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Stereoselective allyl transfer to chiral α-methoxycarbaldehydes: A model study related to the C-9/C-15 fragment of geldanamycin

Tony Horneff,[a] Eberhardt Herdtweck,[b] Sören Randoll[b,†] and Thorsten Bach[a,*]

[a]*Lehrstuhl für Organische Chemie I, Department of Chemistry, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany*
[b]*Lehrstuhl für Anorganische Chemie, Department of Chemistry, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany*

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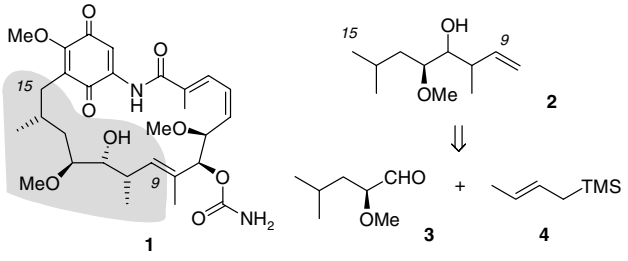
Abstract—The enantiomerically pure α-methoxycarbaldehyde **3** was prepared from L-leucine in five steps and 31% overall yield. The aldehyde was subjected to a diastereoselective BF_3-mediated crotylation with silane **4** and to various reagent-controlled addition reactions. The configuration of aldol addition products **19** and **20** was proven by single crystal X-ray crystallography. Based on these data spectral comparison allowed an unambiguous assignment of the desired *anti,syn*-crotylation product **2b** and of the *syn,syn*-crotylation product **2a**. Unexpectedly, product **2a** of the BF_3-mediated crotylation is formally the product of chelation-control. The *anti,syn*-crotylation product **2b**, which is a model for the C-9/C-15 fragment of geldanamycin, was obtained by a reagent-controlled crotylation with the chiral (*Z*)-crotylborane **23**.

1. Introduction

The ansamycin[1] antibiotic geldanamycin (**1**) was isolated as early as 1970[2] and its structure (Scheme 1) was elucidated shortly thereafter.[3] Although other ansamycin antibiotics subsequently attracted synthetic attention and total syntheses of macbecin I[4] and herbimycin A[5] were reported, geldanamycin was not a focus of synthetic organic chemists until recently.[6] The situation changed when the significant antitumour activity of geldanamycin became public[7] and it changed even more so when its mode of action became increasingly apparent.[8] Without going into details[9] it is now generally accepted that at least part of the antitumour activity of geldanamycin is attributed to its complexation to the heat shock protein 90 (Hsp 90).[10] It binds to the N-terminal ATP/ADP-binding domain of Hsp 90[11] and inhibits the ATPase activity which is essential for the function of the enzyme.[12] The Hsp90 chaperone machinery in turn is a crucial enzyme apparatus required by many proteins overexpressed in cancer cells.[13]

So far, synthetic work on geldanamycin has resulted in one total synthesis by Andrus and et al.[14] Synthetic modifications of natural geldanamycin have been reported[15] as have chimeric compounds[16] combining properties of both geldanamycin and other Hsp90 binding compounds. Synthetic approaches to geldanamycin



Scheme 1. A possible access to a model (**2**) for the C-9/C-15 fragment of geldanamycin (**1**) by allylsilane addition to the chiral aldehyde **3**.

Keywords: Ansamycins; Allyl transfer; Felkin-Anh control; Chelation control; Stereoselective synthesis.
* Corresponding author. Tel.: +49 89 28913330; fax: +49 89 28913315; e-mail: thorsten.bach@ch.tum.de
† Present address: Institut für Anorganische und Analytische Chemie, Technische Universität Carolo-Wilhelmina, Hagenring 30, 38106 Braunschweig, Germany.

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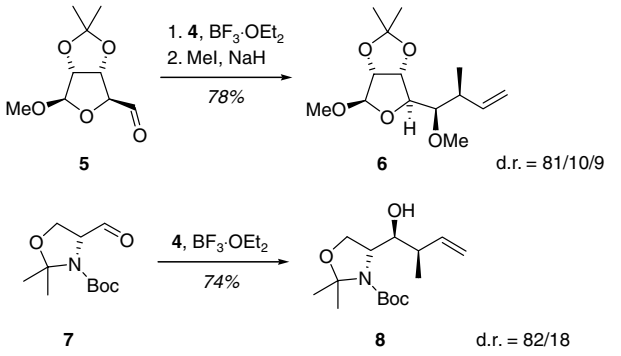


Scheme 2. Precedence for a Felkin-Anh type addition of (*E*)-crotylsilane **4** to α-chiral aldehydes in the presence of BF_3.

and syntheses of simplified geldanamycin analogues have been published.[17]

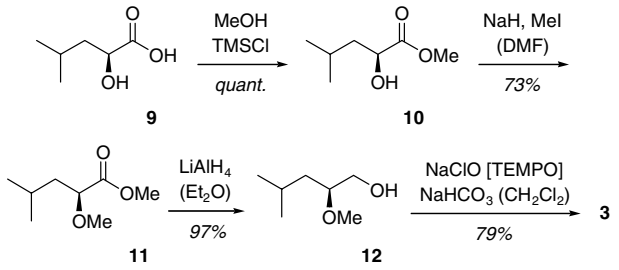
From an inspection of the Hsp90/geldanamycin complex[11a] it is suggested that the stereogenic centres at C-10 to C-12 and at C-14 play an important role in stabilizing the C-shaped conformation of the bound molecule. In a modular approach to geldanamycin analogues it will consequently be important to successfully address the question of how to stereoselectively construct this part of the molecule. A possible access to the C-9/C-15 fragment of geldanamycin and more specifically to the stereogenic centres at C-10 and C-11 is a substrate-controlled Felkin-Anh type crotylation of an α-chiral methoxycarbaldehyde with (*E*)-crotylsilane (**4**). Precedence for diastereoeselective reactions of this type exists (Scheme 2). Danishefsky et al.[18] reported on the reaction of aldehyde **5** with silane **4** in the presence of $BF_3{\cdot}OEt_2$ and Taddei et al.[19] observed a similar selectivity in the addition to the chiral α-aminoaldehyde **7**. In both cases the Felkin-Anh products **6** and **8** predominated.

Encouraged by this precedence we considered the γ-branched α-methoxycarbaldehyde **3** as a reasonable model to mimic a more complex aldehyde related to geldanamycin (Scheme 1). We hoped for a selective addition of silane **4** to yield the *anti*,*syn*-diastereoisomer **2b** of alcohol **2**. In this paper, we disclose the results of our study. The preparation of aldehyde **3** and its crotylation are described. An unambiguous configuration assignment required the synthesis of structurally characterized 1,3-diols for comparison, the syntheses of which are also presented. The unexpected result that the BF_3-promoted crotylation led to the *syn,syn*-alcohol **2a** is discussed. Finally, it was shown that a reagent-controlled crotylation of aldehyde **3** to **2b** is feasible.

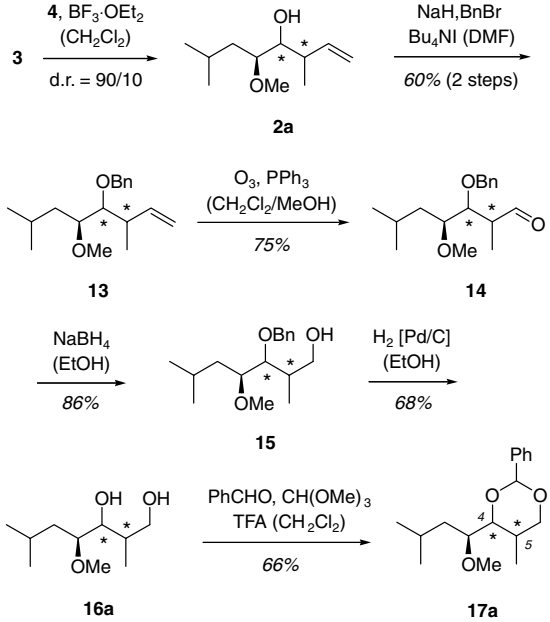
2. Synthesis of aldehyde *3* and crotylation

The synthesis of aldehyde **3** commenced with the known stereospecific hydroxy-de-amination of L-leucine conducted with $NaNO_2$ in 2 N H_2SO_4.[20] Acid **9** furnished methyl ester **10** upon activation with trimethylsilyl chloride (TMSCl) employing methanol as the solvent and 2,2-dimethoxypropane as additional dehydrating reagent (Scheme 3). The hydroxy ester **10** was O-methylated with sodium hydride and methyl iodide in DMF at ambient temperature. The sequence esterification/methylation was higher yielding than the double methylation of acid **9** with NaH/MeI (50% yield). Further conversion to the desired aldehyde **3** was achieved by complete reduction of ester **11** to alcohol **12** and subsequent tetramethylpiperidine-*N*-oxyl(TEMPO)-catalyzed[21] oxidation. The enantiomeric purity of alcohol **12** was determined by preparation of the corresponding α-methoxy-α-trifluoromethylphenyl acetate (Mosher's ester). The diastereomerically pure product prepared from **12** and (*S*)-Mosher's acid[22] was compared with the diastereomeric mixture prepared from **12** and racemic Mosher's acid. The crotylation reagent **4** was prepared from (*E*)-crotyl chloride in two steps according to a literature procedure.[19]

The crotylation of aldehyde **3** was attempted under various conditions. Particular emphasis was given to non-chelating Lewis acids as promoters in order to achieve the desired Felkin-Anh-control. Indeed, $BF_3{\cdot}OEt_2$ turned out to be an efficient catalyst and allowed for the silane addition at −78 °C (Scheme 4).



Scheme 3. Preparation of aldehyde **3** from the L-leucine derived enantiomerically pure α-hydroxycarboxylic acid **9**.



Scheme 4. Allyltransfer to aldehyde **3** with (*E*)-crotylsilane **4** and subsequent conversion of its product **2a** to diol **16a** and acetal **17a**.

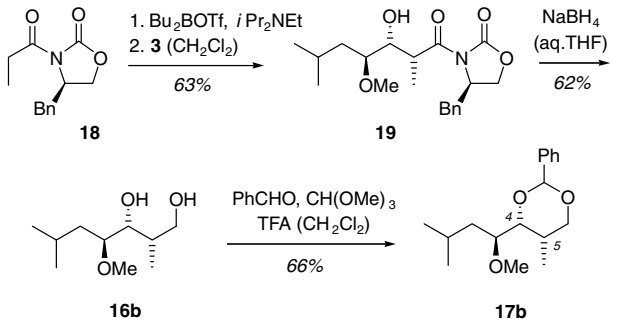
Overstoichiometric amounts of $BF_3{\cdot}OEt_2$ (1.5 equivalents relative to **3**) were employed to facilitate a smooth conversion. ^{1}H NMR analysis of the crude product mixture revealed a diastereomeric ratio (d.r.) of 90/10 in favour of product **2a**. The stereochemical result with two equivalents $BF_3{\cdot}OEt_2$ were similar (d.r. $\geqslant$90/10). One equivalent of $BF_3{\cdot}OEt_2$ delivered a mixture of three diastereoisomers in a ratio of 2:1:1 with **2a** being the predominant diastereoisomer. Due to its instability the isolation and storage of major product **2a** was difficult and it was therefore converted into the benzyl ether **13**. At the benzyl ether stage the separation of diastereoisomers was feasible and diastereomerically pure product **13** was obtained in 60% from aldehyde **3** over two steps.

In order to determine the relative configuration among the newly formed stereogenic centres marked with an asterisk (*) benzyl ether **13** was converted to diol **16a** in three steps. Ozonolysis and reductive work-up yielded aldehyde **14**, which was further reduced to primary alcohol **15**. Hydrogenolytic cleavage of the benzyl ether gave the desired diol **16a**. Acetal formation delivered 1,3-dioxane **17a** which allowed for the assignment of the relative configuration at the stereogenic centres C-4 and C-5 in the dioxane ring. The coupling constant ^3J between H-4 and H-5 was determined as 2.3 Hz. Coupling constants of H-5 to the protons at C-6 were equally small (1.5 and 2.0 Hz) indicating that all hydrogen atoms are in an anti- or synclinal conformation (eq/eq, eq/ax, or ax/eq relative to each other). This observation leads to the immediate conclusion that the phenyl group and the substituent at C-4 are equatorially positioned and the methyl group at C-5 axially. The simple diastereoselectivity of the crotylation step to product **2a** had consequently led to the expected *syn*-connectivity between the methyl group and the hydroxy group.

The configuration of the newly formed stereogenic centres relative to the stereogenic centre of the α-methoxycarbaldehyde (facial diastereoselectivity) had to be proven by comparison with synthetic samples. Despite the precedence for Felkin-Anh-control (Scheme 2) this effort seemed appropriate because there was reasonable doubt about the desired *anti*,*syn*-configuration of product **2a**. The doubt originated from the crotylation experiments we conducted in the presence of chelating Lewis acids, such as $TiCl_4$. With $TiCl_4$ as catalyst, two products were formed in equal quantities, one of which was identical to compound **2a**. It was difficult to understand why $TiCl_4$ should lead to the product resulting from Felkin-Anh-control and it was equally difficult to understand why BF_3 would lead to the *syn*,*syn* chelation-control product.

3. Aldol addition reactions to aldehyde 3

Diols **16** appeared to be easily accessible from the corresponding aldol addition products by reduction. Using the well-established Evans methodology,[23] aldol addition product **19** was generated and subsequently reduced to diol **16b** (Scheme 5). The relative configuration of



Scheme 5. Preparation of diol **16b** and acetal **17b** by auxiliary-controlled Evans aldol addition to aldehyde **3** and consecutive transformations.

compound **19** was established by single crystal X-ray crystallography (Fig. 1). Suitable crystals were grown by adding pentane to a saturated solution of **19** in CH_2Cl_2. As soon as the solution became turbid it was cooled to −5 °C and allowed to stand at this temperature. The crystallographic result was in line with the expectation for an auxiliary-controlled aldol addition with *N*-propionyl-(*S*)-4-benzyl-2-oxazolidinone (**18**).[24] Diol **16b**, however, was not identical to diol **16a** obtained in the crotylation studies nor was the corresponding 1,3-dioxane **17b** identical with **17a**.

^{1}H NMR studies with dioxane **17b** resulted in the coupling constants (see chapter 2) typical for a *syn*-aldol product, that is, the coupling constants for H-4 and H-5 (^3J = 2.3 Hz) as well as for H-5 and both protons at C-6 (1.6 and 2.4 Hz) were small. Since the *anti*,*syn*-diol **16b** was not identical with **16a** and since the relative configuration of **16a** is *syn* at the CHMe-CHOH part (vide infra), diol **16a** must have the *syn*,*syn*-configuration resulting from a *syn*,*syn*-crotylation product **2a**.

Additional proof for this assignment came from another aldol addition we conducted with the propionate equivalent **18** (Scheme 6). Under conditions earlier described by Heathcock et al.[25] using two equivalents of Bu_2BOTf a major addition product was isolated, the configuration of which was also elucidated by single crystal X-ray crystallography (Fig. 2). It turned out to be the *syn*,*syn*-diastereoisomer **20**. Reduction of product **20** gave diol **16a** and further acetal formation yielded **17a**.

By comparison of their analytical data, the identity of compounds **16a** and **17a** obtained either from **20** or from

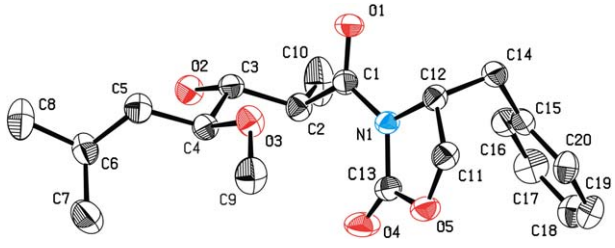
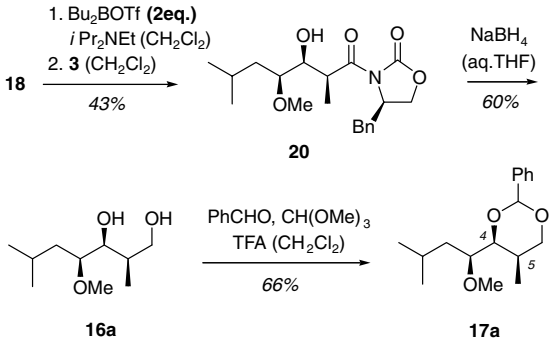
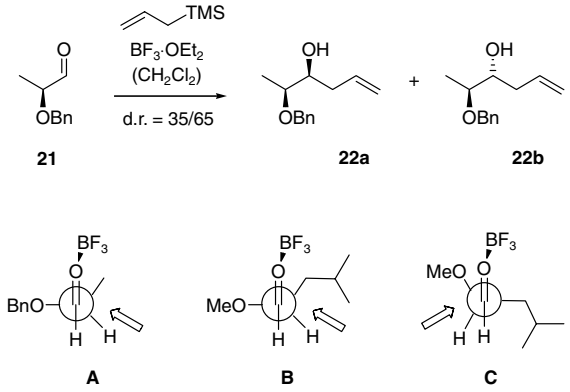


Figure 1. Structure of compound **19** in the crystal.



Scheme 6. Preparation of *syn*,*syn*-diol **16a** by aldol addition of a boron enolate generated from *N*-propionyloxazolidinone **18** and 2 equivalents Bu_2BOTf.



Scheme 7. Allylation of aldehyde **21** and possible reactive conformations A–C for carbonyl addition to α-alkoxyaldehydes **21** and **3**.

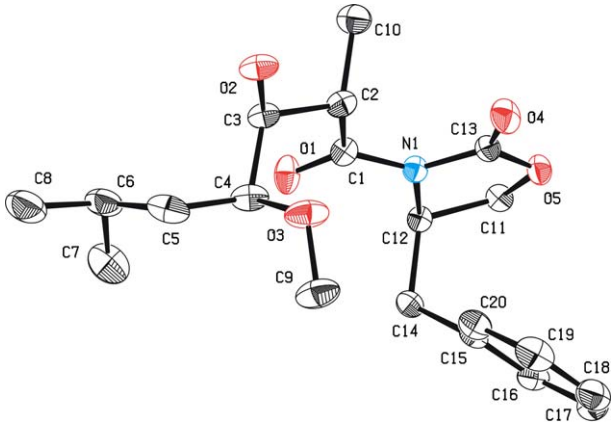


Figure 2. Structure of compound **20** in the crystal.

crotylation product **2a** was unequivocally established. The specific rotation of the compounds was identical proving that all steps leading from acid **9** to product **17a** had proceeded racemization-free.

It had to be concluded from these studies that the BF_3-promoted addition of crotylsilane **4** to aldehyde **3** (Scheme 4) proceeded to the formal product of a chelation-controlled addition.

4. Discussion

Felkin-Anh-control has been observed in the BF_3-promoted addition of allyltrimethylsilane to aldehydes. A typical substrate is the *O*-benzyl protected chiral aldehyde **21** (Scheme 7).[26]

The excess of product **22b** has been interpreted by the conformation **A** and a preferential *Re* face attack.[27] A similar conformation **B** for **3** is not in line with the result we obtained. Rather it appears as if the *iso*-butyl group resides in the position perpendicular to the carbonyl group which is normally adopted by the best σ*-acceptor (**C**).[28] A conformation related to **C** has been suggested to account for a deviation from the Felkin-Anh model in the BF_3-mediated addition of a silyl enol ether to an α-chiral aldehyde.[29] In the latter case, an α-silyloxyaldehyde was involved as the electrophile but not an α-methoxyaldehyde. An increase of formal chelation product upon an increase in $BF_3{\cdot}OEt_2$ concentration (3 equiv instead of 1.2. equiv) was observed in the addition of allyltin compounds to cyclohexylidene glyceraldehyde.[30] The $BF_3{\cdot}OEt_2$-mediated crotylation of a chiral α-benzyloxycarbaldehyde with crotylstannane resulted in the preferred formation of the formal chelation versus Felkin-Anh product (d.r. = 67/33).[31]

The fact that superstoichiometric amounts of $BF_3{\cdot}OEt_2$ were required to achieve a high facial diastereoselectivity in the crotylation of **3** (vide infra) indicates that more than one molecule of BF_3 is complexed to substrate **3**. From data of related methyl ethers the pK_{HB} of the methyl ether group in **3** is estimated at around 1.1, while diethyl ether has a pK_{HB} of 1.01 and benzyl ethers of 0.7.[32] The pK_{HB} of the carbonyl group in an aliphatic aldehyde (acetaldehyde) was determined as 0.65.[33] The basicity of acetal groups ROCHR'OR (cf. substrate **5**) is lower (0.58 if statistically corrected for the presence of two Lewis basic groups).[32] Other studies support the given order of Lewis basicity.[34,35] Based on these data it is assumed that BF_3 complexation to aldehyde **3** occurs primarily at the methoxy group as depicted in Figure 3. Reetz et al. have suggested that double Lewis acid coordination of BF_3 to **21** leads to a conformation in which the carbonyl oxygen and the benzyloxy group are antiperiplanar (Cornforth[36] model).[26b] In our case, we favour the notion that additional activation by a second BF_3 molecule leads to conformation **C′** which in turn accounts for the observed *Si* face attack. A *Si* face view on the putative transition state TS-1 of the addition of crotylsilane[37] reveals that the incoming nucleophile

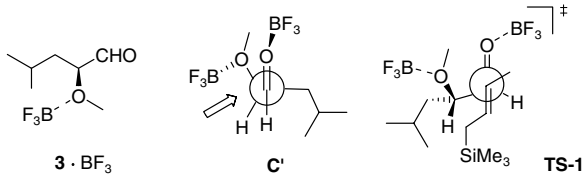
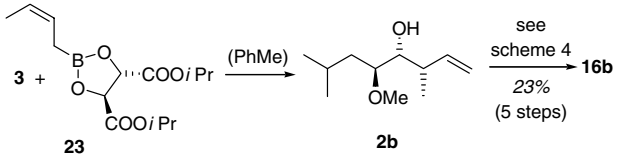


Figure 3. Model to explain the facial diastereoselectivity observed upon allyltransfer to aldehyde **3**.



Scheme 8. Reagent-controlled crotylation of aldehyde **3** to the *syn,anti*-product **2b** and its conversion to diol **16b**.

can readily approach the doubly complexed aldehyde without interfering with the methoxy group. It might be this interaction which forces the methoxy group out of its preferred position.[38]

The suggested transition state **TS-1** accommodates the simple diastereoselectivity of the C–C bond formation. The Lewis-acid coordination to the methoxy group is also in line with the outcome of the modified aldol reaction depicted in Scheme 6 via an open transition state. *Si* face attack at **3** and *Re* face attack at the chelated boron enolate derived from **18** lead to the formation of the observed major diastereoisomer **20**. A related transition state was put forward by Panek et al. to explain the unexpectedly high diastereoselectivity observed in the addition of a chiral silane to aldehyde **21**.[39]

Given the unexpected result of the crotylation studies with **3** it appeared appropriate to test a well-established reagent-controlled crotylation reaction for its suitability in the reaction of α-methoxycarbaldehydes. The method established by Roush et al.[40] was chosen for this purpose.[41] It was shown by transformation to diol **16b** that reagent **23** indeed delivers the expected product **2b**, which contains the desired *anti,syn*-stereotriade of geldanamycin.

The reagent-controlled approach apparently offers a viable solution for a diastereoselective *anti,syn*-crotylation of aldehyde **3** (Scheme 8) and for an analogous *anti,-syn*-aldol reaction (Scheme 5). Nonetheless, work in our laboratory on selective substrate-controlled crotylation reactions of α-methoxycarbaldehydes continues and will be reported in due course.

5. Experimental section

5.1. General

All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Tetrahydrofuran and diethyl ether were distilled from sodium immediately prior to use. Dichloromethane and diisopropylethylamine were distilled from calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or coloration with cerium ammonium molybdate (CAM). Optical Rotation: Perkin-Elmer 241 MC. NMR: Bruker AC-250, AV-360, AV-500. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. IR: Perkin-Elmer 1600 FT-IR. MS: Finnigan MAT 8200 (EI). Elemental Analysis: Elementar Vario EL. Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (ca. 50 g for 1 g of material to be separated) with the indicated eluent. Common solvents for chromatography [pentane (P), ethyl acetate (EA), dichloromethane (CH_2Cl_2)] were distilled prior to use.

5.1.1. (*S*)-2-Hydroxy-4-methylpentanoic acid methyl ester (10). Trimethylsilylchloride (190 μL, 163 mg, 1.50 mmol) was added to a solution of acid **9**[20] (1.98 g, 15.0 mmol) in dimethoxypropane (24 mL) and MeOH (6 mL). The mixture was stirred for 16 h at rt and the solvent removed in vacuo. The residue was diluted with Et_2O (20 mL), washed with H_2O (2× 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give **10** as a colourless oil (2.19 g, 15.0 mmol, 100%) R_f = 0.49 (P/EA 8:2) [CAM]; $[\alpha]_D^{20}$ −14.5 (*c* 0.98, Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.92 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.94 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 1.53 [ddd, 1 H, ^2J = 13.9 Hz, ^3J = 8.0 Hz, ^3J = 6.2 Hz, C*H*HCH(CH$_3$)$_2$], 1.57 [ddd, 1 H, ^2J = 13.9 Hz, ^3J = 7.9 Hz, ^3J = 5.2 Hz, C*H*HCH(CH$_3$)$_2$], 1.67 [*virt*. septet, $^3J \cong$ 6.9 Hz, 1 H, C*H*(CH$_3$)$_2$], 2.66 (s, 1 H, OH), 3.77 (s, 3 H, OCH$_3$), 4.17–4.23 (m, 1 H, C*H*OH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ = 21.6 [q, CH(*C*H$_3$)$_2$], 23.2 [q, CH(*C*H$_3$)$_2$], 24.4 [d, *C*H(CH$_3$)$_2$], 43.5 [t, *C*H$_2$CH(CH$_3$)$_2$], 52.4 [q, CO$_2$*C*H$_3$), 69.1 (d, CHOH), 176.3 (s, *C*OOCH$_3$); IR (neat): $\tilde{\nu}$ = 3478 cm^{-1} (br, OH), 2959 (s, CH), 2871 (m, CH), 1740 (s, C=O), 1470 (m, CH_2), 1439 (m), 1214 (s, COC), 1142 (s), 1089 (COC); MS (EI, 70 eV), *m/z* (%): 90 (26), 87 (43) [$C_5H_{11}O^+$], 69 (100), 59 (33) [$C_2H_3O_2^+$], 55 (11); elemental analysis calcd (%) for $C_7H_{14}O_3$ (146.18): C, 57.51; H, 9.65. Found: C, 57.12; H, 9.80.

5.1.2. (*S*)-2-Methoxy-4-methylpentanoic acid methyl ester (11). A solution of alcohol **10** (2.00 g, 13.6 mmol) in DMF (5 mL) was slowly added at 0 °C to a solution of sodium hydride (60% in mineral oil; 1.09 g, 27.4 mmol) and methyl iodide (4.28 mL; 9.71 g, 68.4 mmol) in DMF (30 mL). The mixture was stirred at rt for 5 h and then satd aq NH_4Cl (20 mL) was added. The mixture was diluted with H_2O (350 mL) and extracted with Et_2O (3× 150 mL). The combined organic layers were washed with brine (150 mL), dried ($NaSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography (P/EA 9/1) to give **11** as a colourless oil (1.59 g, 9.94 mmol, 73%). R_f = 0.34 (P/EA 9:1) [CAM]; $[\alpha]_D^{20}$ −45.1 (*c* 0.75, Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.90 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.91 [d, ^3J = 6.8 Hz, 3 H, CH(CH_3)$_2$], 1.48 [ddd, ^2J = 14.0 Hz, ^3J = 8.4 Hz, ^3J = 4.5 Hz, 1 H, C*H*HCH(CH$_3$)$_2$], 1.64 [ddd, ^2J = 14.0 Hz, ^3J = 9.0 Hz, ^3J = 5.4 Hz, 1 H, C*H*HCH(CH$_3$)$_2$], 1.67–1.84 [m, 1 H, C*H*(CH$_3$)$_2$], 3.33 (s, 3 H, CHOC*H*$_3$), 3.71 (s, 3 H,

$COOCH_3$), 3.78 (dd, $^3J = 9.0$ Hz, $^3J = 4.5$ Hz, 1 H, C*H*OCH_3); ^{13}C NMR (90.6 MHz, $CDCl_3$) $\delta = 21.7$ [q, CH(*C*H_3)$_2$], 22.9 [q, CH(*C*H_3)$_2$], 24.4 [d, *C*H$(CH_3)_2$], 41.7 [t, *C*H_2CH$(CH_3)_2$], 51.7 (q, CO_2*C*H_3), 58.0 (q, CHO*C*H_3), 79.2 (d, *C*HOCH_3), 173.6 (s, *C*$OOCH_3$); IR (neat): $\tilde{\nu} = 2958$ cm^{-1} (s, CH), 2871 (m, CH), 2828 (m, CH), 1753 (s, C=O), 1468 (m, CH_2), 1435 (m), 1270 (m), 1197 (s, COC), 1135 (s), 1113 (COC); MS (EI, 70 eV), *m/z* (%): 101 (100) [$C_6H_{13}O^+$], 69 (69), 59 (49) [$C_2H_3O_2^+$], 45 (40) [CHO_2^+]; elemental analysis calcd (%) for $C_8H_{16}O_3$ (160.21): C, 59.97; H, 10.07. Found: C, 59.69; H, 10.02.

5.1.3. (*S*)-2-Methoxy-4-methylpentan-1-ol (12). A solution of ester **11** (900 mg, 5.62 mmol) in Et_2O (5 mL) was slowly added at 0 °C to a suspension of sodium hydride (60% in mineral oil, 256 mg, 6.74 mmol) in Et_2O (20 mL). The mixture was stirred at rt for 3 h and then H_2O (20 mL) was added carefully. The organic layer was separated, washed with satd aq $NaHCO_3$ (2× 20 mL) and brine (20 mL), dried ($NaSO_4$), filtered and concentrated in vacuo to give **12** as a colourless oil (720 mg, 5.45 mmol, 97%). $R_f = 0.27$ (P/EA 9:1) [CAM]; $[\alpha]_D^{20}$ −7.9 ($c = 1.0$, Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.88$ [d, $^3J = 6.6$ Hz, 3 H, CH(C*H*$_3$)$_2$], 0.89 [d, $^3J = 6.6$ Hz, 3 H, CH(C*H*$_3$)$_2$], 1.20 [ddd, $^2J = 13.9$ Hz, $^3J = 7.2$ Hz, $^3J = 6.2$ Hz, 1 H, C*H*HCH$(CH_3)_2$], 1.45 [d *virt*. t, $^2J = 13.9$ Hz, $^3J \cong 6.9$ Hz, 1 H, C*H*HCH$(CH_3)_2$], 1.57–1.72 [m, 1 H, C*H*$(CH_3)_2$], 2.41 (s, 1 H, OH), 3.29 (dd *virt.* t, $^3J = 6.8$ Hz, $^3J = 3.3$ Hz, $^3J \cong 6.2$ Hz, 1 H, C*H*OCH_3), 3.37 (s, 3 H, OCH_3), 3.42 (dd, $^2J = 11.6$ Hz, $^3J = 6.0$ Hz, 1 H, C*H*HOH), 3.65 (dd, $^2J = 11.5$ Hz, $^3J = 3.3$ Hz, 1 H, C*H*HOH); ^{13}C NMR (90.6 MHz, $CDCl_3$) $\delta = 22.8$ [q, CH(*C*H_3)$_2$], 22.9 [q, CH(*C*H_3)$_2$], 24.7 [d, *C*H$(CH_3)_2$], 39.7 [t, *C*H_2CH$(CH_3)_2$], 56.9 (q, CHO*C*H_3), 64.0 (t, *C*H_2OH), 80.0 (d, *C*HOCH_3); IR (neat): $\tilde{\nu} = 3420$ cm^{-1} (br, OH), 2955 (s, CH), 2832 (s, CH), 2870 (s, CH), 2826 (m, CH), 1467 (m, CH_2), 1367 (m), 1100 (s, COC), 1053 (m); MS (EI, 70 eV), *m/z* (%): 101 (100) [$C_6H_{13}O^+$], 75 (22) [$C_3H_7O_2^+$], 69 (91), 59 (69) [$C_3H_7O^+$], 45 (70) [$C_2H_5O^+$], 43 (40); elemental analysis calcd (%) for $C_7H_{16}O_2$ (132.20): C, 63.60; H, 12.20. Found: C, 63.44; H, 12.33.

5.1.4. (*S*)-2-Methoxy-4-methylpentanal (3). A solution of TEMPO (1.77 mg, 11.0 μmol) and potassium bromide (13.5 mg, 114 μmol) in 5% aq $NaHCO_3$ (0.54 mL) and CH_2Cl_2 (2.5 mL) was treated with alcohol **12** (150 mg, 1.14 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After addition of 13% aq NaOCl (0.6 mL), the reaction mixture was monitored by TLC and more aq NaOCl (0.3 mL) was added (1 h). After complete conversion of the alcohol, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (2× 3 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (2× 3 mL) and brine (2× 3 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give **3** as a colourless oil (116 mg, 900 μmol, 79%). $R_f = 0.89$ (P/Et_2O 4/6) [CAM]; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.93$ [d, $^3J = 6.6$ Hz, 3 H, CH(C*H*$_3$)$_2$], 0.94 [d, $^3J = 6.7$ Hz, 3 H, CH(C*H*$_3$)$_2$], 1.42 [ddd, $^2J = 14.2$ Hz, $^3J = 8.3$ Hz, $^3J = 4.8$ Hz 1 H, C*H*HCH$(CH_3)_2$], 1.54 [ddd, $^2J = 14.2$ Hz, $^3J = 8.8$ Hz, $^3J = 5.7$ Hz, 1 H, C*H*HCH$(CH_3)_2$], 1.57–1.90 [m, 1 H, C*H*$(CH_3)_2$], 3.40 (s, 3 H, OCH_3), 3.60 (ddd, $^3J = 8.8$ Hz, $^3J = 4.8$ Hz, $^3J = 2.2$ Hz, 1 H, C*H*OCH_3), 9.64 (d, $^3J = 2.2$ Hz 1 H, CHO); ^{13}C-NMR (90.6 MHz, $CDCl_3$) $\delta = 21.9$ [q, CH(*C*H_3)$_2$], 23.1 [q, CH(*C*H_3)$_2$], 24.2 [d, *C*H$(CH_3)_2$], 38.5 [t, *C*H_2CH$(CH_3)_2$], 58.3 (q, CHO*C*H_3), 84.5 (d, *C*HOCH_3), 204.0 (d, CHO); IR (neat): $\tilde{\nu} = 2958$ cm^{-1} (s, CH), 2872 (s, CH), 2826 (m, CH), 1734 (s, C=O), 1468 (m, CH_2), 1368 (m), 1100 (s, COC); MS (EI, 70 eV), *m/z* (%): 101 (91) [$C_6H_{13}O^+$], 71 (22), 69 (95), 59 (100) [$C_3H_7O^+$], 55 (18) [$C_4H_7^+$].

5.1.5. (3*R*,4*S*,5*S*)-5-Methoxy-3,7-dimethyl-oct-1-en-4-ol (2a). A solution of aldehyde **3** (148 mg, 1.14 mmol) in CH_2Cl_2 (3 mL) was added at −78 °C to a solution of $BF_3{\cdot}Et_2O$ (210 μL, 242 mg, 1.70 mmol) in CH_2Cl_2 (15 mL). After 20 min, the mixture was treated with (*E*)-crotyltrimethylsilane[19] (182 mg, 1.42 mmol) and was stirred for 12 h at −78 °C. H_2O (20 mL) was added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (2× 15 mL). The combined organic extracts were combined, washed with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), dried ($NaSO_4$), filtered and concentrated to give the crude product (*dr* 9/1, determined by ^{1}H NMR) as a yellow oil. The residue was purified by flash chromatography for NMR analysis (P/Et_2O 8/2) to yield **2a** as a colourless oil (35.4 mg, 190 μmol, 17%, 2 steps). Due to the instability of the compound, for preparative purposes the crude product was directly used in the next reaction leading to higher yields. $R_f = 0.24$ (P/Et_2O 8/2) [CAM]; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.90$ [d, $^3J = 6.6$ Hz, 3 H, CH(C*H*$_3$)$_2$], 0.94 [d, $^3J = 6.6$ Hz, 3 H, CH(C*H*$_3$)$_2$], 1.07 [d, $^3J = 6.8$ Hz, 3 H, C(OH)CHC*H*$_3$], 1.42 [*virt*. t, $^3J \cong 7.0$ Hz, 1 H, C*H*HCH$(CH_3)_2$], 1.43 [*virt.* t, $^3J \cong 6.6$ Hz, 1 H, C*H*HCH$(CH_3)_2$], 1.67 [*virt*. septet, $^3J \cong 6.7$ Hz, 1 H, C*H*$(CH_3)_2$], 2.09 (d, $^3J = 7.6$ Hz, 1 H, OH), 2.37 [*virt*. sex, $^3J \cong 7.4$ Hz, 1 H, C(OH)C*H*CH_3], 3.18–3.24 (m, 1 H, C*H*OH), 3.30 (d *virt*. t, $^3J = 3.1$ Hz, $^3J \cong 6.6$ Hz, 1 H, C*H*OCH_3), 3.39 (s, 3 H, OCH_3), 5.04 (ddd, $^2J = 1.9$ Hz, $^3J = 10.3$ Hz, $^4J = 0.7$ Hz, 1 H, CH=CH*H*), 5.07 (ddd, $^2J = 1.9$ Hz, $^3J = 17.2$ Hz, $^4J = 1.0$ Hz, 1 H, CH=CH*H*), 5.73 (ddd, $^3J = 17.2$ Hz, $^3J = 10.3$ Hz, $^3J = 8.2$ Hz, 1 H, C*H*=CH_2); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 16.0$ [q, C(OH)CH*C*H_3], 22.8 [q, CH(*C*H_3)$_2$], 23.1 [q, CH(*C*H_3)$_2$], 24.6 [d, *C*H$(CH_3)_2$], 39.8 [t, *C*H_2CH$(CH_3)_2$], 41.7 [d, C(OH)*C*HCH_3], 57.8 (q, OCH_3), 76.2 (d, *C*HOH), 78.8 (d, *C*HOCH_3), 114.9 (t, CH=*C*H_2), 141.6 (d, *C*H=CH_2); IR (neat): $\tilde{\nu} = 3458$ cm^{-1} (br, OH), 2958 (s, CH), 2933 (s, CH), 2870 (s, CH), 2825 (s, CH), 1640 (w, C=C), 1466 (m, CH_2), 1367 (m), 1102 (s, COC), 913 (m, C=C); MS (EI, 70 eV), *m/z* (%): 131 (48) [$C_7H_{15}O_2^+$], 101 (83) [$C_6H_{13}O^+$], 81 (32), 74 (34), 69 (97), 59 (65) [$C_3H_7O^+$], 55 (100); HRMS: *m/z*: calcd for $C_{11}H_{20}O$ [$M^+ - H_2O$]: 168.1514; found: 168.1510.

5.1.6. 1-(((3*R*,4*S*,5*S*)-5-Methoxy-3,7-dimethyl-oct-1-on-4-yloxy)-methyl)-benzene (13). Sodium hydride (60% in mineral oil, 68.6 mg, 1.72 mmol), benzyl bromide (328 μL, 469 mg, 2.74 mmol) and Bu_4NI (5.07 mg, 13.7 μmol) were added at rt to the solution of the crude

alcohol **2a** in DMF (10 mL). After 1.5 h stirring at rt, the suspension was treated with H_2O (30 mL) and the aqueous layer extracted with Et_2O (3× 15 mL). The combined organic layers were washed with H_2O (2× 15 mL) and brine (2× 15 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (P/Et_2O 97/3) to give **13** as a colourless oil (190 mg, 686 μmol, 60%, 2 steps). $R_f = 0.20$ (P/Et_2O 97/3) [CAM]; $[\alpha]_D^{20}$ −43.3 (*c* 1.1, Et_2O); ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.91$ [d, $^3J = 6.6$ Hz, 3 H, CH(CH_3)$_2$], 0.92 [d, $^3J = 6.6$ Hz, 3 H, CH(CH_3)$_2$], 1.09 [d, $^3J = 6.9$ Hz, 3 H, C(OBn)CHCH_3], 1.34 [ddd, 1 H, $^2J = 13.7$ Hz, $^3J = 8.2$ Hz, $^3J = 7.5$ Hz, CHHCH(CH$_3$)$_2$], 1.44 [ddd, 1 H, $^2J = 13.7$ Hz, $^3J = 8.2$ Hz, $^3J = 5.7$ Hz, CHHCH(CH$_3$)$_2$], 1.67–1.79 [m, 1 H, CH(CH$_3$)$_2$], 2.54 [dqddd, $^3J = 7.3$ Hz, $^3J = 6.9$ Hz, $^3J = 6.4$ Hz, $^4J = 1.1$ Hz, $^4J = 0.9$ Hz, 1 H, C(OBn)CHCH$_3$], 3.25 (dd, $^3J = 6.4$ Hz, $^3J = 4.9$ Hz, 1 H, CHOBn), 3.34 (d *virt*. t, $^3J = 8.2$ Hz, $^3J \cong 4.8$ Hz, 1 H, CHOCH$_3$), 3.40 (s, 3 H, OCH$_3$), 4.50–4.72 (m, 2 H, CH$_2$Ph), 4.99 (ddd, $^2J = 1.9$ Hz, $^3J = 10.3$ Hz, $^4J = 0.9$ Hz, 1 H, CH=CHH), 5.06 (ddd, $^2J = 1.9$ Hz, $^3J = 17.2$ Hz, $^4J = 1.1$ Hz, 1 H, CH=CHH), 5.88 (ddd, $^3J = 17.2$ Hz, $^3J = 10.3$ Hz, $^3J = 7.3$ Hz, 1 H, CH=CH$_2$), 7.27–7.38 (m, 5 H, CH$_{ar}$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 15.5$ [q, C(OH)CH*C*H$_3$], 22.4 [q, CH(*C*H$_3$)$_2$], 23.4 [q, CH(*C*H$_3$)$_2$], 24.6 [d, *C*H(CH$_3$)$_2$], 39.7 [t, *C*H$_2$CH(CH$_3$)], 40.2 [d, C(OBn)*C*HCH$_3$], 58.6 (q, OCH$_3$), 74.3 (t, CH$_2$Ph), 80.4 (d, *C*HOCH$_3$), 84.6 (d, CHOBn), 113.8 (t, CH=*C*H$_2$), 127.4 (d, C$_{ar}$H), 127.8 (d, C$_{ar}$H), 128.4 (d, C$_{ar}$H), 139.0 (s, C$_{ar}$), 142.1 (d, *C*H=CH$_2$); IR (neat): $\tilde{\nu} = 2955\ cm^{-1}$ (s, CH), 2931 (s, CH), 2869 (s, CH), 1639 (w, C=C), 1465 (m, CH$_2$), 1368 (m), 1093 (s, COC), 912 (m, C=C), 733 (m, C$_{ar}$H), 696 (s, C$_{ar}$H); MS (EI, 70 eV), *m*/*z* (%): 221 (17) [$C_{14}H_{21}O_2^+$], 175 (6) [$C_{12}H_{15}O^+$], 147 (8), 91 (100) [$C_7H_7^+$], 69 (25), 59 (13) [$C_3H_7O^+$], 45 (14) [$C_2H_5O^+$]; HRMS: *m*/*z*: calcd for $C_{18}H_{28}O_2$: 267.2089; found: 267.2089.

5.1.7. (2*S*,3*S*,4*S*)-3-Benzyloxy-4-methoxy-2,6-dimethylheptanal (14). Olefin **13** (92.0 mg, 333 μmol) was dissolved in CH_2Cl_2 (30 mL) and MeOH (8 mL). Ozone was bubbled through the solution at −78 °C until the colourless solution turned blue (2 min). After changing the atmosphere to nitrogen (5 min), the mixture was treated with triphenylphosphine (199 mg, 760 μmol), warmed to rt (15 min) and stirred for 30 min. The solvent was removed in vacuo and the crude product purified by flash chromatography (P/Et_2O 8/2) to give **14** as a colourless oil (69.0 mg, 248 μmol, 75%). $R_f = 0.21$ (P/Et_2O 8/2) [CAM]; ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.87$ [d, $^3J = 6.5$ Hz, 3 H, CH(CH_3)(CH$_3$)], 0.88 [d, $^3J = 6.5$ Hz, 3 H, CH(CH_3)(CH$_3$)], 1.10 [d, $^3J = 7.0$ Hz, 3 H, C(OBn)CHCH_3], 1.40–1.46 [m, 2 H, CH_2CH(CH$_3$)$_2$], 1.55 [m, 1 H, CH(CH$_3$)$_2$], 2.69 [qdd, $^3J = 7.1$ Hz, $^3J = 5.5$ Hz, $^3J = 1.2$ Hz, 1 H, C(OBn)CHCH$_3$], 3.27 (s, 3 H, OCH$_3$), 3.29 (ddd, $^3J = 7.1$ Hz, $^3J = 6.1$ Hz, $^3J = 3.8$ Hz, 1 H, CHOCH$_3$), 3.71 (dd, $^3J = 5.5$ Hz, $^3J = 3.7$ Hz, 1 H, CHOBn), 4.57–4.71 (m, 2 H, CH$_2$Ph), 7.27–7.38 (m, 5 H, CH$_{ar}$), 9.75 (d, $^3J = 1.2$ Hz, 1 H, CHO); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 10.0$ [q, C(OBn)CH*C*H$_3$], 22.7 [q, CH(*C*H$_3$)$_2$], 22.9 [q, CH(*C*H$_3$)$_2$], 24.7 [d, *C*H(CH$_3$)$_2$], 38.9 [t, *C*H$_2$CH(CH$_3$)], 46.8 [d, C(OBn)*C*HCH$_3$], 57.8 (q, OCH$_3$), 73.1 (t, *C*H$_2$Ph), 78.7 (d, *C*HOCH$_3$), 80.4 (d, *C*HOBn), 127.9 (d, C$_{ar}$H), 128.2 (d, C$_{ar}$H), 128.4 (d, C$_{ar}$H), 137.9 (s, C$_{ar}$), 202.4 (d, CHO); IR (neat): $\tilde{\nu} = 2955\ cm^{-1}$ (s, CH), 2933 (s, CH), 2869 (s, CH), 2826 (m, CH), 1720 (s, C=O), 1454 (m, CH$_2$), 1093 (s, COC), 912 (m), 784 (s, C$_{ar}$H), 699 (m, C$_{ar}$H).

5.1.8. (2*R*,3*S*,4*S*)-3-Benzyloxy-4-methoxy-2,6-dimethylheptan-1-ol (15). Sodium borohydride (7.77 mg, 210 μmol) was added at rt to a solution of aldehyde **14** (52.0 mg, 187 μmol) in EtOH (5 mL). After stirring at rt for 30 min, the reaction mixture was treated with 1 N HCl (5 mL) and the aqueous layer extracted with Et_2O (3× 10 mL). The combined organic layers were washed with H_2O (3× 10 mL) and brine (2× 10 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (P/Et_2O 1/1) to give **15** as a colourless oil (45.0 mg, 161 μmol, 86%). $R_f = 0.21$ (P/Et_2O 1/1) [CAM]; $[\alpha]_D^{20}$ −51.2 (*c* 2.0, Et_2O), ^1H NMR (360 MHz, $CDCl_3$): $\delta = 0.92$ [d, $^3J = 6.9$ Hz, 3 H, CH(CH_3)$_2$], 0.93 [d, $^3J = 6.9$ Hz, 3 H, CH(CH_3)$_2$], 0.95 [d, $^3J = 6.9$ Hz, 3 H, C(OBn)CHCH_3], 1.32–1.40 [m, 1 H, CHHCH(CH$_3$)$_2$], 1.42–1.51 [m, 1 H, CHHCH(CH$_3$)$_2$], 1.63–1.76 [m, 1 H, CH(CH$_3$)$_2$], 1.92–2.03 [m, 1 H, C(OBn)CH(CH$_3$)], 2.73 (s, 1 H, OH), 3.37–3.42 [m, 2 H, CH(OCH$_3$)CH(OBn)], 3.44 (s, 3 H, OCH$_3$), 3.49 (dd, $^2J = 12.6$ Hz, $^3J = 8.2$ Hz, 1 H, CHHOH), 3.59 (dd, $^2J = 11.6$ Hz, $^3J = 4.2$ Hz, CHHOH), 4.60–4.72 (m, 2 H, CH$_2$Ph), 7.27–7.36 (m, 5 H, CH$_{ar}$); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 12.8$ [q, C(OBn)CH*C*H$_3$], 22.2 [q, CH(*C*H$_3$)$_2$], 23.4 [q, CH(*C*H$_3$)$_2$], 24.7 [d, *C*H(CH$_3$)$_2$], 36.8 [d, C(OBn)*C*HCH$_3$], 38.9 [t, *C*H$_2$CH(CH$_3$)], 58.4 (q, OCH$_3$), 65.8 (t, CH$_2$OH), 73.6 (t, *C*H$_2$Ph), 80.2 (d, *C*HOCH$_3$), 81.8 (d, *C*HOBn), 127.6 (d, C$_{ar}$H), 128.0 (d, C$_{ar}$H), 128.3 (d, C$_{ar}$H), 138.5 (s, C$_{ar}$); IR (neat): $\tilde{\nu} = 2955\ cm^{-1}$ (s, CH), 2931 (s, CH), 2869 (s, CH), 1465 (m, CH$_2$), 1368 (m), 1154 (m), 1104 (s, COC), 1028 (s), 734 (s, C$_{ar}$H), 698 (m, C$_{ar}$H); MS (EI, 70 eV), *m*/*z* (%): 179 (13) [$C_{11}H_{15}O_2^+$], 101 (28) [$C_6H_{13}O^+$], 91 (100) [$C_7H_7^+$], 69 (30), 59 (15) [$C_3H_7O^+$], 45 (17) [$C_2H_5O^+$]; HRMS: *m*/*z*: calcd for $C_{17}H_{28}O_3$: 280.2039. Found: 280.2037.

5.1.9. (2*R*,3*S*,4*S*)-4-Methoxy-2,6-dimethylheptan-1,3-diol (16a). Method A (from **15**). Palladium on carbon (10%, 10.6 mg, 9.99 μmol) was added to a solution of alcohol **15** (28.0 mg, 99.9 μmol) in EtOH (4 mL). This mixture was vigorously stirred for 10 h under hydrogen atmosphere (800–900 Torr) at rt. Evaporation of the solvent in vacuo and flash chromatography (P/Et_2O 1/9) of the residue on silica gel afforded **16a** as a colourless oil (13.3 mg, 69.9 μmol, 70%). **Method B** (from **20**): sodium borohydride (127 mg, 3.36 mmol) was added at 0 °C to a solution of oxazolidinone **20** (110 mg, 303 mmol) in THF/H_2O (5/1, 5 mL). After stirring at rt for 10 h, the reaction mixture was treated with 2 N HCl (4 mL) and the aqueous layer extracted with Et_2O (3× 5 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product

was purified by flash chromatography (P/Et_2O 1/9) to give **16a** as a colourless oil (42.0 mg, 221 μmol, 73%). R_f = 0.27 (P/Et_2O 1/9) [CAM]; $[\alpha]_D^{20}$ −20.9 (*c* 1.0, Et_2O), ^1H NMR (360 MHz, $CDCl_3$): δ = 0.93 [d, ^3J = 6.8 Hz, 3 H, $CH(CH_3)_2$], 0.96 [d, ^3J = 6.3 Hz, 3 H, $CH(CH_3)_2$], 0.96 [d, ^3J = 7.0 Hz, 3 H, $C(OH)CHCH_3$], 1.31 [ddd, ^2J = 14.4 Hz, ^3J = 8.2 Hz, ^3J = 4.9 Hz, 1 H, $CHHCH(CH_3)_2$], 1.40 [ddd, ^2J = 14.4 Hz, ^3J = 7.0 Hz, ^3J = 5.7 Hz, 1 H, $CHHCH(CH_3)_2$], 1.63–1.84 [m, 2 H, $C(OH)CHCH_3$, $CH(CH_3)_2$], 2.40 (br s, 2 H, OH), 3.26 (ddd, ^3J = 7.1 Hz, ^3J = 7.0 Hz, ^3J = 4.9 Hz, 1 H, $CHOCH_3$), 3.45 (s, 3 H, OCH_3), 3.65 [dd, ^3J = 7.1 Hz, ^3J = 2.7 Hz, 1 H, $C(OCH_3)CHOH$], 3.65 (dd, ^2J = 10.8 Hz, ^3J = 6.1 Hz, 1 H, $CHHOH$), 3.72 (dd, ^2J = 10.8 Hz, ^3J = 4.3 Hz, 1 H, $CHHOH$); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 10.3 [q, $C(OH)CHCH_3$], 22.6 [q, $CH(CH_3)_2$], 23.5 [q, $CH(CH_3)_2$], 24.6 [d, $CH(CH_3)_2$], 36.7 [d, $C(OH)CHCH_3$], 39.5 [t, $CH_2CH(CH_3)$], 57.6 (q, OCH_3), 67.2 (t, CH_2OH), 75.4 (d, $C(CH_3)COH$), 80.6 (d, $CHOCH_3$); ^1H NMR (360 MHz, C_6D_6): δ = 0.85 [*virt.* t, $^3J \cong 6.6$ Hz, 6 H, $CH(CH_3)_2$], 0.96 [d, ^3J = 7.0 Hz, 3 H, $C(OH)CHCH_3$], 1.20 [ddd, ^2J = 14.3 Hz, ^3J = 8.2 Hz, ^3J = 4.7 Hz, 1 H, $CHHCH(CH_3)_2$], 1.30 [ddd, ^2J = 14.3 Hz, ^3J = 7.3 Hz, ^3J = 5.5 Hz, 1 H, $CHHCH(CH_3)_2$], 1.65–1.88 [m, 2 H, $C(OH)CHCH_3$, $CH(CH_3)_2$], 2.47 (br s, 1 H, OH), 2.78 (br s, 1 H, OH), 3.11 (s, 3 H, OCH_3), 3.25 (ddd, ^3J = 7.3 Hz, ^3J = 7.1 Hz, ^3J = 4.7 Hz, 1 H, $CHOCH_3$), 3.59 [dd, ^2J = 10.5 Hz, ^3J = 4.7 Hz, 1 H, $CHHOH$], 3.62 (dd, ^2J = 10.5 Hz, ^3J = 4.3 Hz, 1 H, $CHHOH$), 3.65 (dd, ^3J = 7.1 Hz, ^3J = 3.6 Hz, 1 H, $C(OCH_3)$-$CHOH$), ^{13}C NMR (90.6 MHz, C_6D_6): δ = 10.6 [q, $C(OH)CHCH_3$], 22.6 [q, $CH(CH_3)_2$], 23.7 [q, $CH(CH_3)_2$], 24.8 [d, $CH(CH_3)_2$], 37.3 [d, $C(OH)CHCH_3$], 39.7 [t, $CH_2CH(CH_3)$], 57.5 (q, OCH_3), 66.9 (t, CH_2OH), 74.9 (d, $C(CH_3)COH$), 81.1 (d, $CHOCH_3$); IR (neat): $\tilde{\nu}$ = 3385 cm^{-1} (br, OH), 2956 (s, CH), 2931 (s, CH), 1466 (m, CH_2), 1379 (m), 1096 (s, COC), 1041 (s); MS (EI, 70 eV), *m*/*z* (%): 131 (4) [$C_7H_{15}O_2^+$], 115 (4), 101 (100) [$C_6H_{13}O^+$], 89 (10) [$C_4H_9O_2^+$], 85 (6), 69 (85), 59 (46) [$C_3H_7O^+$], 45 (50) [$C_2H_5O^+$], 43 (36) [$C_3H_7^+$]; elemental analysis calcd (%) for $C_{10}H_{22}O_3$ (190.28): C, 63.12; H, 11.65. Found: C, 63.42; H, 11.55.

5.1.10. (2*S*,4*S*,5*R*)-4-((*S*)-1-Methoxy-3-methyl-butyl)-5-methyl-2-phenyl-[1,3]dioxane (17a). Trifluoroacetic acid (4.10 μL, 6.29 mg, 55.2 μmol) was added at rt to a solution of diol **16a** (16.0 mg, 84.1 μmol), freshly distilled benzaldehyde (12.0 μL, 12.5 mg, 118 μmol) and trimethoxymethane (18.0 μL, 17.5 mg, 165 μmol) in CH_2Cl_2 (1 mL). After stirring at rt for 20 h, the reaction mixture was treated with NaOMe (2 mg), diluted with Et_2O (2 mL) and filtered through a pad of Celite®. The solvent was removed in vacuo and the crude product purified by flash chromatography (P/Et_2O 95/5) to give **17a** as a colourless oil (16.0 mg, 57.5 μmol, 68%). R_f = 0.27 (P/Et_2O 9/1) [CAM]; $[\alpha]_D^{20}$ −48.4 (*c* = 0.72, Et_2O); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.96 [d, ^3J = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.11 [ddd, ^2J = 13.9 Hz, ^3J = 10.1 Hz, ^3J = 2.3 Hz, 1 H, $CHHCH(CH_3)_2$], 1.18 [d, ^3J = 6.4 Hz, 3 H, $C(OR)CHCH_3$], 1.32 [ddd, ^2J = 13.9 Hz, ^3J = 10.8 Hz, ^3J = 3.3 Hz, 1 H, $CHHCH(CH_3)_2$], 1.54–1.65 [m, 1 H, $C(OR)CHCH_3$], 1.92 [dqqd, ^3J = 10.1 Hz, ^3J = 6.7 Hz, ^3J = 6.7 Hz, ^3J = 3.3 Hz, 1 H, $CH(CH_3)_2$], 3.35 (ddd, ^3J = 10.8 Hz, ^3J = 8.6 Hz, ^3J = 2.3 Hz, 1 H, $CHOCH_3$), 3.54 (s, 3 H, OCH_3), 3.85 (dd, ^3J = 8.6 Hz, ^3J = 2.3 Hz, 1 H, $C(OCH_3)CHOR$), 3.85 [dd, ^2J = 11.2 Hz, ^3J = 1.5 Hz, 1 H, $CHHOR$], 4.08 (dd, ^2J = 11.2 Hz, ^3J = 2.0 Hz, 1 H, $CHHOR$), 5.55 (s, 1 H, CHC_{ar}), 7.29–7.40 (m, 5 H, $C_{ar}H$); ^{13}C-NMR (90.6 MHz, $CDCl_3$): δ = 11.2 [q, $C(OR)CHCH_3$], 21.5 [q, $CH(CH_3)_2$], 24.0 [q, $CH(CH_3)_2$], 24.1 [d, $CH(CH_3)_2$], 30.2 [d, $C(OR)CHCH_3$], 39.4 [t, $CH_2CH(CH_3)_2$], 60.7 (q, OCH_3), 73.7 (t, CH_2OR), 79.5 (d, $CHOCH_3$), 84.8 (d, $C(CH_3)COR$), 101.5 (d, CHC_{ar}), 126.0 (d, $C_{ar}H$), 128.1 (d, $C_{ar}H$), 128.6 (d, $C_{ar}H$), 139.0 (s, C_{ar}); IR (neat): $\tilde{\nu}$ = 2956 cm^{-1} (s, CH), 1464 (m, CH_2), 1378 (m), 1160 (s), 1112 (s, COC), 1056 (s), 1025 (s), 752 (m, C=C), 698 (s, C=C); MS (EI, 70 eV), *m*/*z* (%): 278 (1) [M^+], 177 (100), 107 (32), 101 (42), 79 (11), 59 (25), 40 (22); HRMS: *m*/*z*: calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1881.

5.1.11. (*R*)-4-Benzyl-3-((2*R*,3*R*,4*S*)-3-hydroxy-4-methoxy-2,6-dimethylheptanoyl)-oxazolidin-2-one (19). Dibutylboryl trifluoromethanesulfonate (1 M in CH_2Cl_2, 2.46 mL, 2.46 mmol) and diisopropylethylamine (469 μL, 356 mg, 2.75 mmol) were added at 0 °C to a solution of oxazolidinone **18**[24b] (536 mg, 2.30 mmol) in CH_2Cl_2 (10 mL). After stirring for 45 min at 0 °C, the solution was treated with aldehyde **3** (359 mg, 2.76 mmol) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and 1 h at −10 °C, before a mixture of MeOH (7.5 mL), pH 7, phosphate buffer (2.5 mL) and 30% H_2O_2/MeOH (1:2, 7.5 mL) was slowly added to the solution (reaction temperature must be lower than 10 °C). After stirring for 1 h at rt, the reaction mixture was concentrated and the residue extracted with CH_2Cl_2 (3× 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (P/Et_2O 1/1) and recrystallised from P/CH_2Cl_2 to give **19** as colourless crystals (528 mg, 1.45 mmol, 63%). R_f = 0.22 (P/Et_2O 1/1) [CAM]; mp 85–86 °C; $[\alpha]_D^{20}$ −75.0 (*c* 1.0, Et_2O); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.90 [d, ^3J = 6.6 Hz, 3 H, $CH(CH_3)_2$], 0.93 [d, ^3J = 6.6 Hz, 3 H, $CH(CH_3)_2$], 1.29 [ddd, ^2J = 14.3 Hz, ^3J = 9.1 Hz, ^3J = 3.2 Hz, 1 H, $CHHCH(CH_3)_2$], 1.36 (d, ^3J = 6.8 Hz, 3 H, $COCHCH_3$), 1.50 [ddd, ^2J = 14.3 Hz, ^3J = 8.8 Hz, ^3J = 4.6 Hz, 1 H, $CHHCH(CH_3)_2$], 1.84 [dqqd, ^3J = 9.0 Hz, ^3J = 6.7 Hz, ^3J = 6.7 Hz, ^3J = 4.4 Hz, 1 H, $CH(CH_3)_2$], 2.65 (s, 1 H, OH), 2.79 (dd, ^2J = 13.4 Hz, ^3J = 9.5 Hz, 1 H, $CHHPh$), 3.22–3.27 (m, 2 H, $CHHPh$, $CHOCH_3$), 3.41 (s, 3 H, OCH_3), 3.92–4.01 (m, 2 H, $CH(OH)CHCH_3$), 4.17–4.20 (m, 2 H, CH_2OR), 4.69 (dddd, ^3J = 9.5 Hz, ^3J = 5.9 Hz, ^3J = 4.6 Hz, ^3J = 3.5 Hz, 1 H, $CHNR_2$), 7.19–7.36 (m, 5 H, CH_{ar}); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 13.0 [q, $CH(CH_3)COR$], 22.1 [q, $CH(CH_3)_2$], 23.8 [q, $CH(CH_3)_2$], 24.5 [d, $CH(CH_3)_2$], 37.8 (t, CH_2Ph), 39.3 [d, $CH(CH_3)COR$], 39.5 (t, CH_2CHOMe), 55.1 (d, $CHNR_2$), 57.9 (q, OCH_3), 66.1 (t, CH_2OR), 72.7 (d, CHOH), 80.0 (d, $CHOMe$), 127.4 (d, $C_{ar}H$), 129.0 (d, $C_{ar}H$), 129.4 (d, $C_{ar}H$), 135.0 (s, C_{ar}), 152.7 (s, COOR), 177.0 (s, CH_2COR); IR (neat): $\tilde{\nu}$ = 3457 cm^{-1} (br, OH),

2962 (m, CH), 2930 (m, CH), 1769 (s, COO), 1673 (s, CON), 1380 (s), 1273 (m), 1106 (m), 970 (m), 765 (m, C=C), 707 (m, C=C); MS (EI, 70 eV), *m/z* (%): 363 (1) [M^+], 331 (1) [M^+-OCH_3], 306 (1) [$M^+-C_4H_9$], 262 (67), 233 (3) [$C_{13}H_{15}NO_3^+$], 178 (100), 149 (12), 117 (25), 101 (65), 69 (65), 45 (45); HRMS: *m/z*: calcd for $C_{20}H_{29}NO_5$: 263.2046. Found: 280.2048; elemental analysis calcd (%) for $C_{20}H_{29}NO_5$ (363.44): C, 66.09; H, 8.04; N, 3.85. Found: C, 66.02; H, 8.13; N, 3.82.

5.1.12. (2*S*,3*R*,4*S*)-4-Methoxy-2,6-dimethylheptane-1,3-diol (16b). Method A (from **19**): sodium borohydride (238 mg, 6.29 mmol) was added at 0 °C to a solution of oxazolidinone **19** (458 mg, 1.26 mmol) in THF/H_2O (5/1, 18 mL). After stirring at rt for 10 h, the reaction mixture was treated with 2 N HCl (15 mL) and the aqueous layer extracted with Et_2O (3× 20 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatography (P/Et_2O 1/9) to give **16b** as a colourless oil (214 mg, 1.13 mmol, 89%). **Method B** (from **3**): a solution of freshly prepared (*S*,*S*)-diisopropyl tartrate (*Z*)-crotylboronate[40] (115 mg, 385 μmol) in toluene (2 mL) was treated with powdered molecular sieves (20 mg) and then cooled to −78 °C. A solution of freshly prepared aldehyde **3** (40.0 mg, 307 μmol) in toluene (1 mL) was then added over 15 min. The reaction mixture was stirred over −78 °C for 3 h and then treated with 2 N NaOH (0.3 mL). The two-phase mixture was warmed to 0 °C and stirred for 20 min before being filtered through a pad of Celite®. The aqueous layer was extracted with Et_2O (3× 3 mL), the combined organic phases dried (Na_2SO_4), filtered and the solvent removed in vacuo to yield compound **2b**. Due to the instability of the compound, the crude product was directly used in the next reaction. Alcohol **2b** was converted in four additional steps into diol **16b** (13.3 mg, 69.7 μmol, 23%). The procedure was analogous to the conversion **2a** → **16a**. The analytic data of **16b** so obtained were identical to the data of **16b** obtained from **19**. R_f = 0.29 (P/Et_2O 1/9) [CAM]; $[\alpha]_D^{20}$ −8.3 (*c* 0.90, Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.94 [d, ^3J = 6.7 Hz, 3 H, CH(CH_3)$_2$], 0.95 [d, ^3J = 6.7 Hz, 3 H, CH(CH_3)$_2$], 1.05 [d, ^3J = 7.0 Hz, 3 H, C(OH)CHCH_3], 1.33 [ddd, ^2J = 14.1 Hz, ^3J = 8.7 Hz, ^3J = 3.9 Hz, 1 H, CHHCH(CH$_3$)$_2$], 1.53 [ddd, ^2J = 14.1 Hz, ^3J = 8.8 Hz, ^3J = 5.0 Hz, 1 H, CHH CH(CH$_3$)$_2$], 1.78 [dqqd, ^3J = 8.7 Hz, ^3J = 6.7 Hz, ^3J = 6.7 Hz, ^3J = 5.0 Hz, 1 H, CH(CH$_3$)$_2$], 1.87 [qddd, 1 H, ^3J = 7.0 Hz, ^3J = 5.0 Hz, ^3J = 4.8 Hz, ^3J = 4.8 Hz, C(OH)CHCH$_3$], 2.49 (br s, 2 H, OH), 3.31 (ddd, ^3J = 8.8 Hz, ^3J = 4.9 Hz, ^3J = 3.9 Hz, 1 H, CHOCH$_3$), 3.45 (s, 3 H, OCH$_3$), 3.62 [dd, ^2J = 10.7 Hz, ^3J = 5.0 Hz, 1 H, CHHOH], 3.65 (dd, ^2J = 10.7 Hz, ^3J = 4.8 Hz, 1 H, CHHOH), 3.76 (dd, ^3J = 4.9 Hz, ^3J = 4.8 Hz, 1 H, C(OCH$_3$)CHOH); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 11.6 [q, C(OH)CHCH$_3$], 22.3 [q, CH(CH$_3$)$_2$], 23.7 [q, CH(CH$_3$)$_2$], 24.5 [d, CH(CH$_3$)$_2$], 36.2 [d, C(OH)CHCH$_3$], 39.1 [t, CH$_2$CH(CH$_3$)], 57.7 (q, OCH$_3$), 66.8 (t, CH$_2$OH), 73.9 (d, C(CH$_3$)COH), 80.8 (d, CHOCH$_3$); IR (neat): $\tilde{\nu}$ = 3404 cm^{-1} (br, OH), 2955 (s, CH), 1467 (m, CH$_2$), 1384 (m), 1092 (s, COC), 1033 (s); MS (EI, 70 eV), *m/z* (%): 131 (2) [$C_7H_{15}O_2^+$], 101 (100) [$C_6H_{13}O^+$], 89 (9) [$C_4H_9O_2^+$], 85 (8), 69 (63), 59 (37) [$C_3H_7O^+$], 45 (40) [$C_2H_5O^+$], 43 (27) [$C_3H_7^+$]; elemental analysis calcd (%) for $C_{10}H_{22}O_3$ (190.28): C, 63.12; H, 11.65. Found: C, 62.91; H, 11.49.

5.1.13. (2*R*,4*R*,5*S*)-4-((*S*)-1-Methoxy-3-methyl-butyl)-5-methyl-2-phenyl-[1,3]dioxane (17b). Trifluoroacetic acid (7.36 μL, 11.3 mg, 99.1 μmol) was added at rt to a solution of diol **16b** (29.0 mg, 152 μmol), freshly distilled benzaldehyde (21.7 μL, 22.6 mg, 213 μmol) and trimethoxymethane (31.4 μL, 32.4 mg, 305 μmol) in CH_2Cl_2 (1 mL). After stirring at rt for 20 h, the reaction mixture was treated with NaOMe (3 mg), diluted with Et_2O (2 mL) and filtered through a pad of Celite®. The solvent was removed in vacuo and the crude product was purified by flash chromatography (P/Et_2O 95/5) to give **17b** as a colourless oil (28.0 mg, 100 μmol, 66%). R_f = 0.27 (P/Et_2O 9/1) [CAM]; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.95 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 0.95 [d, ^3J = 6.6 Hz, 3 H, CH(CH_3)$_2$], 1.24 [d, ^3J = 6.8 Hz, 3 H, C(OR)CHCH_3], 1.49 [ddd, ^2J = 14.4 Hz, ^3J = 6.9 Hz, ^3J = 4.9 Hz, 1 H, CHHCH(CH$_3$)$_2$], 1.56 [ddd, ^2J = 14.4 Hz, ^3J = 8.2 Hz, ^3J = 4.1 Hz, 1 H, CHH CH(CH$_3$)$_2$], 1.91–1.96 [m, 2 H, C(OR)CHCH$_3$, CH(CH$_3$)$_2$], 3.38 (ddd, ^3J = 8.5 Hz, ^3J = 6.8 Hz, ^3J = 4.1 Hz, 1 H, CHOCH$_3$), 3.43 (s, 3 H, OCH$_3$), 3.80 (dd, ^3J = 8.5 Hz, ^3J = 2.3 Hz, 1 H, C(OCH$_3$)CHOR), 4.04 [dd, ^2J = 11.2 Hz, ^3J = 1.6 Hz, 1 H, CHHOR], 4.09 (dd, ^2J = 11.2 Hz, ^3J = 2.4 Hz, 1 H, CHHOR), 5.49 (s, 1 H, CHC$_{ar}$), 7.30–7.40 (m, 5 H, C$_{ar}$H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 11.9 [q, C(OR)CHCH$_3$], 22.7 [q, CH(CH$_3$)$_2$], 23.9 [q, CH(CH$_3$)$_2$], 24.5 [d, CH(CH$_3$)$_2$], 29.7 [d, C(OR)CHCH$_3$], 40.2 [t, CH$_2$CH(CH$_3$)$_2$], 57.6 (q, OCH$_3$), 74.2 (t, CH$_2$OR), 78.0 (d, CHOCH$_3$), 81.9 (d, C(CH$_3$)COR), 101.7 (d, CHC$_{ar}$), 126.0 (d, C$_{ar}$H), 128.1 (d, C$_{ar}$H), 128.6 (d, C$_{ar}$H), 138.9 (s, C$_{ar}$).

5.1.14. (*R*)-4-Benzyl-3-((2*S*,3*S*,4*S*)-3-hydroxy-4-methoxy-2,6-dimethylheptanoyl)-oxazolidin-2-one (20). To a solution of oxazolidinone **18**[24b] (165 mg, 707 μmol) in Et_2O (2 mL) at 0 °C was added dibutylboryl trifluoromethanesulfonate (1 M in CH_2Cl_2, 1.41 mL, 1.41 mmol) followed by diisopropylethylamine (138 μL, 105 mg, 2.75 mmol). The resultant yellow slurry was stirred for 30 min at 0 °C and then cooled to −78 °C. Over a 10 min period a solution of aldehyde **3** (115 mg, 883 μmol) was added at −78 °C and the mixture was stirred for 30 min. After addition of tartaric acid (530 mg) at −78 °C, the reaction mixture was warmed to rt and the stirring was continued for 2 h. The suspension was diluted with water (5 mL) and Et_2O (5 mL), the layers separated and the aqueous layer was extracted with Et_2O (2× 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was cooled to 0 °C to which 30% H_2O_2/MeOH (3:1, 2 mL) was added and stirred for 30 min at rt. After addition of H_2O (5 mL) the layers were separated and the aqueous layer extracted with Et_2O (2× 10 mL). The combined organic layers were washed with $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The crude product was purified by flash chromatogra-

phy (P/Et_2O 1/1) and recrystallised from P/CH_2Cl_2 to give **20** as colourless crystals (110 mg, 303 μmol, 43%). R_f = 0.28 (P/Et_2O 1/1) [CAM]; mp 76–78 °C; $[\alpha]_D^{20}$ −23.7 (*c* 0.96, Et_2O); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.94 [*virt.* t, $^3J \cong 6.6$ Hz, 6 H, CH(CH_3)$_2$], 1.26 (d, ^3J = 6.8 Hz, 3 H, COCHCH_3), 1.46–1.52 [m, 1 H, CH_2CH(CH_3)$_2$], 1.75 [*virt.* nonet, $^3J \cong 6.7$ Hz, 1 H, C*H*(CH_3)$_2$], 2.52 (s, 1 H, OH), 2.74 (dd, ^2J = 13.3 Hz, ^3J = 9.7 Hz, 1 H, C*H*HPh), 3.23 (ddd, ^3J = 6.5 Hz, ^3J = 6.5 Hz, ^3J = 3.4 Hz, 1 H, C*H*OCH_3), 3.31 (dd, ^2J = 13.3 Hz, ^3J = 3.3 Hz, 2 H, C*H*HPh), 3.42 (s, 3 H, OCH_3), 3.87–4.05 (m, 2 H, C*H*(OH)C*H*CH_3), 4.11–4.26 (m, 2 H, CH_2OR), 4.68–4.78 (m, 1 H, $CHNR_2$), 7.21–7.37 (m, 5 H, CH_{ar}); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 12.3 [q, CH(*C*H_3)COR], 22.7 [q, CH(*C*H_3)$_2$], 22.9 [q, CH(*C*H_3)$_2$], 24.5 [d, *C*H(CH_3)$_2$], 38.0 (t, CH_2Ph), 38.4 (t, *C*H_2CHOMe), 40.8 [d, *C*H(CH_3)COR], 55.1 (d, *C*HNR_2), 57.8 (q, OCH_3), 66.0 (t, CH_2OR), 73.2 (d, CHOH), 80.3 (d, *C*HOMe), 127.3 (d, C_{ar}H), 128.9 (d, C_{ar}H), 129.4 (d, C_{ar}H), 135.2 (s, C_{ar}), 153.1 (s, COOR), 175.5 (s, CH_2*C*OR); IR (neat): $\tilde{\nu}$ = 3494 cm^{-1} (br, OH), 2955 (s, CH), 1762 (s, COO), 1694 (s, CON), 1394 (s), 1219 (s), 1145 (m), 1092 (m), 969 (m), 766 (m, C=C), 699 (m, C=C); MS (EI, 70 eV), *m*/*z* (%): 331 (1) [M^+−OCH_3], 306 (1) [M^+−C_4H_9], 262 (62), 233 (17) [$C_{13}H_{15}NO_3^+$], 178 (100), 142 (17), 117 (34), 101 (57), 91 (63) [$C_7H_7^+$], 69 (55), 57 (80); elemental analysis calcd (%) for $C_{20}H_{29}NO_5$ (363.44): C, 66.09; H, 8.04; N, 3.85. Found: C, 66.08; H, 8.13; N, 3.78.

Crystal structure analysis of compound **19**: $C_{20}H_{29}NO_5$, M_r = 363.44, colourless fragment (0.32 × 0.34 × 0.51 mm^3), orthorhombic, $P2_12_12_1$ (No.: 19), *a* = 10.0837(1), *b* = 10.1263(1), *c* = 19.5048(3) Å, *V* = 1991.65(4) Å^3, *Z* = 4, d_{calc} = 1.212 g cm^{-3}, F_{000} = 784, μ = 0.086 mm^{-1}. Preliminary examination and data collection were carried out on a κ-CCD device (NONIUS, MACH3) with an Oxford Cryosystems cooling system at the window of a rotating anode (NONIUS FR591) with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Data collection was performed at 173 *K* within the Θ range of 2.27° < Θ < 25.33°. A total of 40,700 intensities were integrated. Raw data were corrected for Lorentz, polarization, and, arising from the scaling procedure, for latent decay and absorption effects. After merging (R_{int} = 0.045), 3608 [3357: $I_o > 2\sigma(I_o)$] independent reflections remained and all were used to refine 243 parameters. The structure was solved by a combination of direct methods and difference-Fourier syntheses. All non-hydrogen atoms were refined with an-isotropic displacement parameters. All hydrogen atoms were placed in calculated positions and refined using a riding model. Full-matrix least-squares refinements were carried out by minimizing $\sum w(F_o^2 - F_c^2)^2$ and converged with *R*1 = 0.0335 [$I_o > 2\sigma(I_o)$], *wR*2 = 0.0723 [all data], GOF = 1.086 and shift/err <0.001. The final difference-Fourier map shows no striking features ($\Delta e_{min/max}$ = +0.11/−0.16 eÅ^{-3}).[42]

Crystal structure analysis of compound **20**: $C_{20}H_{29}NO_5$, M_r = 363.44, colourless fragment (0.13 × 0.30 × 0.91 mm^3), monoclinic, $P2_1$ (No. 4), *a* = 9.1693(1), *b* = 8.7691(1), *c* = 13.4455(2) Å, β = 109.2870(5)°, *V* = 1020.43(2) Å^3, *Z* = 2, d_{calc} = 1.183 g cm^{-3}, F_{000} = 392, μ = 0.084 mm^{-1}. Preliminary examination and data collection was carried out on a κ-CCD device (NONIUS, MACH3) with an Oxford Cryosystems cooling system at the window of a rotating anode (NONIUS FR591) with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Data collection were performed at 123 *K* within the Θ range of 2.35° < Θ < 25.31°. A total of 26,177 intensities were integrated. Raw data were corrected for Lorentz, polarization, and, arising from the scaling procedure, for latent decay and absorption effects. After merging (R_{int} = 0.040), 3716 [3559: $I_o > 2\sigma(I_o)$] independent reflections remained and all were used to refine 351 parameters. The structure was solved by a combination of direct methods and difference-Fourier syntheses. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were found and refined with individual isotropic displacement parameters. Full-matrix least-squares refinements were carried out by minimizing $\sum w(F_o^2 - F_c^2)^2$ and converged with *R*1 = 0.0299 [$I_o > 2\sigma(I_o)$], *wR*2 = 0.0693 [all data], GOF = 1.082 and shift/error <0.001. The final difference-Fourier map shows no striking features ($\Delta e_{min/max}$ = +0.13/−0.15 eÅ^{-3}).[42]

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-602502 (**19**) and CCDC-602503 (**20**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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