the aldehyde **19**, which was homogeneous according to the ^{1}H-NMR spectrum. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.90 (t, *J* = 7.4 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.55 (m, 2H), 2.50 (m, 1H), 3.86 (q, broad, *J* = 5.5 Hz, 1H), 9.73 (d, *J* = 2.3 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.4, 8.8, 10.4, 18.0, 25.7, 27.4, 50.5, 74.5, 204.9.

8) *(1Z,3S*,4S*,5R*,6S*)-6-(tert-Butyldimethylsilyloxy)-1-chloro-3,5-dimethyl-1-octen-4-ol* (**14**): 5.00 g of crude **5** was dissolved in 50 ml of petroleum ether (b.p. 40–60 °C) and treated with 30 ml each of a buffer solution (pH = 4)[15] until the aqueous phase maintained pH = 4. The combined aqueous phases were extracted 3 times with 10 ml each of petroleum ether (b.p. 40–60 °C). The combined organic phases were dried with $MgSO_4$ and concentrated to give 4.0–4.2 g of acid-free **5**. – 1.20 g (5.5 mmol) of the crotylboronate **5** thus obtained (purity ca. 70%)[13], and 0.46 g (2.0 mmol) of the (2*R**,3*R**)-2-methyl-3-(*tert*-butyldimethylsilyloxy)pentanal (**19**) were dissolved in 5 ml of toluene and kept for 60 h at room temperature as described in ref.[1]. Chromatography over 40 g of silica gel with petroleum ether (b.p. 40–60 °C)/ether, 4:1, yielded 440 mg (69%) of the alcohol **14** as colourless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 7.1 Hz, 3H), 1.65 (m, 2H), 1.75 (m, 1H), 2.86 (m, 1H), 3.37 (s, 1H), 3.67 (ddd, *J* = 8.6, 5.2 and 2.8 Hz, 1H), 3.78 (d, broad, *J* = 8 Hz, 1H), 5.84 (dd, *J* = 8.9 and 7.1 Hz, 1H), 6.06 (dd, *J* = 7.1 and 0.9 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.9, −4.6, 9.8, 11.0, 16.1, 17.8, 25.7, 27.4, 35.3, 35.6, 73.8, 79.6, 117.9, 135.4.

$C_{16}H_{33}ClO_2Si$ (321.0) Calcd. C 59.87 H 10.37
Found C 59.98 H 10.24

9) *(1Z,3R,4R,5S,6S)-6-(tert-Butyldimethylsilyloxy)-1-chloro-3,5-dimethyl-1-octene-4-ol* (**15**): 2.40 g (10 mmol) of the crude racemic crotylboronate **5** and 0.67 g (2.9 mmol) of the aldehyde **11** were dissolved in 5 ml of toluene as described in ref.[1]. Chromatography over 95 g of silica gel with petroleum ether (b.p. 40–60 °C)/ether, 4:1, furnished 300 mg (32%) of crude **15** as colourless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.79 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.89 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.22 (s, 1H), 1.52 (m, 2H), 1.66 (m, 1H), 2.94 (m, 1H), 3.54 (dd, *J* = 6.9 and 4.0 Hz, 1H), 3.73 (td, *J* = 6.9 and 3.0 Hz, 1H), 5.82 (dd, *J* = 9.3 and 7.1 Hz, 1H), 6.06 (dd, *J* = 7.1 and 0.8 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = −4.8, −4.0, 6.9, 9.5, 16.7, 17.8, 25.7, 27.4, 35.4, 38.1, 76.1, 77.2, 117.7, 133.7.

10) *(3R,4R,5S,6S)-6-(tert-Butyldimethylsilyloxy)-3,5-dimethyl-1-octen-4-ol* (**25**): To a solution of 3.45 g (19.5 mmol) of 2-[(*E*)-2-butenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**24**)[16] in 20 ml of petroleum ether (b.p. 40–60 °C) was added at 0 °C 4.18 g (18.2 mmol) of (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-methylpentanal (**11**). After reaching room temperature, the mixture was left standing for 14 h; then 3.00 g (20 mmol) of triethanolamine in 3 ml of CH_2Cl_2 was added. After 4 h of stirring at room temperature, the mixture was filtered through 40 g of silica gel with CH_2Cl_2 (500 ml). Concentration at 50 °C/1 Torr left 5.20 g (99%) of crude **25**. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3H), 0.07 (s, 3H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 1.55 (dq, *J* = 7.5 and 7.5 Hz, 2H), 1.75 (m, 1H), 2.30 (q, *J* = 7.5 Hz, 1H), 2.38 (m, 1H), 3.42 (dd, *J* = 7.5 and 2.0 Hz, 1H), 3.72 (m, 1H), 5.05 (m, 2H), 5.81 (ddd, *J* = 16.5, 10.0 and 8.0 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = −4.5, −3.9, 6.8, 9.5, 16.8, 18.1, 25.9, 27.2, 37.0, 41.8, 77.0, 77.6, 115.2, 141.6.

For analysis, a small sample was purified by preparative gas chromatography (140 °C, column "B"). – $[\alpha]_{365}^{20}$ = +58.9 (*c* = 4.5, $CDCl_3$).

$C_{16}H_{34}O_2Si$ (286.5) Calcd. C 67.07 H 11.96
Found C 67.02 H 12.12

11) *(3R,4R,5S,6S)-6-(tert-Butyldimethylsilyloxy)-4-(p-methoxybenzyloxy)-3,5-dimethyl-1-octene* (**26**): To a suspension of 1.4 g (35 mmol) of potassium hydride in 10 ml of dry THF was added over 15 min at room temperature a solution of 5.50 g (18.0 mmol) of the alcohol **25** in 20 ml of dry THF. After stirring for 1 h at room temperature, 7.4 g (35 mmol) of *p*-methoxybenzyl bromide was added. The mixture was refluxed for 5 h. It was carefully quenched after cooling with 150 ml of water. The phases were separated and the aqueous phase was extracted three times with 100 ml each of diethyl ether. The organic phases were dried with Na_2SO_4 and concentrated to give 10.4 g of a dark oil which was chromatographed over 100 g of silica gel with petroleum ether (b.p. 40–60 °C)/ether, 10:1, giving 5.9 g (80%) of **26** as a colourless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.81 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.50 (m, 2H), 1.76 (m, 1H), 2.55 (q, 1H), 3.30 (m, 1H), 3.59 (m, 1H), 3.79 (s, 3H), 4.51 (m, 2H), 4.98 (m, 2H), 5.90 (m, 1H), 6.85 (d, *J* = 8 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.5, −3.9, 9.5, 9.6, 18.0, 18.1, 25.9, 27.3, 39.6, 41.1, 55.2, 74.2, 74.4, 83.8, 113.7, 114.4, 129.0, 131.5, 141.0, 159.0.

For analysis, a sample was purified by gas chromatography (210 °C, column "B").

$C_{24}H_{42}O_3Si$ (406.7) Calcd. C 70.88 H 10.41
Found C 70.47 H 10.22

12) *(2S,3S,4S,5S)-5-(tert-Butyldimethylsilyloxy)-3-(p-methoxybenzyloxy)-2,4-dimethylheptanal* (**20**): Into a solution of 2.44 g (6.0 mmol) of the alkene **26** in 20 ml of dry CH_2Cl_2 was introduced at −78 °C a stream of ozone (ca. 1 mmol/min). After 20 min, the excess of ozone was removed with a stream of nitrogen. 0.60 g (10 mmol) of zinc powder, 1.3 ml of acetic acid, and 0.5 ml of water were added, and the mixture was allowed to reach room temperature under stirring. After 1 h, the mixture was filtered and the residue was washed with 20 ml of CH_2Cl_2. The combined filtrates were slowly added to 50 ml of saturated aqueous $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted 3 times with 40 ml each of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and concentrated i.vac. to give 2.43 g (98%) of **20** as a colourless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.4–1.6 (m, 3H), 1.88 (m, 1H), 2.77 (m, 1H), 3.64 (m, 1H), 3.79 (s, 3H), 4.48 (s, 2H), 6.85 (d,

J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 9.80 (d, J = 2.4 Hz, 1H). – ^{13}C NMR (25 MHz, $CDCl_3$): δ = −4.5, −4.0, 9.6, 10.2, 11.8, 18.1, 25.9, 26.8, 40.4, 49.4, 55.1, 74.2, 74.4, 81.9, 113.6, 129.1, 130.5, 159.2, 204.7.

For analysis, 700 mg of the crude product was chromatographed over 95 g of silica gel with CH_2Cl_2 to give 600 mg of purified **20** as an oily liquid.

$C_{23}H_{40}O_4Si$ (408.7) Calcd. C 67.60 H 9.87
Found C 67.87 H 10.22

13) *(1E,3S,4S,5R,6R,7S,8S)-8-(tert-Butyldimethylsilyloxy)-1-chloro-6-(p-methoxybenzyloxy)-3,5,7-trimethyl-1-decen-4-ol* (**22**): 290 mg (0.7 mmol) of the aldehyde **20** and 220 mg (1.0 mmol) of crude (*S*)-**5** (purity ca. 70%)[13] were dissolved in 2 ml of toluene in the presence of a few beads of molecular sieve (4 Å) for 60 h as described in ref.[1]. Chromatography on 40 g of silica gel with petroleum ether (b.p. 40–60 °C)/ether, 4:1, furnished 200 mg (56%) of **22** as a colourless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3H), 0.06 (s, 3H), 0.81 (t, J = 7.5 Hz, 3H), 0.90 (s, 9H), 0.92 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 7.1 Hz, 3H), 1.93 (m, 2H), 2.32 (m, 1H), 3.48 (dd, J = 8.4 and 2.6 Hz, 1H), 3.52 (ddd, J = 8.2, 5.7 and 2.4 Hz, 1H), 3.61 (d, broad, J = 9 Hz, 1H), 3.78 (s, 3H), 4.49 and 4.57 (AB system, J = 10.3 Hz, 2H), 5.93 (dd, J = 13.3 and 7.8 Hz, 1H), 6.00 (d, J = 13.3 Hz, 1H), 6.83 (m, 2H), 7.22 (m, 2H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6, −3.7, 9.1, 9.9, 11.3, 16.5, 18.1, 25.9, 27.7, 35.1, 39.1, 39.3, 55.2, 73.8, 74.0, 76.2, 87.4, 113.9, 116.9, 129.4, 130.2, 137.4, 159.4.

The corresponding *Z*-isomer **23** was prepared similarly from the aldehyde **20** and racemic **5**. It showed the following ^{13}C-NMR data (100 MHz, $CDCl_3$): δ = −4.7, −3.7, 9.1, 9.8, 11.6, 16.3, 18.1, 25.9, 27.7, 35.5, 35.9, 39.1, 55.2, 74.0, 74.2, 76.1, 87.5, 113.9, 117.9, 129.2, 130.3, 135.6, 159.4.

14) *(3R,5S,6S)-6-[(1R,2Z)-3-Chloro-1-methyl-2-propenyl]-tetrahydro-3,5-dimethyl-2H-pyran-2-one* (**29**): To a solution of 1.78 g (8.2 mmol) of crude, acid-free [see 8)] (*S*)-**5** (purity ca. 70%) in 5 ml of toluene were added a few beads of molecular sieve (4 Å) and at 0 °C 1.30 g (8.2 mmol) of methyl (2*R*,4*S*)-2,4-dimethyl-5-oxopentanoate (**27**)[8]. After 1 d at room temperature, the solvent was removed i.vac. The residue was taken up in 100 ml of ether and treated with 1.23 g (8.2 mmol) of triethanolamine. After stirring for 4 h, the mixture was filtered and concentrated. The crude **28** was dissolved in 5 ml of water/methanol, 2:1, to which was added 0.9 g (16 mmol) of potassium hydroxide. After 4 h at 50 °C, the mixture was extracted twice with 5 ml each of ether. The aqueous phase was acidified with conc. hydrochloric acid. Extraction with ether (3 × 10 ml), drying of the extracts with $MgSO_4$, and concentration yielded the crude lactone **29**, which was purified by chromatography over 120 g of silica gel with petroleum ether (b.p. 40–60 °C)/ethyl acetate, 3:2, to give 0.98 g (52%) of **29** as a colorless oil. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01, (d, J = 6.6 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.34 (q, J = 13 Hz, 1H), 1.72 (m, 1H), 1.86 (ddd, J = 13.3, 6.1 and 3.2 Hz, 1H), 2.42 (ddq, J = 12.7, 7.0 and 6.1 Hz, 1H), 3.14 (m, 1H), 3.90 (dd, J = 10.6 and 1.7 Hz, 1H), 5.73 (dd, J = 9.8 and 7.2 Hz, 1H), 6.11 (d, broad, J = 7 Hz, 1H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 17.1, 17.4, 32.1, 34.1, 36.2, 37.3, 90.1, 119.3, 130.9, 174.3.

Attempted purification by gas chromatography (165 °C, column "A") led to epimerisation at C-3. Of the mixture the following signals of 3-*epi*-**29** could be recorded: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J = 7.0 Hz, 3H), 1.64 (ddd, J = 9.1, 7.6 and 1.2 Hz, 1H), 1.72 (m, 1H), 2.62 (m, 1H), 3.88 (dd, J = 10.3 and 1.9 Hz, 1H), 5.83 (dd, J = 9.8 and 7.1 Hz, 1H), 6.11 (d, J = 7 Hz, 1H). – ^{13}C NMR (20 MHz, $CDCl_3$): δ = 16.3, 17.8, 29.4, 32.5, 33.6, 35.2, 86.4.

15) *(2S)-2-[(2S,3S,5R)-Tetrahydro-3,5-dimethyl-6-oxo-2H-pyran-2-yl]propionic Acid* (**31**): 240 mg of the mixture of **29** and 3-*epi*-**29** obtained above were ozonized as described under 5). Chromatography over 45 g silica gel with petroleum ether (b.p. 40–60 °C)/ether, 7:3, furnished 190 mg (80%) of **30** and its epimer.

30: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.6 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.35 (q, broad, J = 13 Hz, 1H), 1.89 (ddd, J = 13.3, 6.0 and 3.5 Hz, 1H), 2.21 (m, 1H), 2.49 (ddq, J = 12.5, 7.0 and 6.0 Hz, 1H), 2.86 (dq, J = 7.2 and 2.8 Hz, 1H), 3.67 (s, 3H), 4.15 (dd, J = 10.3 and 2.8 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.6, 16.8, 17.1, 31.1, 35.8, 37.0, 41.9, 51.4, 87.3, 172.5, 173.6.

5-*epi*-**30**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.2, 16.3, 17.4, 28.1, 32.1, 34.6, 41.9, 51.4, 84.2, 172.6, 175.0. – 180 mg (0.84 mmol) of the above mixture was treated with a solution of 80 mg (2.0 mmol) of NaOH in 1 ml of water. After 12 h, the mixture was carefully acidified with conc. hydrochloric acid and then extracted 3 times with 5 ml each of ether. The combined organic extracts were dried with $MgSO_4$. A trace of *p*-toluenesulfonic acid was added, and the solution was refluxed for 4 h. Concentration gave 90 mg (58%) of **31** admixed with its 5-epimer. The products were identified on the basis of their 100-MHz ^{13}C-NMR spectra, which corresponded with those reported in ref.[12].

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