An Aldol Approach to a Building Block corresponding to the C21–C26-Part of FK506

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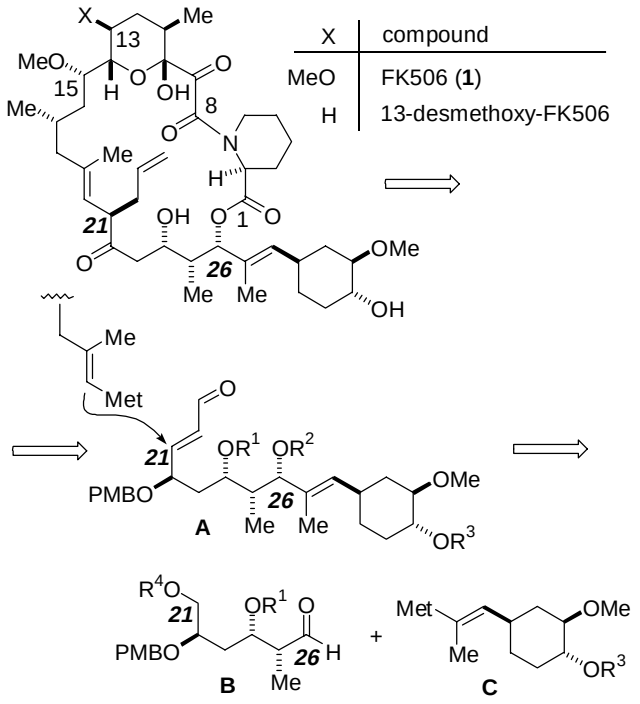
Abstract. Starting from D-tartrate **2**, the chiral aldehyde **10** was prepared in 8 steps. Key steps include the reductive opening of the *p*-methoxybenzyl acetal **4** and the elongation of the aldehyde **7** *via* Wittig and hydroboration reaction providing the alcohol **9**. Subsequent Evans aldol reaction provided compound **12** which corresponds to the C21–C26 part of the immunosuppressive FK506.

The immunosuppressive FK506, first described in 1987 [1, 2], has now entered the clinic as a useful drug. Biological studies with FK506, the structurally related rapamycin, and the cyclic peptide cyclosporin have greatly enhanced the understanding of signal transduction with regard to the activation of T-cells [3, 4]. Due to the biological importance considerable synthetic efforts have been undertaken to prepare the natural product [5–7] as well as analogs thereof [8, 9]. In the course of the synthesis of analogs of the immunosuppressive FK506 it was planned to construct the target molecule from several subunits as depicted in Scheme 1 [10]. Basically, we envisioned to construct the C10–C20 part that subsequently would undergo a stereoselective cuprate addition to C21 of an α,β-unsaturated aldehyde of type



Scheme 1

A. After retrosynthetic removal of the cyclohexyl part, a C21–C26 insert of type **B** emerges as a subgoal. The additional stereo center at C22 will be used to control the stereochemical outcome of the Michael addition [11]. In this paper we describe studies to toward a chiral building block of type **B**.

The *syn*-orientation of the methyl and the hydroxyl substituent at C25 and C24, respectively, suggests an aldol approach to establish these two stereocenters. We choose the Evans aldol reaction for the easy availability of the chiral auxiliary [12] and the predictable stereochemical outcome [13]. The stereocenter at C22 was provided from D-tartrate. Thus, aldehyde **10** in which the carbonyl function at C21 is hidden as a protected 1,2-diol was synthesized from diethyl tartrate **2** (Scheme 2). Building on a report by Somfai *et al*., the vicinal diol was converted to the 4-methoxybenzylidene derivative **3** [14]. The following step, the reduction of the diester **3** to the corresponding diol **4** with sodium borohydride in the presence of lithium chloride [14] turned out difficult to reproduce and was accompanied by cleavage of the rather labile acetal. However, changing the reducing agent to lithium aluminium hydride suppressed these problems [15]. In the paper of Horita *et al*. the subsequent reductive opening of the benzylidene acetal was done on the silicon-protected derivative [15]. In our hands this detour was not necessary. The conversion of the acetal **4** to the *p*-methoxybenzyl ether **5** could be accomplished with the borane–dimethylsulfide complex [16]. After removal of the boron as trimethylborate the triol can be purified by chromatography. An aqueous work-up was not necessary. The two vicinal hydroxyl groups were then selectively protected by forming an acetal with 3,3-dimethoxypentane [15]. However, in this step the loss of the 4-methoxybenzylether can be a problem. The chain extension was then tried by a S_N2 reaction (NaCN) on the corresponding mesylate. Since this was not successful we choose a route based on a Wittig reaction. Thus, Dess–Martin

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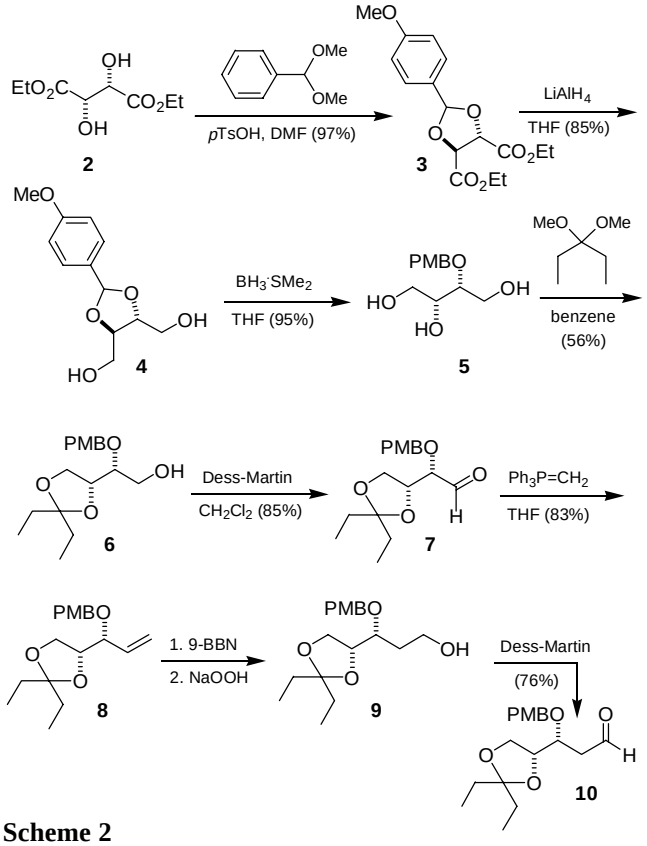
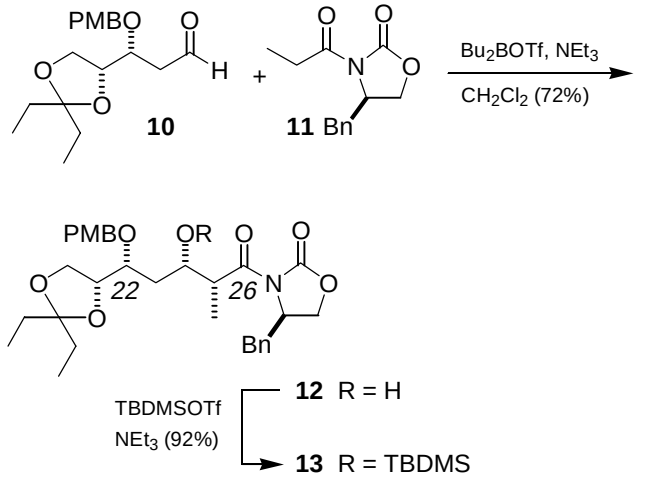


Scheme 2

oxidation [17, 18] of the alcohol **6** provided the aldehyde **7** which was converted to the terminal alkene **8** in good yield. Conversion of the alkene **8** to the primary alcohol **9** was achieved by hydroboration with 9-BBN in THF [19]. Application of the Dess–Martin periodinane on alcohol **9** provided the aldehyde **10**.

The stage was now set for the crucial aldol reaction. The 3-propionyloxazolidinone [12] **11** was converted to the boron enolate which was followed by the addition of the aldehyde **10** at –70 °C. This way the aldol



Scheme 3

adduct **12** was produced in good yield and with high diastereoselectivity. The ^{1}H NMR spectrum showed only one methyl dublett at δ = 1.22 ppm. The stereochemical purity was confirmed by HPLC analysis (RP-18, 7 µm, LiChrosorb 250-4, MeOH/H_2O, 9:1, 1.0 ml/min, λ = 233 nm, *RT* = 4.0 min) showing only the presence of one peak. Moreover, the ^{13}C chemical shifts for the carbinol (δ = 69.9 ppm), the methine carbon (δ = 42.5 ppm) and the methyl group (δ = 10.9 ppm) are in accordance with the *syn*-configuration [20]. A subsequent protection of the hydroxyl function led to the key building block **13**.

In summary, we developed an efficient synthetic route to the C21–C26 building block **13**. The stereocenters of **13** were derived from D-tartrate and from an Evans aldol reaction. Further work is underway to incorporate this fragment into designed FK506 analogs.

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Experimental

^{1}H NMR: Bruker AC 200 F, Varian Gemini 200, Bruker AM 400; all spectra were recorded in $CDCl_3$ as solvent with tetramethylsilane as internal standard. – ^{13}C NMR: Bruker AC 200 F (50 MHz), Bruker AM 400 (100 MHz), broad-band decoupling. The signal multiplicities were determined by means of the DEPT 135 or the APT technique; + for CH or CH_3, – for CH_2, × for C. – IR: Mattson Polaris and Perkin-Elmer Spectrum 1 000. – The optical rotations were measured at 22 °C. Flash chromatography: J. T. Baker silica gel 30 – 60 µm. – Thin-layer chromatography: Macherey, Nagel & Co precoated TLC plates Polygram SIL G/UV_{254}. – All experiments were carried out under nitrogen or argon. Petroleum ether with a boiling range of 35–65 °C was used; THF was distilled from sodium benzophenone ketyl immediately before use. The following reagents were prepared according to literature procedures: 4-methoxybenzaldehyde dimethylacetal [21], 3,3-dimethoxypentane [22].

(2R,3R)-2,3-O-(4-Methoxybenzylidene)-butan-1,4-diol (**4**)

A solution of the diester **3** (23.84 g, 73.5 mmol) in dry THF (50 ml) was added dropwise at 0 °C to a stirred suspension of $LiAlH_4$ (11.16 g, 294.0 mmol) in dry THF (150 ml). After complete addition, the cooling bath was removed and the mixture allowed to reach room temperature. The reaction was quenched by careful addition of methanol (25 ml), stirred for 1 h and then filtered over Celite. The subsequent evaporation of the solvent has to be done carefully in order to prevent excessive foaming. The residue was purified by flash chromatograpy (ethyl acetate) to remove *para*-methoxybenzylalcohol. Yield of **4** 15.01 g (85%) as a colorless oil. – TLC (ethyl acetate): R_f = 0.38. – $[\alpha]_D$ = –10.9 (*c* = 2.0, $CHCl_3$). – ^{1}H NMR (200 MHz, $CDCl_3$): δ/ppm = 2.24 (s, br., 2H, OH),

3.74–3.93 (m, 4H, $\underline{C}H_2OH$), 3.81 (s, 3H, OCH_3), 4.12–4.22 (m, 2H, CHOR), 5.93 (s, 1H, benzylidene H), 6.88–6.94 and 7.38–7.44 (2 m, 2H each, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 55.3 (+, OCH_3), 62.2, 62.4 (2 –, $\underline{C}H_2OH$), 78.2, 79.2 (2 +, CHOR), 103.8 (+, benzylidene C), 113.9 , 128.0 (2 +, aromatic C), 129.3, 160.6 (2 ×, aromatic C). – MS *m/z* (%): 240 (28) [M^+], 239 (79) [M^+ – H], 209 (40), 137 (60), 135 (100), [$CH_3OC_6H_4CO^+$], 121 (31) [$CH_3OC_6H_4CH_2^+$].

(2R,3R)-3-(4-Methoxybenzyloxy)-butan-1,2,4-triol (**5**)

A solution of the dioxolane **4** (4.76 g, 19.8 mmol) in dry THF (100 ml) was added dropwise to borane dimethylsulfide complex (10M, 13.9 ml, 139 mmol) at 0 °C. After complete addition, the mixture was allowed to reach room temperature within 30 min and then heated for 3 h (oil bath temperature 75 °C). Subsequently the mixture was cooled to 0 °C and the excess borane hydrolyzed carefully with methanol. Stirring was continued for 30 min before the mixture was concentrated *in vacuo*. The residue was treated again with methanol (20 ml) followed by removal of the solvent. Purification by flash chromatography (ethyl acetate/methanol, 10:1) gave the triol **5** as a viscous, colorless oil; yield 4.57 g (95%). – TLC (ethyl acetate/methanol, 10:1): R_f = 0.39. – $[\alpha]_D$ = –29.6 (*c* = 0.75, $CHCl_3$). – ^1H NMR (200 MHz, $CDCl_3$): δ/ppm = 3.43–3.59 (m, 3H, CHOR, CH_2OH), 3.62–3.86 (m, 3H, CHOH), 3.79 (s, 3H, OCH_3), 4.47, 4.61 (d, *J*/Hz = 11.3, 1H, aryl-CH_2), 6.85–6.89, 7.23–7.27 (2 d, *J*/Hz = 8.6, 2H each, aromatic H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ/ppm = 55.3 (+, OCH_3), 60.8 (–, CH_2OH), 63.1 (–, CH_2OH), 71.7 (+, CHOH), 72.1 (–, benzylic CH_2), 78.8 (+, CHOR), 114.0, 129.6 (2 +, aromatic C), 129.7, 159.5 (×, aromatic C). – MS *m/z* (%): 242 (6) [M^+], 137 (27), 135 (5) [$CH_3OC_6H_4CO^+$], 121 (100) [$CH_3OC_6H_4CH_2^+$].

(2R)-2-[(4R)-2,2-Diethyl-[1,3]dioxolan-4-yl]-2-(4-methoxybenzyloxy)ethan-l-ol (**6**)

To a solution of the triol **5** (5.33 g, 22.0 mmol) in benzene (40 ml) that has been dissolved with the help of a sonication bath were added 3,3-dimethoxypentane (8.71 g, 66.0 mmol) and *p*-toluenesulfonic acid hydrate (21 mg, 0.11 mmol). The reaction was controlled by TLC. Although after 30–60 min there was still starting material present, the formation of byproducts increased. The reaction was therefore quenched by the addition of triethylamine (0.1 ml). After removal of the solvents *in vacuo*, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) to give **6** as a colorless oil; yield 3.84 g (56%). – TLC (petroleum ether/ethyl acetate, 3:2): R_f 0.36. – $[\alpha]_D$ = +24.2 (*c* = 1.48, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.90, 0.92 (2 t, *J*/Hz = 7.4, 3H each, CH_3), 1.61–1.71 (m, 4H, $C\underline{H}_2CH_3$), 2.25 (s, br., 1H, OH), 3.50–3.57 (m, 2H, CH_2OH), 3.66 (m, 1H, CHOPMB), 3.68 (dd, *J*/Hz = 8.1, 1H, dioxolane CH_2), 3.81 (s, 3H, OCH_3), 4.00 (dd, *J*/Hz = 8.3, 6.4, 1H, dioxolane CH_2), 4.26 (dt, *J*/Hz = 8.3, 6.4, 1H, dioxolane CH), 4.62, 4.74 (2 d, *J*/Hz = 11.5, 1H each, benzyl CH_2), 6.87–6.90, 7.27–7.31 (2 d, *J*/Hz = 8.6 Hz, 2H each, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.1, 8.2 (2 +, $CH_2\underline{C}H_3$), 29.1, 29.6 (2 –, $\underline{C}H_2CH_3$), 55.3 (+, OCH_3), 61.9 (–, CH_2OH), 66.2 (–, dioxolane CH_2), 72.5 (–, benzyl CH_2), 77.3 (+, dioxolane CH), 79.1 (+, $\underline{C}$HOPMB), 113.3 (×, dioxolane C), 113.9, 129.6 (2 +, aromatic C), 130.4, 159.3 (2 ×, aromatic C). – MS *m/z* (%): 310 (1.5) [M^+], 281 (2) [M^+ – Et), 224 (11), 129 (10), [$C_7H_{13}O_2^+$], 121 (100) [$CH_3OC_6H_4CH_2^+$].

(2R)-2-[(4R)-2,2-Diethyl-[1,3]dioxolan-4-yl]-2-(4-methoxybenzyloxy)-acetaldehyde (**7**)

To a solution of Dess-Martin periodinane (2.86 g, 6.74 mmol) in dry dichloromethane (40 ml) was added the alcohol **6** (1.39 g, 4.49 mmol), dissolved in dry dichloromethane (5 ml). The mixture was stirred for 2 h at room temperature (TLC control). Addition of diethyl ether led to a white suspension which was then treated with 1.3N NaOH (25 ml). This mixture was stirred for 30 min before the phases were separated. The aqueous phase was extracted with diethyl ether (4 × 30 ml). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1) to yield 1.18 g, (85%) of **7** as a colorless oil. Upon prolonged standing it becomes yellow. – TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.36. – $[\alpha]_D$ = –24.8 (*c* = 0.97, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.88, 0.90 (2 t, *J*/Hz = 7.5, 3H each, $CH_2C\underline{H}_3$), 1.58–1.71 (m, 4H, $C\underline{H}_2CH_3$), 3.80–3.86 (m, 2H, CHOPMB, dioxolane CH_2), 3.81 (s, 3H, OCH_3), 4.05 (dd, *J*/Hz = 8.5, 6.6, 1H, dioxolane CH_2), 4.30–4.35 (m, 1H, dioxolane CH), 4.63, 4.71 (2 d, *J*/Hz = 11.7, 1H each, benzyl CH_2), 6.87–6.91, 7.27–7.30(2 d, *J*/Hz = 8.7, 2H each, aromatic H), 9.68 (s, 1H, CHO). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.0, 8.1 (2 +, $CH_2\underline{C}H_3$), 28.7, 29.3 (2 –, CH_2CH_3), 55.2 (+, OCH_3), 65.8 (–, dioxolane CH_2), 73.0 (–, benzyl CH_2), 75.6 (+, dioxolane CH), 82.6 (+, $\underline{C}$HOPMB), 113.6 (×, dioxolane C), 113.9 (2 +, aromatic C), 129.0 (×, aromatic C), 129.8 (+, aromatic C), 159.6 (×, aromatic C), 202.2 (+, CHO). – MS *m/z* (%): 308 (0.3) [M^+], 279 (2), 135 (100) [$CH_3OC_6H_4CO^+$], 129 (8), 121 (40) [$CH_3OC_6H_4CH_2^+$], 107 (18), 92 (13). – IR (film): ν/cm^{-1} = 2 973 (s), 2 940 (s), 1 733 (vs), 1 612 (s), 1 515 (vs), 1 250 (vs).

$C_{17}H_{24}O_5$	Calcd.:	C 66.21	H 7.84
(308.4)	Found:	C 65.64	H 7.80.

(3R)-3-[(4R)-2,2-Diethyl-[1,3]dioxolan-4-yl]-3-(4-methoxybenzyloxy)propene (**8**)

A stirred suspension of methyltriphenylphosphonium bromide (447 mg, 1.25 mmol) in dry THF (12 ml) was treated at 0 °C with *n*-BuLi (500 µl, 2.5M in hexane, 1.25 mmol). Stirring was continued for 1 h at this temperature and then the aldehyde **7** (296 mg, 0.96 mmol), dissolved in THF (2 ml), was added dropwise. After further 2 h of stirring at room temperature, the mixture was diluted with diethyl ether (15 ml), treated with H_2O (2.5 ml) and stirred for about 15 min. The phases were separated, the aqueous phase extracted with diethyl ether (3 × 10 ml), and the combined organic layers were washed with brine. Drying of the organic phase with $MgSO_4$, filtration and concentration *in vacuo* gave the crude alkene **8** which was purified by flash chromatography (petroleum ether/ethyl acetate, 4:1); yield 245 mg (83%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.55. – $[\alpha]_D$ = –17.2 (*c* = 0.98, $CHCl_3$). – ^1H NMR (400 MHz, $CDCl_3$):

δ/ppm = 0.88, 0.89 (t, *J*/Hz = 7.5, 3H each, $CH_2C\underline{H}_3$), 1.58–1.67 (m, 4H, $C\underline{H}_2CH_3$), 3.65 (dd, *J*/Hz = 8.2, 7.1, 1H, dioxolane CH_2), 3.80 (s, 3H, OCH_3), 3.83 (dd, *J*/Hz = 7.6, 7.1, 1H, CHOPMB), 3.93 (dd, *J*/Hz = 8.2, 6.7, 1H, dioxolane CH_2), 4.18 (q, *J*/Hz = 6.7, 1H, dioxolane CH), 4.43, 4.62 (2 d, *J*/Hz = 11.9, 1H each, benzyl CH_2), 5.29, 5.34 (m, 2H, $CH=C\underline{H}_2$), 5.66–5.75 (m, 1H, $C\underline{H}=CH_2$), 6.85–6.88, 7.26–7.29 (2 d, *J*/Hz = 8.7 Hz, 2H each, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.0, 8.1 (2 +, $CH_2\underline{C}H_3$), 29.1, 29.6 (2 –, $\underline{C}H_2CH_3$), 55.2 (+, OCH3), 66.3 (–, dioxolane CH_2), 69.8 (–, benzyl CH_2), 77.8 (+, dioxolane CH), 80.7 (+, CHOPMB), 113.6 (×, dioxolane C), 113.6 (+, aromatic C), 119.8 (–, $CH=\underline{C}H_2$), 129.3 (+, aromatic C), 130.3 (×, aromatic C), 134.3 (+, $\underline{C}H=CH_2$), 159.1 (×, aromatic C). – MS *m/z* (%): 306 (0.5) [M^+], 277 (7) [$M^+ - C_2H_5$), 181 (5), 135 (4) [$CH_3OC_6H_4CO^+$], 129 (34), 121 (100) [$CH_3OC_6H_4CH_2^+$]. – IR (film): ν/cm^{-1} = 1 614 (m), 1 514 (s), 1 249 (s), 1 081 (s).

$C_{18}H_{26}O_4$	Calcd.:	C 70.56	H 8.55
(306.4)	Found:	C 71.04	H 8.80.

(3R)-3-[(4R)-2,2-Diethyl-1,3]dioxolan-4-yl]-3-(4-methoxybenzyloxy)-propan-1-ol (**9**)

The alkene **8** (865 mg, 2.82 mmol), dissolved in THF (2 ml) was added dropwise to a solution of 9-BBN (448 mg, 3.67 mmol) in THF (9.0 ml) at room temperature. After stirring for 3 h, the mixture was treated under ice-cooling with water (0.5 ml), 3M sodium hydroxide solution (2 ml) and 30% hydrogen peroxide (2 ml). The mixture was stirred for 30 min at room temperature, diluted with diethyl ether, and then the phases were separated. The aqueous phase was extracted with diethyl ether (5 × 20 ml). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:3) gave the alcohol **9** as a colorless oil; yield 842 mg (92%). – TLC (petroleum ether/ethyl acetate, 2:3): R_f = 0.53. – $[\alpha]_D$ = + 46.2 (*c* = 0.72, CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.92, 0.93 (t, *J*/Hz = 7.5, 3H, $CH_2C\underline{H}_3$), 1.60–1.72 (m, 6H, $C\underline{H}_2CH_3$, $C\underline{H}_2CH_2OH$), 2.31 (s, br., 1H, OH), 3.58 (dd, *J*/Hz = 8.3, 1H, CHOPMB), 3.62–3.73 (m, 3H, CH_2OH, dioxolane CH_2), 3.80 (s, 3H, OCH_3), 3.99 (dd, *J*/Hz = 7.9, 6.4, 1H, dioxolane CH_2), 4.22 (dt, *J*/Hz = 8.4, 6.6, 1H, dioxolane CH), 4.61, 4.78 (2 d, *J*/Hz = 11.3 Hz, 1H each, benzyl CH_2), 6.85–6.90, 7.27–7.31 (2 d, *J*/Hz = 8.7 Hz, 2H each, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.1, 8.2 (2 +, $CH_2\underline{C}H_3$), 29.3, 29.6 (2 –, $\underline{C}H_2CH_3$), 33.2 (–, $\underline{C}H_2CH_2OH$), 55.2 (+, OCH_3), 59.9 (–, CH_2OH), 66.6 (–, dioxolane CH_2), 72.5 (–, benzyl CH_2), 77.9 (+, dioxolane CH), 79.3 (+, CHOPMB), 113.5 (×, dioxolane C), 113.8, 129.7 (2 +, aromatic C), 130.4, 159.3 (2 ×, aromatic C). – MS *m/z* (%): 324 (0.5) [M^+], 135 (16) [$CH_3OC_6H_4CO^+$], 129 (17), 121 (100) [$CH_3OC_6H_4CH_2^+$]. – IR (film): ν/cm^{-1} = 2 961 (vs), 2 933 (vs), 2 876 (s), 2 862 (s), 1 728 (vs), 1 514 (s), 1 464 (s), 1 287 (vs), 1 276 (vs), 1 125 (s), 1 074 (s). A correct elemental analysis could not be obtained.

(3R)-3-[(4R)-2,2-Diethyl-[1,3]dioxolan-4-yl]-3-(4-methoxybenzyloxy)propanal (**10**)

As described for compound **7**, the alcohol **9** (818 mg, 2.52 mmol) was oxidized with the periodinane (1.60 g, 3.78 mmol) in dichloromethane (20 ml). The reaction was complete after 1 h at room temperature. Purification by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave the aldehyde **10** (615 mg, 76%) as a slightly yellow oil. – TLC (petroleum ether/ethyl acetate, 3:2): R_f = 0.53. – $[\alpha]_D$ = + 25.6 (*c* = 0.83, CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.89, 0.92 (2 t, *J*/Hz = 7.5, 3H each, $CH_2C\underline{H}_3$), 1.60–1.72 (m, 4H, $C\underline{H}_2CH_3$), 2.51–2.65 (m, 2H, $C\underline{H}_2CHO$), 3.68 (dd, *J*/Hz = 8. 1, 1H, dioxolane CH_2), 3.80 (s, 3H, OCH_3), 3.98 (dd, *J*/Hz = 8.1, 6.6, 1H, dioxolane CH_2), 4.10 (m, 1H, dioxolane CH), 4.26 (dt, *J*/Hz = 7.9, 6.4, 1H, CHOPMB), 4.59, 4.66 (d, *J*/Hz = 11.2, 1H each, benzyl CH_2), 6.85–6.89, 7.00–7.23 (2 d, *J*/Hz = 8.6, 2H each, aromatic H), 9.74 (s, 1H, CHO). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.1, 8.2 (2 +, $CH_2\underline{C}H_3$), 28.7, 29.4 (2 –, $\underline{C}H_2CH_3$), 44.7 (–, $\underline{C}H_2CHO$), 55.2 (+, OCH_3), 65.9 (–, dioxolane CH_2), 72.5 (–, benzyl CH_2), 73.9 (+, dioxolane CH), 77.3 (+, CHOPMB), 113.6 (×, dioxolane C), 113.8, 129.5 (2 +, aromatic C), 130.0, 159.3 (2 ×, aromatic C), 200.5 (+, CHO). – MS *m/z* (%): 322 (2) [M^+], 293 (3), 155 (9), 150 (8), 135 (34) [$CH_3OC_6H_4CO^+$], 129 (10), 121 (100) [$CH_3OC_6H_4CH_2^+$]. – IR (film): ν/cm^{-1} = 2 973 (vs), 2 940 (vs), 2 883 (s), 1 728 (vs), 1 726 (vs), 1 614 (vs), 1 515 (vs), 1 465 (vs), 1 249 (vs), 1 174 (vs), 1 084 (vs), 1 060 (vs).

$C_{18}H_{26}O_5$	Calcd.:	C 67.06	H 8.13
(324.4)	Found:	C 66.97	H 8.21.

(4R)-4-Phenylmethyl-3-[[(5R)-5-[(4R)-2,2-diethyl-[1,3]dioxolan-4-yl]]-(2R,3R)-3-hydroxy-5-(4-methoxybenzyloxy)-2-methyl-pentanoyl]-oxazolidin-2-one (**12**)

To a solution of the oxazolidinone **11** (140 mg, 0.60 mmol) in dry dichloromethane (1.8 ml) was added by a syringe dibutylboron triflate (1M in dichloromethane, 720 µl, 0.72 mmol) at –25 °C. This was followed by the addition of triethylamine (110 µl, 0.78 mmol). Subsequently, the solution was stirred for 30 min at –20 °C and 30 min at 0 °C before it was cooled to –70 °C. At this point, a solution of the aldehyde **10** (213 mg, 0.66 mmol) in dichloromethane (1.2 ml) was added dropwise. The mixture was stirred for 60 min between –10 and –50 °C and finally for 30 min between –5 and 0 °C. For the work-up phosphate buffer solution (pH 7, 750 µl) and methanol (2.0 ml) were added at 0 °C, followed by a mixture of methanol and 30% aqueous hydrogen peroxide (2:1, 2.0 ml). The resulting suspension was stirred for 20 min at room temperature. Water (5 ml) and diethyl ether (30 ml) were added and the phases separated. The aqueous phase was extracted with diethyl ether (4 × 10 ml). The combined organic layers were washed with 5% aqueous $NaHCO_3$ solution, brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave the aldol adduct **12** as a viscous colorless oil; yield 241 mg (72%). – TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.31. – $[\alpha]_D$ = –27.7 (*c* = 0.69, CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.91, 0.92 (2 t, *J*/Hz = 7.4, 3H each, $CH_2C\underline{H}_3$), 1.22 (d, *J*/Hz = 7.0, 3H, $CHC\underline{H}_3$), 1.53–1.71 (m, 6H, $C\underline{H}_2CH_3$, $CHC\underline{H}_2CH$), 2.76 (dd, *J*/Hz = 13.3, 9.6, 1H, CH_2Ph), 3.26 (dd, *J*/Hz = 13.3, 3.2 Hz, 1H, CH_2Ph), 3.59 (dd, *J*/Hz = 8.2, 1H, CHOPMB), 3.65–3.71 (m, 2H, $C\underline{H}CO$, dioxolane CH_2), 3.79 (s, 3H, OCH_3), 4.01 (dd, *J*/Hz = 7.9, 6.4, 1H, dioxolane CH_2), 4.08–4.13 (m, 1H, dioxolane CH), 4.14–4.26 (m, 3H, $CHC\underline{H}_2O$,

CHOH), 4.59 (d, *J*/Hz = 11.3, 1H, PMBCH$_2$), 4.64–4.68 (m, 1H, CHN), 4.79 (d, *J*/Hz = 11.3, 1H, PMBCH$_2$), 6.85 (d, *J*/Hz = 8.6, 2H, aromatic H), 7.19–7.35 (m, 7H, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 8.1, 8.3 (2 +, CH_2CH_3), 10.9 (+, $CHCH_3$), 29.3, 29.7 (2 –, CH_2CH_3), 34.7 (–, CH_2CHOH), 37.8 (–, $PhCH_2$), 42.5 (+, CHCO), 55.3 (+, OCH_3), 55.4 (+, benzylic C), 66.1, 66.6 (2 –, CH_2OCO, dioxolane CH_2), 69.9 (+, CHOH), 72.3 (–, aryl CH_2), 78.7, 79.1 (2 +, dioxolane CH, CHOPMB), 113.6 (×, dioxolane C), 113.8, 127.4, 129.0, 129.4, 129.8 (5 +, aromatic C), 130.3, 135.2, 153.0, 159.2 (4 ×, aromatic C), 176.0 (CO). – MS *m/z* (%): 555 (0.1) [M^+], 233 (10), 178 (11), 135 (12) [$CH_3OC_6H_4CO^+$], 129 (11), 121 (100) [$CH_3OC_6H_4CH_2^+$], 113 (20). – IR (CCl_4): ν/cm^{-1} = 1 790 (vs), 1 686 (m), 1 513 (m), 1 246 (s), 1 086 (s).

$C_{31}H_{41}NO_8$	Calcd.:	C 67.01	H 7.44	N 2.52
(555.7)	Found:	C 66.30	H 7.33	N 2.46.

(4R)-4-Phenylmethyl-3-[[(5R)-5-[(4R)-2,2-diethyl-[1,3]dioxolan-4-yl]]-(2R,3R)-3-tert-butyldimethylsilyloxy-5-(4-methoxybenzyloxy)-2-methyl-pentanoyl]-oxazolidin-2-one (**13**)

A solution of the aldol product **12** (137 mg, 0.247 mmol) and triethylamine (138 µl (0.988 mmol) in dichloromethane (8 ml) was treated at –15 °C with *tert*-butyldimethylsilyl triflate (113 µl, 0.494 mmol). After warming to room temperature within 30 min, the mixture was stirred for further 3 h. Then diethyl ether (20 ml) and satd. $NaHCO_3$ solution (4 ml) were added. The phases were separated and the aqueous phase extracted with diethyl ether (3 × 7 ml). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) provided the silyl ether **13** (151 mg, 92%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 4:1): R_f = 0.36. – $[\alpha]_D$ = – 39.0 (*c* = 0.45, CH_2Cl_2). – ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 0.05 [s, 6H, $Si(CH_3)_2$], 0.87, 0.90 (2 t, *J*/Hz = 7.5, 3H each, CH_2CH_3), 0.89 (s, 9H, *t*-butyl), 1.24 (d, *J*/Hz = 6.9, 3H, $CHCH_3$), 1.54–1.68 (m, 6H, CH_2CH_3, $CHCH_2CH$), 1.78–1.85 (m, 1H, CHOSi), 2.68 (dd, *J*/Hz = 13.3, 9.6, 1H, CH_2Ph), 3.17 (dd, *J*/Hz = 13.3, 3.3, 1H, CH_2Ph), 3.54 ("dt", *J*/Hz = 8.1, 2H, CHCO, dioxolane CH_2), 3.76 (s, 3H, OCH_3), 3.76–3.82 (m, 1H, dioxolane CH_2), 3.92–3.98 (m, 2H, dioxolane CH, CHOPMB), 4.10–4.23 (m, 2H, $CHCH_2O$), 4.37–4.44 (m, 1H, NCH), 4.55, 4.80 (2 d, *J*/Hz = 11.2, 1H each, $CH_3OC_6H_4CH_2$),6.79–6.83, 7.14–7.17 (2 d, *J*/Hz = 8.7, 2H each, aromatic H), 7.22–7.33 (m, 5H, aromatic H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = –4.8, –4.1 [2 +, $Si(CH_3)_2$], 8.1, 8.3 (2 +, CH_2CH_3), 14.2 (+, $CHCH_3$), 18.0 [×, $C(CH_3)_3$], 25.9 [+, $C(CH_3)_3$], 29.3, 29.7 (2 –, CH_2CH_3), 36.1 (–, CH_2CHOSi), 37.7 (–, $PhCH_2$), 42.3 CHCO), 55.3 (+, OCH_3), 55.4 (+, Bzl CH), 65.8, 66.8 (2 –, CH_2OCO, dioxolane CH_2), 70.4 (+, CHOSi), 71.4 (–, aryl CH_2), 75.4, 78.9 (2 +, dioxolane CH, CHOPMB), 113.5 (×, dioxolane C; +, aromatic C), 127.3, 128.9, 129.0 (3 +, aromatic C), 129.5 (+, PMB C), 131.5, 135.5 (2 ×, aromatic C), 152.8 (×, OCON), 158.9 (×, aroma-tic C),175.5 (×, C=O). – MS *m/z* (%): 669 (0.1) [M^+], 241 (5), 175 (8), 135 (4), 131 (2) [$TBDMSiO^+$], 129 (6), 121 (100). – IR (CCl_4): ν/cm^{-1} = 1 786 (vs), 1 382 (m), 1 248 (s). A correct elemental analysis could not be obtained. For a HRMS the intensity of the molecular ion peak was too low.

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