Synthesis of a Diels–Alder Precursor for the Elisabethin A Skeleton

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Received 25 April 2002; revised 21 June 2002

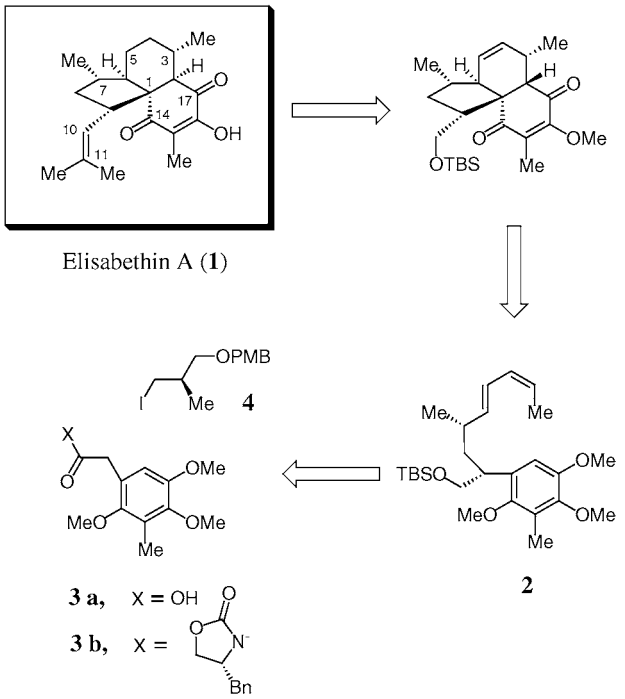
Abstract: A synthesis of a precursor **2** for the Elisabethin A skeleton is reported. Containing a masked quinone and a (*E*,*Z*)-diene subunit, it has the required elements for the envisaged intramolecular Diels–Alder reaction to form the tricyclic system of Elisabethin A. Starting from methylresorcinol, the sequence involves the preparation of an arylacetic acid, which was α-alkylated by a chiral building block. Subsequent HWE reaction and *cis*-selective Wittig olefination furnished the diene with the desired geometry.

Key words: total synthesis, natural products, alkylations, Wittig reactions, stereoselectivity

Elisabethin A (**1**) is a marine diterpenoid, which was isolated in 1998 from the chemically rich Caribbean gorgonian *Pseudopterogorgia elisabethae* (Octocorallia).[1] It acts as a highly bioactive terpenoid secondary metabolite. Studies to assess the biological properties of this compound are currently underway. The structure of Elisabethin A is representative for previously undescribed natural products possessing a novel carbon skeleton.[2]

The retrosynthetic disconnection is shown in Scheme 1. We planned to introduce the required olefinic unit (C10–C11) in a late stage of the synthesis. Further disconnection implies an intramolecular Diels–Alder reaction of an (*E*,*Z*)-diene to a *p*-benzoquinone. The precursor for the key step is molecule **2**, which contains a masked quinone. Compound **2** is derived from arylacetic acid **3a**, which has to be α-alkylated with iodide **4**. In our first approach we converted **3a** into the Evans oxazolidinone derivative **3b** to achieve a highly diastereocontrolled alkylation.

The synthesis of **3a** and **3b** started with methylresorcinol (**5**), which was acetylated by a Friedel–Crafts type reaction with acetic anhydride and $BF_3{\cdot}OEt_2$ as Lewis acid. During the subsequent attempt to protect both hydroxy groups as methyl ethers it turned out, that under mild conditions selective methylation of the *p*-hydroxy group is possible in high yield (>90%). This is due to the fact that the *o*-hydroxy group is more hindered and a strong hydrogen bond to the ketone exists (sharp signal in the ^1H NMR). This result might be useful for an orthogonal protecting group strategy. Under more drastic conditions dimethylated compound **8** was obtained in 95% yield. Bayer–Villiger oxidation with MCPBA gave the desired ester, which was hydrolysed and methylated to yield trimethoxytoluene **10** (Scheme 2). Compound **10** is known,



Scheme 1 Retrosynthetic disconnection

however this new route gives better yields than the described syntheses.[3]

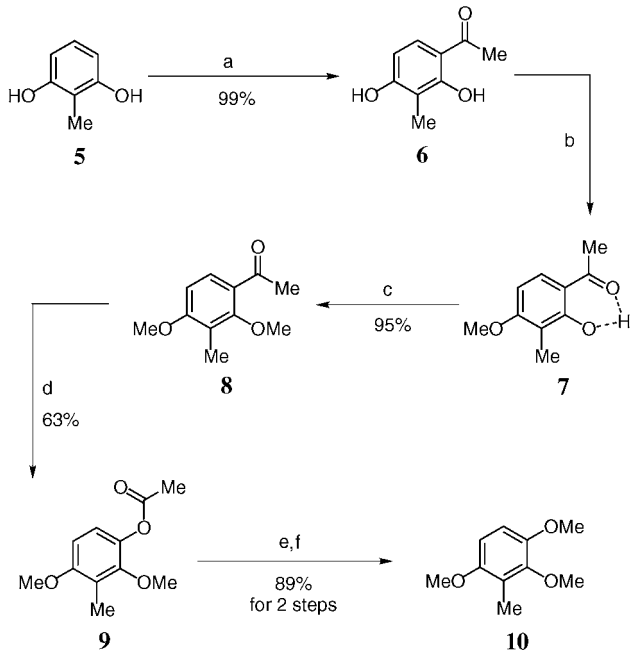
Regioselective introduction of a chloromethyl group via Blanc reaction furnished **11** in 94% yield. Subsequent conversion to the nitrile using TMSCN/TBAF at room temperature afforded **12**,[4] which was hydrolysed under basic conditions to yield the arylacetic acid **3a** (Scheme 3). Conversion into **3b** was achieved via the mixed anhydride, whereas the chloride did not react.

The chiral alkylation agent for **3a/b** was synthesised as shown in Scheme 4. PMB-protection of the hydroxy group of the commercially available (*R*)-(–)-3-hydroxy-2-methylpropionic acid ester **13** followed by reduction of the methyl ester with $LiAlH_4$ gave the alcohol **14**, that was converted into the iodide **4** by an Appel reaction (Scheme 4). Compound **4** is known, however, no synthetic procedures nor spectroscopic data are available; the synthesis outlined below surpasses, by far, the yield described in literature (60% overall compared with 46%).[5]

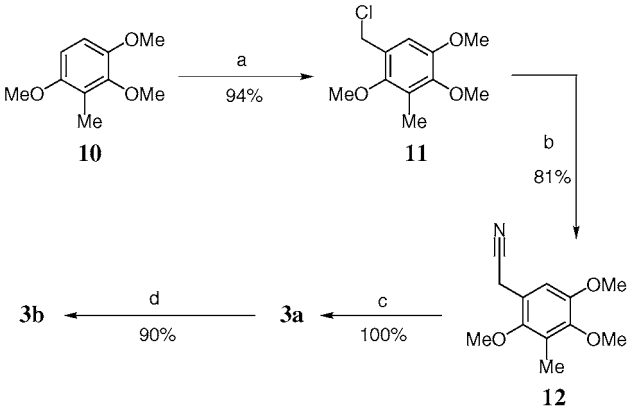
In the next operation, it turned out that deprotonated **3b** would not react with iodide **4**. Obviously, the bulky oxazolidinone moiety shielded the α-position so efficiently that the access of the alkylating agent was prevented. To

Synthesis 2002, No. 13, Print: 20 09 2002.
Art Id.1437-210X,E;2002,0,13,1857,1866,ftx,en;T05102SS.pdf.

ISSN 0039-7881

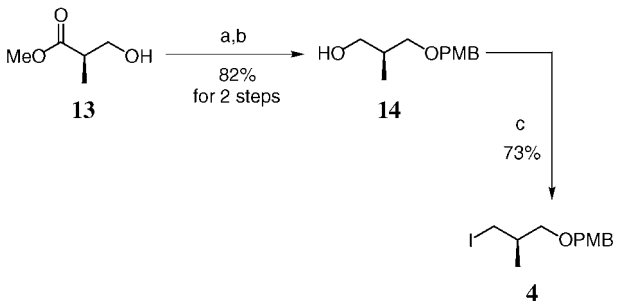


Scheme 2 *Reagents and conditions:* a) Ac_2O (1.1 equiv), $BF_3{\cdot}Et_2O$ (2.4 equiv), 80 °C, 6 h, 99% (recrystalised from H_2O–MeOH); b) K_2CO_3 (4.0 equiv), Me_2SO_4 (4.0 equiv), acetone, 14 h, r.t., 90% (with 1.0 equiv/1.0 equiv >95%); c) K_2CO_3 (2.0 equiv), Me_2SO_4 (2.0 equiv), acetone, 48 h, reflux, 95%; d) MCPBA (2.0 equiv), $TosOH{\cdot}H_2O$ (0.03 equiv), CH_2Cl_2, 14 h, r.t., 63%; e) KOH (2.0 equiv), MeOH–H_2O, 3 h, reflux, 98%; f) K_2CO_3 (2.0 equiv), Me_2SO_4 (2.0 equiv), acetone, 14 h, r.t., 91% (MCPBA = *m*-chloroperbenzoic acid, TosOH = *p*-toluenesulfonic acid).

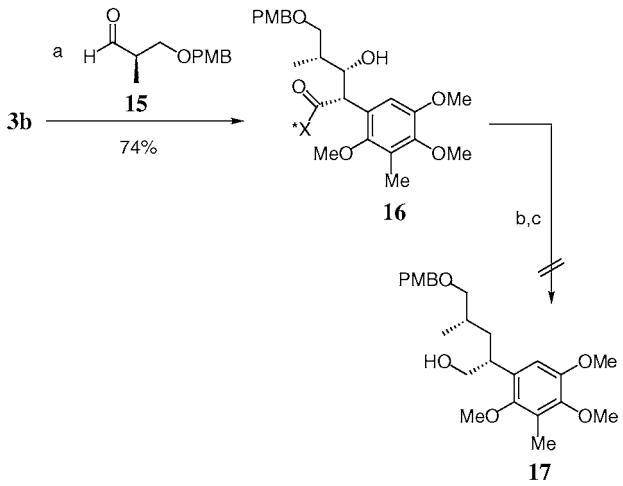


Scheme 3 *Reagents and conditions:* a) HCHO 37% (5.0 equiv), HCl 32% (3.0 equiv), HCl gas, 1 h, 70 °C, 94%; b) TMSCN (1.5 equiv), TBAF (1.5 equiv), MeCN, 10 h, r.t., 81%; c) NaOH (2.0 equiv), H_2O, 8 h, reflux, ~100%; d) PivCl (1.1 equiv), Et_3N (1.3 equiv), Evans oxazolidinone (1.2 equiv), THF, 10 h, –78 °C→r.t., 90% (PivCl = pivaloyl chloride, TBAF = tetrabutylammonium fluoride, TMSCN = trimethylsilyl cyanide).

remedy this situation we envisaged an aldol addition of **3b** and the known aldehyde **15**,[6] with ensuing removal of the superfluous hydroxyl function via deoxygenation. In fact, the aldol addition did stereoselectively furnish adduct **16**. All attempts, however, to convert **16** into **17** were unsuccessful (Scheme 5).



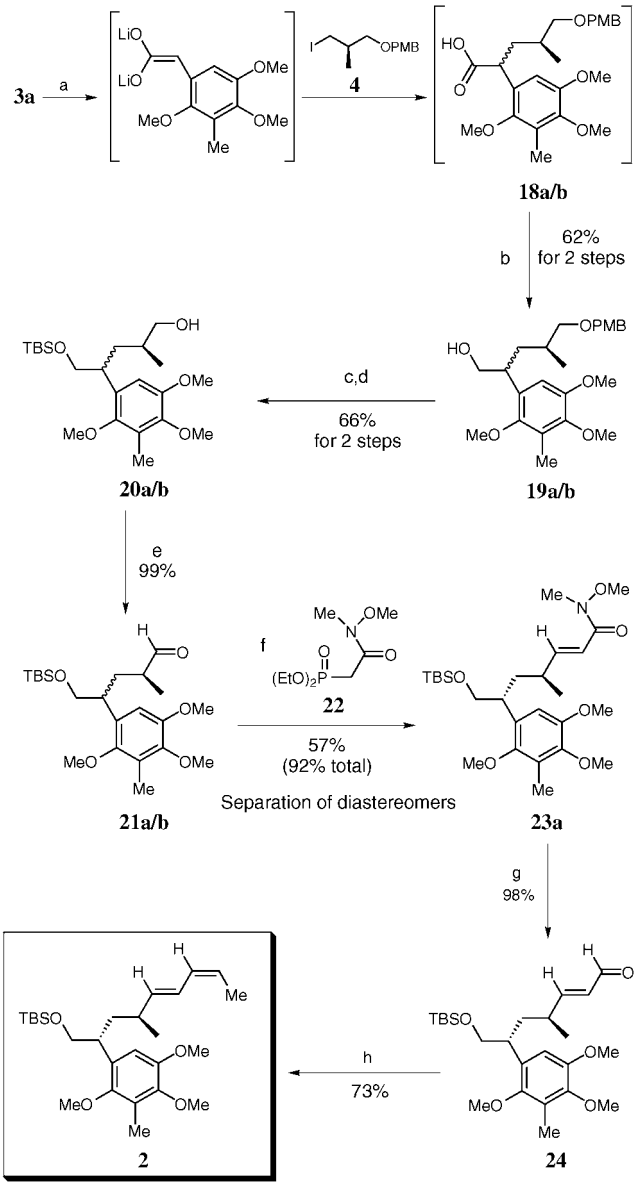
Scheme 4 *Reagents and conditions:* a) PMB-TCAI (2.0 equiv), CSA (0.1 equiv), CH_2Cl_2, 14 h, r.t., 84%; b) $LiAlH_4$ (2.5 equiv), Et_2O, 18 h, r.t., 97%; c) Im (2.5 equiv), Ph_3P (2.5 equiv), I_2 (2.0 equiv), benzene, 3 h, r.t., 73% (Im = imidazole, PMB-TCAI *p*-methoxybenzyltrichloroacetimidate, CSA = camphorsulfonic acid).



Scheme 5 *Reagents and conditions:* a) Bu_2BOTf (1.2 equiv), Et_3N (1.3 equiv), then add **15** (1.0 equiv), CH_2Cl_2, 6 h, –78 °C→0 °C, 74%, 91% de; b) MesCl (5.0 equiv), Et_3N (1.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, 6 h, r.t.; c) $LiAlH_4$ (2.5 equiv), Et_2O, 10 h, r.t.

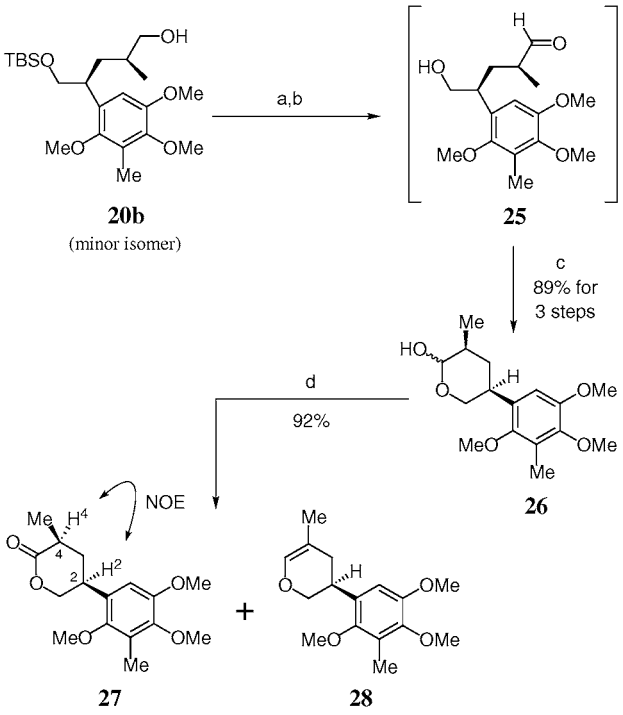
Thus, we returned to the free acid **3a**. Treatment with two equivalents of BuLi resulted in the formation of the deep red dianion, which was alkylated with iodide **4** (Scheme 6). The α-alkylation proceeded with acceptable yield, leading to the formation of two diastereomers **18a**/**b** in a ratio of 66:34, as determined from the ^1H NMR spectrum. As the isolation of acids **18a**/**b** was difficult, the crude product mixture was reduced either with $LiAlH_4$ or $Me_2S{\cdot}BH_3$ to the corresponding alcohols **19a**/**b** with 62% overall yield (Scheme 6). Without separation, compounds **19a/b** were protected as TBS-ethers and the PMB-protecting group was cleaved with DDQ to yield alcohols **20a**/**b**. Subsequent Swern oxidation furnished the aldehydes **21a**/**b** quantitatively without any racemization. To introduce the first double bond, a Horner–Wadsworth–Emmons reaction was carried out to give the desired amides **23a**/**b** in 92% total yield (diastereomeric mixture) and excellent *trans*-selectivity (>95:5). At this stage of the synthesis it was possible to separate the diastereomers completely by normal flash chromatography. The major isomer **23a** was isolated in 57% yield and reduced to the aldehyde **24** with

three equivalents of DIBAL-H in 98% yield. (*Z*)-Selective Wittig reaction of **24** with $Ph_3P{=}CHCH_3$ furnished the desired key intermediate **2** (Scheme 6).



Scheme 6 *Reagents and conditions:* a) BuLi (2.0 equiv), then add **4**, THF, 0 °C, 5 h; b) $Me_2S{\cdot}BH_3$ (1.5 equiv), THF, –40 °C→r.t., 18 h, 62% over 2 steps; c) Im (2.5 equiv), TBSCl (1.2 equiv), DMF, r.t., 24 h, 95%; d) DDQ (1.5 equiv), CH_2Cl_2/H_2O (18:1), 3 h, r.t., 69%; e) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, –78 °C→r.t., 99%; f) **22** (1.3 equiv), NaH (1.3 equiv) then **21a**/**b** (1.0 equiv), THF, 4 h, 0 °C → r.t., 92%; g) DIBAL-H (3.0 equiv), THF, 1 h, –78 °C, 98%; h) $CH_3CH_2Ph_3P^+Br^-$ (1.5 equiv), NaHMDS (1.5 equiv), THF, 14 h, –78 °C → r.t., 73% (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL-H = diisobutylaluminum hydride, NaHMDS = sodium bis(trimethylsilyl)amide, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl).

To assign the configuration of the major α-alkylation product **18a**, the minor diastereomer **20b** was converted into lactone **27** according to Scheme 7. Swern oxidation furnished the enantiopure aldehyde, which was deprotected with TBAF to give hydroxy aldehyde **25**. Upon heating with K_2CO_3 in methanol the desired lactol **26** was formed as a 45:55 mixture of anomers. To simplify the NMR spectra for the required NOE experiments of the cyclic compound, the anomeric center was destroyed by oxidation to the lactone **27** (along with elimination product **28**) using Dess–Martin periodinane (Scheme 7).



Scheme 7 Assignment of the stereochemistry. *Reagents and conditions:* a) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, –78 °C→r.t.; b) TBAF (2.0 equiv), THF, r.t., 1 h; c) K_2CO_3 (2.0 equiv), MeOH, reflux, 2.5 h, 89% over 3 steps; d) DMP (5.0 equiv), $NaHCO_3$ (20.0 equiv), CH_2Cl_2, r.t., 1 h, 92% (**27** + **28**, ~1:1) (TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane).

The NOE between H-2 and H-4 indicated that lactone **27** possesses the shown stereochemistry 2*S*,4*S* and therefore the main product of the α-alkylation (**3a**→**18a**/**b**) has to be the desired 2*R*,4*S*-isomer.

In conclusion, a facile route to diastereomerically pure Elisabethin A precursor **2** was developed. Particularly noteworthy in this sequence is the high C-nucleophilicity of the dianion which even reacts smoothly with poor electrophiles such as iodide **4**. Evans alkylations are of very limited applicability in these cases.

All moisture sensitive reactions were carried out under Argon. Anhyd solvents were obtained as follows: THF distilled from sodium/benzophenone ketyl; Et_2O distilled from $LiAlH_4$; acetone, CH_2Cl_2 and DMF distilled from P_2O_5; Et_3N distilled from CaH_2. All other solvents were HPLC grade. Column chromatography was performed with Merck silica gel (0.040–0.63 μm, 240–400 mesh) under low pressure of 5–10 psi. TLC was carried out with E. Merck silica gel 60-F254 plates. Mps were determined on a Leica Galen III apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600 Series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Optical rotations were measured on a P 341

Perkin-Elmer polarimeter. NMR spectra were recorded on either a Bruker Avance DPX 250 MHz, a Bruker Avance DRX 400 MHz or a Bruker Avance DRX 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, δ = 7.26; ^{13}C, δ = 77.0). All ^1H and ^{13}C shifts are given in ppm (s = singlet, d = doublet, t = triplet, q = quadruplet, quin = quintet, sex = sextet, sep = septet, oct = octet, m = multiplet, br s = broad signal). Coupling constants *J* are given in Hz; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments or correlated spectroscopy. Mass spectra were measured on a Micro Mass, Trio 200 Fisions Instrument. High resolution mass spectra (HRMS) were taken with a Finnigan MAT 8230 with a resolution of 10000. Elemental analyses were recorded on a Perkin-Elmer-240-Elementaranalyser.

1-(2,4-Dihydroxy-3-methylphenyl)ethanone (6)

To a solution of $BF_3{\cdot}OEt_2$ (247 g, 1.74 mol) under argon (in a flask equipped with reflux condenser, dropping funnel and argon-tap) was added methylresorcinol (Aldrich 90%, **5**; 100 g, 725 mmol). This suspension was warmed to 70 °C until a red, clear solution was obtained. This solution was allowed to cool down to r.t. and Ac_2O (Fluka 95%, 85.8 g, 798 mmol) was added dropwise to the solution over a period of 1 h. To keep the reaction under control the mixture was occasionally cooled with a water/ice bath. After the addition was complete, the mixture was heated for 6 h at 80 °C whereby the clear, red solution turned into a orange-yellow suspension, with the Et_2O, liberated from the boron-complex, floating on the top. After cooling down to r.t., ice water (500 mL) was added and the water layer was extracted with Et_2O (4 × 100 mL). The Et_2O was removed under reduced pressure to give yellow crystals, which were recrystallised from a large volume (~5 L) of boiling H_2O/MeOH. The precipitate was filtered off, washed with H_2O and dried in high vacuum; 119.2 g (99%) of colourless crystals were obtained; R_f 0.21 (SiO_2, hexane–EtOAc, 7:3); mp 120–122 °C (Lit.[7] mp 124–125 °C).

^1H NMR (250 MHz, MeOD): δ = 13.02 (s, 1 H, OH), 7.46 (d, *J* = 8.8 Hz, 1 H, ArH), 6.34 (d, *J* = 8.8 Hz, 1 H, ArH), 4.95 (br s, 1 H, OH), 2.46 (s, 3 H, CH_3CO), 2.02 (s, 3 H, Ar*C*H_3).

^{13}C NMR (62.9 MHz, MeOD): δ = 204.3, 163.9, 163.8, 131.0, 113.9, 112.2, 107.9, 26.1, 7.6.

MS (EI, 70 eV): *m*/*z* (%) = 166 (40, $[M]^+$), 161 (100, $[M - CH_3]^+$).

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_9H_{10}O_3$: 166.0630; found: 166.0632.

1-(2-Hydroxy-4-methoxy-3-methylphenyl)ethanone (7)

Compound **6** (114.9 g, 691 mmol) was dissolved in acetone (1 L). To this orange solution was added K_2CO_3 (382 g, 2.76 mol) to give a weak red solution. Over a period of 15 min, Me_2SO_4 was added dropwise whereby the colour changed to citrus yellow. The solution was stirred for 17 h at r.t., then the K_2CO_3 was filtered off and approximately half of the solvent was removed under reduced pressure. H_2O (500 mL) was added and the mixture was extracted with Et_2O (3 × 400 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The Me_2SO_4 was distilled off under vacuum (1.8 mbar/47 °C) to give **7** as a red oil (111.7 g, 90%). Higher yields (>95%) of the monomethylated product are accessible if one uses 1 equiv of K_2CO_3 and 1 equiv of Me_2SO_4; R_f 0.58 (SiO_2, hexane–EtOAc, 6:4).

^1H NMR (250 MHz, $CDCl_3$): δ = 12.64 (s, 1 H, OH), 7.55 (d, *J* = 8.9 Hz, 1 H, ArH), 6.41 (d, *J* = 8.9 Hz, 1 H, ArH), 3.86 (s, 3 H, OCH_3), 2.53 (s, 3 H, CH_3CO), 2.06 (s, 3 H, Ar*C*H_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 202.8, 163.4, 161.8, 129.7, 113.9, 113.2, 101.7, 55.6, 26.1, 7.3.

MS (EI, 70 eV): *m*/*z* (%) = 178 (57, $[M]^+$), 163 (100, $[M - CH_3]^+$), 120 (69), 87 (46).

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_9H_{10}O_3$: 178.0994; found: 178.0998.

1-(2,4-Dimethoxy-3-methylphenyl)ethanone (8)

K_2CO_3 (191 g, 1.38 mol) was added to a solution of phenol **7** (111.7 g, 620 mmol) in acetone (500 mL). Within 15 min, Me_2SO_4 (174 g, 1.38 mol) was added dropwise and the mixture was kept under reflux for 2 d. The K_2CO_3 was filtered off, H_2O (500 mL) was added, the mixture was extracted with Et_2O (3 × 400 mL), the Et_2O layer was dried (Na_2SO_4) and concentrated. Finally the Me_2SO_4 was distilled off (1.8 mbar/47 °C) to give 114.5 g (95%) of the dimethylated compound **8** as a brown oil; R_f 0.52 (SiO_2, hexane–EtOAc, 6:4).

^1H NMR (250 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.7 Hz, 1 H, ArH), 6.59 (d, *J* = 8.7 Hz, 1 H, ArH), 3.79 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 2.54 (s, 3 H, CH_3CO), 2.09 (s, 3 H, Ar*C*H_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 198.4, 161.9, 159.1, 128.7, 125.2, 119.9, 105.6, 61.5, 55.4, 29.9, 8.6.

MS (EI, 70 eV): *m*/*z* (%) = 194 (22, $[M]^+$), 178 (100, $[M - CH_3]^+$), 136 (12, $[M - CH_3 - CH_3CO]^+$), 91 (12).

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{11}H_{14}O_3$: 194.0943; found: 194.0937.

Acetic Acid 2,4-Dimethoxy-3-methylphenyl Ester (9)

The acetophenone **8** (114.5 g, 590 mmol) was dissolved in CH_2Cl_2 (700 mL) together with *p*-toluenesulfonic acid hydrate (3.00 g, 15.0 mmol). Under vigorous stirring *m*-chloroperbenzoic acid (Fluka 70%, 291 g, 1.18 mmol) was added carefully in small portions over a long period (~1 h). (**CAUTION!** Changing the order of addition or a too rapid addition might result in a sudden exothermic reaction). The colour of the solution changed from green over yellow to orange; the powder funnel was replaced by a reflux condenser. After ~20 min, a strong evolution of heat was observed and the CH_2Cl_2 started to reflux. The mixture was stirred for another 15 h at r.t., then aq sat. $NaHCO_3$ solution (500 mL) was added and extracted with CH_2Cl_2 (3 × 300 mL). Solvents were removed from the combined organic layers and the crystalline residue was shaken with aq sat. $NHCO_3$ solution (5 × 500 mL) to remove 3-chlorobenzoic acid. After decanting, the residue was dissolved in Et_2O, passed through $MgSO_4$ and the solvent was evaporated. Subsequent column chromatography (hexane–EtOAc, 8:2) furnished 78.1 g (63%) of the desired ester **9**; R_f 0.53 (SiO_2, hexane–EtOAc, 6:4).

^1H NMR (250 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 8.9 Hz, 1 H, ArH), 6.59 (d, *J* = 8.9 Hz, 1 H, ArH), 3.80, 3.75 (2 s, each 3 H, OCH_3), 2.32 (s, 3 H, CH_3CO), 2.17 (s, 3 H, $ArCH_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 169.5, 156.3, 150.4, 137.5, 121.0, 119.6, 105.5, 61.7, 55.6, 20.6, 9.0.

MS (EI, 70 eV): *m*/*z* (%) = 210 (12, $[M]^+$), 168 (100, $[M - C_2H_2O]^+$), 153 (60), 125 (16).

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{11}H_{14}O_4$: 210.0892; found: 210.0889.

1,2,4-Trimethoxy-3-methylbenzene (10)

A solution of KOH (32.3 g, 576 mmol) in MeOH–H_2O (200 mL, 9:1) was added dropwise to a solution of ester **9** (60.5 g, 288 mmol) in MeOH (200 mL) at r.t. The solution was then refluxed for 3 h and after cooling, as much as possible of the MeOH was removed under reduced pressure. After the addition of H_2O (50 mL), the solution was acidified with HCl (16%) and more H_2O was added, as long as all precipitated salts were dissolved. Extraction with Et_2O (5 × 100 mL), drying (Na_2SO_4) and evaporation of the solvent gave a brown crude oil, which was flashed through a short column of silica gel (hexane–EtOAc, 9:1). 2,4-Dimethoxy-3-methylphenol was ob-

tained as pale yellow oil in 98% (47.5 g) yield; R_f 0.48 (SiO_2, hexane–EtOAc, 6:4).

2,4-Dimethoxy-3-methylphenol

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.76 (d, *J* = 8.9 Hz, 1 H, ArH), 6.53 (d, *J* = 8.9 Hz, 1 H, ArH), 5.51 (br s, 1 H, OH), 3.77 (s, 6 H, OCH_3), 2.18 (s, 3 H, Ar*CH*$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 151.8, 145.9, 142.9, 128.9, 111.7, 106.7, 60.7, 55.9, 9.2.

MS (EI, 70 eV): *m*/*z* (%) = 168 (100, $[M]^+$), 153 (65, $[M - CH_3]^+$), 125 (49, $[M - CH_3 - CO]^+$), 110 (14), 107 (13), 85 (25), 84 (37).

HRMS (50 °C, 70 eV): *m*/*z* calcd for $C_9H_{12}O_3$ 168.0786; found 168.0790.

The phenol (41.67 g, 247 mmol) from the above reaction was dissolved in anhyd acetone (300 mL), and K_2CO_3 (68.3 g, 494 mmol) and Me_2SO_4 (62.2 g, 494 mmol) were added to this yellow suspension. The mixture was stirred for 20 h at r.t., then refluxed for 2 h to convert traces of starting material to the methyl ether. The suspension was passed through a plug of $MgSO_4$ to remove the salts and then concentrated in vacuo. The excess of Me_2SO_4 was removed by distillation (1.8 mbar/47 °C), then the product was distilled (~0.5 mbar/75–80 °C). Upon standing the trimethoxytoluene **10** crystallised as a colourless solid; R_f 0.44 (SiO_2, hexane–EtOAc, 8:2); mp 32–33 °C (Lit.[3] mp 30–31 °C).

10

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.69 (d, *J* = 8.9 Hz, 1 H, ArH), 6.53 (d, *J* = 8.9 Hz, 1 H, ArH), 3.81, 3.80, 3.78 (3 s, each 3 H, OCH_3), 2.17 (s, 3 H, Ar*CH*$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 152.4, 148.1, 147.1, 121.0, 108.5, 105.1, 60.2, 56.1, 55.7, 8.8.

MS (EI, 70 eV): *m*/*z* (%) = 182 (100, $[M]^+$), 167 (78, $[M - CH_3]^+$), 152 (18, $[M - CH_3 - CH_3]^+$), 139 (43, $[M - CH_3 - CO]^+$), 124 (25), 107 (14), 91 (12), 85 (10), 83 (15), 53 (12).

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{10}H_{14}O_3$: 182.0943; found: 182.0940.

1-Chloromethyl-2,4,5-trimethoxy-3-methylbenzene (11)

Trimethoxytoluene **10** (33.2 g, 182 mmol) was placed in a flask together with HCHO (Apoka 37%, 63.7 mL, 910 mmol) and HCl (Riedel de Häen 32%, 63.7 mL, 558 mmol). Over a period of 1 h 15 min HCl gas (prepared by dropping H_2SO_4 to NaCl) was passed through the mixture; during this procedure a strong heat tone (60–80 °C) was observed and the colour changed from salmon pink to pale orange. Finally the reaction product was poured on ice/water and extracted with Et_2O (5 × 50 mL), the Et_2O layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The product was isolated in 94% (39.52 g) yield as colourless crystals; R_f 0.48 (SiO_2, hexane–EtOAc, 8:2); mp 33–35 °C (Lit.[3] mp 39–40 °C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.77 (s, 1 H, ArH), 4.63 (s, 2 H, CH_2Cl), 3.83, 3.79, 3.77 (3 s, each 3 H, OCH_3), 2.21 (s, 3 H, Ar*CH*$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 150.8, 149.3, 148.4, 125.7, 125.4, 110.9, 61.4, 60.1, 55.8, 41.5, 9.4.

MS (EI, 70 eV): *m*/*z* (%) = 232 {23, $[M(^{37}Cl)]^+$}, 230 {71, $[M(^{35}Cl)]^+$}, 215 {20, $[M - CH_3]^+$}, 195 {100, $[M - {}^{37}Cl - {}^{35}Cl]^+$}, 165 (39), 152 (13), 150 (23), 137 (12), 105 (17), 91 (11), 77 (13).

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{11}H_{15}{}^{35}ClO_3$: 230.0710; found: 230.0707.

(2,4,5-Trimethoxy-3-methylphenyl)acetonitrile (12)

To a solution of **11** (12.4 g, 53.0 mmol) in MeCN (500 mL) was added TMSCN (8.05 g, 79.5 mmol) and) and TBAF (1 M in THF, 79.5 mL, 79.5 mmol). The clear, slightly yellow solution was stirred at r.t. for 10 h, then the solvent was removed under reduced pressure to give a yellow syrup, which was subjected straight to column chromatography (hexane–EtOAc, 9:1). The desired nitrile **12** was obtained as a colourless, crystalline solid in 81% (9.49 g) yield after evaporation of solvents; R_f 0.18 (SiO_2, hexane–EtOAc, 8/2), mp 64–66 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.74 (s, 1 H, ArH), 3.82, 3.77, 3.70 (3 s, each 3 H, OCH_3), 3.68 (s, 2 H, CH_2CN), 2.19 (s, 3 H, $ArCH_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 150.0, 149.3, 147.9, 125.7, 125.7, 118.1, 118.0, 109.8, 60.6, 60.0, 55.8, 18.1, 9.4.

MS (EI, 70 eV): *m*/*z* = 221 (72, $[M]^+$), 207 (12, $[M - N]^+$), 206 (100, $[M - CH_3]^+$), 178 (20, $[M - CH_3 - CO]^+$), 85 (29), 83 (48).

HRMS (30 °C, 70 eV): *m*/*z* calcd for $C_{12}H_{15}NO_3$: 221.1052; found: 221.1058.

Anal. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.17; H, 6.95; N, 6.36.

(2,4,5-Trimethoxy-3-methylphenyl)acetic Acid (3a)

To the nitrile **12** (8.54 g, 38.5 mmol) was added a solution of NaOH (3.08 g, 77 mmol) in H_2O (9.3 mL) to give a milky-white suspension. This mixture was kept under reflux for 8 h, whereby the progress of the hydrolysis was monitored by indicator paper sitting on the top of the reflux condenser (liberation of NH_3). After a few hours the suspension turned into a clear, slightly yellow solution. Finally the solution was acidified with H_2SO_4 (20%, 15 mL), the precipitated acid was filtered and washed with H_2O. The mother liquor was extracted with $CHCl_3$, the organic layer was combined with the precipitate and solvents were removed in vacuo. After drying in high vacuum for 16 h, the acid was isolated in ~100% (9.23 g) yield as colourless crystals; R_f 0.13 (SiO_2, hexane–EtOAc, 8:2); mp 258–260 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.64 (s, 1 H, ArH), 6.32 (br s, 1 H, CO_2H), 3.82, 3.79, 3.70 (3 s, each 3 H, OCH_3), 3.65 (s, 2 H, CH_2CO_2H), 2.22 (s, 3 H, Ar*CH*$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 176.6, 150.6, 149.3, 147.5, 125.6, 121.5, 111.4, 60.8, 60.2, 55.9, 35.6, 9.7.

MS (EI, 70 eV): *m*/*z* (%) = 241 (15, $[M + H]^+$), 240 (100, $[M]^+$), 225 (11, $[M - CH_3]^+$), 221 (13, $[M - H_3O]^+$), 207 (12), 206 (16), 196 (10), 195 (40, $[M - CHO_2]^+$), 181 (67), 165 (17), 138 (12), 137 (10).

HRMS (70 °C, 70 eV): *m*/*z* calcd for $C_{12}H_{16}O_5$: 240.0998; found: 240.1003.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.82; H, 6.79.

(*R*)-4-Benzyl-3-[2-(2,4,5-trimethoxy-3-methylphenyl)acetyl]oxazolidin-2-one (3b)

To a solution of **3a** (4.71 g, 19.6 mmol) in anhyd THF (200 mL) was added Et_3N (2.58 g, 25.5 mmol) and pivaloyl chloride (2.6 g, 21.6 mmol) at –78 °C. The milky-white mixture was allowed to warm to 0 °C over a period of 2 h. After cooling down again to –78 °C, a suspension of (*R*)-4-benzyl-2-oxazolidinone (4.16 g, 23.5 mmol), deprotonated with BuLi (2.5 M in hexane, 9.5 mL, 23.5 mmol) in anhyd THF at –78 °C/30 min, was transferred via canula to the mixed anhydride at –78 °C. The mixture was allowed to warm to r.t. overnight (~14 h), then quenched with aq NH_4Cl (130 mL). After extraction with Et_2O (3 × 150 mL) and removal of solvents under reduced pressure, the remaining crude oil was further purified by column chromatography on silica gel using hexane–EtOAc (6:4) as

eluent. Compound **3b** was obtained as a clear, highly viscous oil in 90% (7.05 g) yield; R_f 0.39 (SiO_2, hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +48.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 5 H, C_6H_5), 6.62 (s, 1 H, ArH), 4.78–4.63 (m, 1 H, NCH), 4.26 (s, 2 H, ArC*H*$_2$), 4.24–4.20 (m, 2 H, OCH_2), 3.83, 3.81, 3.69 (3 s, each 3 H, OCH_3), 3.34 (dd, *J* = 2.1, 14.2 Hz, 1 H, PhC*H*$_2$), 2.79 (dd, *J* = 8.6, 14.2 Hz, 1 H, PhC*H*$_2$), 2.24 (s, 3 H, ArC*H*$_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.4, 153.6, 151.0, 149.1, 147.4, 135.3, 129.4, 128.9, 127.3, 125.5, 121.8, 111.9, 66.3, 60.7, 60.2, 55.9, 55.5, 37.8, 37.1, 8.8.

MS (EI, 70 eV): *m*/*z* (%) = 399 (23, $[M]^+$), 223 (23), 222 (100), 207 (37), 195 (15), 149 (12).

HRMS (120 °C, 70 eV): *m*/*z* calcd for $C_{22}H_{25}NO_6$ 399.1682; found 399.1675.

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.32; H, 6.18; N, 3.72.

(*S*)-(–)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (14)

To a solution of **13** (7.15 g, 60.5 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of *p*-methoxybenzyltrichloroacetimidate (34.2 g, 121 mmol, prepared from *p*-methoxybenzyl alcohol and trichloroacetonitrile[8]) in anhyd CH_2Cl_2 (75 mL). After cooling to –5 °C, camphorsulfonic acid (1.41 g, 6.05 mmol) was added and the milky-cloudy mixture was stirred for 30 h at r.t. Then the suspension was filtered through a silica gel/Celite plug, to remove the precipitated trichloroacetamide. The silica gel/Celite plug was washed twice with hexane–CH_2Cl_2 (100 mL, 2:1), the combined filtrates were concentrated in vacuo and purified by silica gel column chromatography using hexane–EtOAc (10:1) as eluent. The PMB-protected derivative of compound **13** was isolated in 84% (12.1 g) yield as a colourless oil; R_f 0.48 (SiO_2, hexane–EtOAc, 8:2); $[\alpha]_D^{20}$ –12.5 (*c* 1.00, CH_2Cl_2).

PMB-Protected Derivative of Compound 13

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H, ArH), 6.86 (d, *J* = 8.6 Hz, 2 H, ArH), 4.44 (s, 2 H, ArC*H*$_2$), 3.79, 3.68 (2 s, each 3 H, OCH_3), 3.63 (dd, *J* = 7.3, 9.1 Hz, 1 H, MeCHC*H*$_2$O), 3.45 (dd, *J* = 5.9, 9.1 Hz, 1 H, MeCHC*H*$_2$O), 2.76 (m, 1 H, MeC*H*), 1.16 (d, *J* = 7.3 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.3, 159.2, 129.7, 129.4, 114.3, 72.8, 71.7, 55.4, 51.7, 40.2, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 238 (12, $[M]^+$), 138 (14), 137 (100, $[M – MeO_2CHCH_3]^+$), 122 (15), 121 (96, $[M – MeO_2CHCH_3O]^+$), 109 (13), 78 (10), 77 (14).

HRMS (20 °C, 70 eV): *m*/*z* calcd for $C_{13}H_{18}O_4$: 238.1205; found: 238.1212.

To a suspension of $LiAlH_4$ (3.18 g, 83.8 mmol) in anhyd Et_2O (50 mL) was added slowly a solution of the PMB-protected derivative of the Roche alcohol **13** (7.96 g, 33.4 mmol) from the above reaction, in anhyd Et_2O (50 mL). The mixture was stirred for 18 h at r.t., then carefully quenched under cooling with H_2O (~5.5 mL) until gas development stopped, followed by the addition aq 1 N NaOH (~25 mL) until all grey $LiAlH_4$ was converted into white $Al(OH)_3$. The precipitated salts were filtered off, H_2O (100 mL) was added to the filtrate and extracted with Et_2O (3 × 50 mL). Finally the combined organic layers were passed through a plug of $MgSO_4$ and the solvent was evaporated under reduced pressure to give 6.79 g (97%) of the desired alcohol **14** as a colourless oil; R_f 0.18 (SiO_2, hexane–EtOAc, 7:3); $[\alpha]_D^{20}$ –10.8 (*c* 1.20, CH_2Cl_2).

14

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H, ArH), 6.88 (d, *J* = 8.8 Hz, 2 H, ArH), 4.45 (s, 2 H, ArC*H*$_2$), 3.80 (s, 3 H, OCH_3), 3.62–3.55 (m, 2 H, C*H*$_2$OH), 3.52 (dd, *J* = 4.7, 8.9 Hz, 1 H, MeCHC*H*$_2$O), 3.39 (dd, *J* = 8.0, 8.9 Hz, 1 H, MeCHC*H*$_2$O), 2.53 (br s, 1 H, OH), 2.21–1.97 (m, 1 H, MeC*H*), 0.87 (d, *J* = 7.1 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.3, 130.2, 129.3, 113.9, 75.2, 73.1, 67.9, 55.3, 35.6, 13.5.

MS (EI, 70 eV): *m*/*z* (%) = 210 (6, $[M]^+$), 138 (20), 137 (63, $[M – HOCH_2CH(CH_3)CH_2]^+$), 122 (13), 121 (100, $[M – HOCH_2CHMeCH_2O]^+$), 109 (16), 77 (13).

HRMS (50 °C, 70 eV): *m*/*z* calcd for $C_{12}H_{18}O_3$: 210.1256; found: 210.1252.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 74.60; H, 10.11. Found: C, 74.68; H, 10.21.

(*S*)-(–)-1-(3-Iodo-2-methylpropoxymethyl)-4-methoxybenzene (4)

To a solution of alcohol **14** (5.79 g, 27.7 mmol) in anhyd benzene (240 mL) was added imidazole (4.71 g, 69.2 mmol), Ph_3P (18.1 g, 69.2 mmol) and I_2 (14.1 g, 55.3 mmol) at 0 °C. After 5 min, the cooling bath was removed and the reaction mixture was stirred for 3 h at r.t. whereby the colour changed from brown to bright yellow. Then the reaction was quenched by the addition of a aq sat. $Na_2S_2O_3$ solution (200 mL), the liquid phases were decanted and the solid residue was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed once with aq sat. $Na_2S_2O_3$ solution and brine. After drying ($MgSO_4$), solvents were evaporated to give 20.5 g of a white solid, which was dissolved under heating in a minimum amount of a 4:1 mixture of hexane–Et_2O. This solution was kept in the freezer at –40 °C for several hours, then the precipitated white solid (Ph_3PO/PPh_3) was filtered off, solvents were removed and the residue was further purified by column chromatography on silica gel, eluting with hexane–EtOAc (15:1). Finally 6.49 g (73%) of the iodide **4** was obtained as a colourless oil; R_f 0.59 (SiO_2, hexane–EtOAc, 7:3); $[\alpha]_D^{20}$ –13.5 (*c* 1.15, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2 H, ArH), 6.88 (d, *J* = 8.6 Hz, 2 H, ArH), 4.44 (s, 2 H, ArC*H*$_2$), 3.81 (s, 3 H, OCH_3), 3.39–3.23 (m, 4 H, CH_2I and MeCHC*H*$_2$O), 1.76 (m, 1 H, MeC*H*), 0.98 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 159.2, 130.4, 129.2, 113.8, 73.9, 72.9, 67.9, 55.3, 35.2, 17.7, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 320 (20, $[M]^+$), 122 (11), 121 (100, $[CH_2C_6H_4OMe\text{-}4]^+$).

HRMS (50 °C, 70 eV): *m*/*z* calcd for $C_{12}H_{17}O_2I$ 320.0273; found 320.0268.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 45.02; H, 5.35. Found: C, 45.18; H, 5.19.

4-Benzyl-3-[3-hydroxy-5-(4-methoxybenzyloxy)-4-methyl-2-(2,4,5-trimethoxy-3-methylphenyl)pentanoyl]oxazolidin-2-one (16)

Compound **3b** (5.14 g, 12.9 mmol) was dissolved in anhyd CH_2Cl_2 (11 mL), then Et_3N (1.69 g, 16.7 mmol) and Bu_2BOTf (4.24 g, 15.5 mmol, freshly prepared[9]) were added at 0 °C. The clear yellow-orange solution was stirred for 3.5 h at 0 °C, cooled to –78 °C and aldehyde **15**[6] (4.26 g, 12.9 mmol), dissolved in anhyd CH_2Cl_2 (11 mL), was transferred via syringe into the flask. The solution was allowed to warm to 0 °C over a period of 6 h. To quench the reaction pH 7 buffer (15 mL) was added, followed by the addition of MeOH (20 mL) and a 2:1 mixture of MeOH–H_2O_2 (43 mL) and this solution was stirred for 1 h at r.t. Finally most of the solvents were evaporated under reduced pressure and the residue was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), solvents were evaporated and the crude oil was further purified by column chromatography eluting with hexane–EtOAc

(7:3). The desired adduct **16** was isolated in 74% (4.64 g, clear oil) yield as a single diastereomer. The diastereomeric excess of the reaction was 91%, as determined from the ^{1}H NMR spectrum of the crude product; R_f 0.47 (SiO_2, hexane–EtOAc, 6:4); $[\alpha]_D^{20}$ +31.6 (*c* 1.00, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 7 H, C_6H_5 and $CH_2C_6H_4$OMe-4), 6.92 (s, 1 H, ArH), 6.88 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 5.70 (d, *J* = 10.8 Hz, 1 H, ArCH), 4.68 (m_c, 1 H, NCH), 4.44 (dd, *J* = 2.4, 10.8 Hz, 1 H, ArCHC*H*), 4.38 (s, 2 H, CH_2C$_6$H$_4$OMe-4), 4.07–3.98 (m, 2 H, OCH_2CHN), 3.82 (s, 3 H, $CH_2C_6H_4$OCH_3-4), 3.72 (s, 9 H, 3 OCH_3), 3.20, 3.11 (2 m_c, each 1 H, OCH_2CHMe), 3.06 (dd, *J* = 1.9, 9.4 Hz, 1 H, PhCH_2), 2.53 (dd, *J* = 6.4, 9.4 Hz, 1 H, PhCH_2), 2.18 (s, 3 H, ArCH_3), 1.96–1.86 (m, 1 H, C*H*Me), 1.05 (d, *J* = 6.6 Hz, 3 H,CHCH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.2, 159.6, 153.1, 152.4, 149.7, 147.9, 144.6, 135.3, 133.4, 129.2, 128.8, 127.6, 126.1, 123.9, 109.8, 87.1, 74.7, 67.6, 66.0, 61.7, 60.8, 56.4, 55.3, 46.6, 37.7, 37.5, 21.4, 14.6, 10.8, 10.6.

MS (EI, 70 eV): *m*/*z* (%) = 607 (6, $[M]^+$), 486, (21), 399 (45), 330 (18), 121 (100).

HRMS (50 °C, 70 eV): *m*/*z* calcd for $C_{34}H_{41}O_9N$: 607.2781; found: 607.2792.

Anal. Calcd for $C_{34}H_{41}O_9N$: C, 67.20; H, 6.80; N, 2.30. Found: C, 67.48; H, 6.97; N, 2.01.

(4*S*)-5-(4-Methoxybenzyloxy)-4-methyl-2-(2,4,5-trimethoxy-3-methylphenyl)pentan-1-ol (19a/b)

The arylacetic acid **3a** (500 mg, 2.08 mmol) was dissolved in anhyd THF (4 mL) and treated with BuLi (1.66 mL, 2.5 M in hexane, 4.16 mmol) at 0 °C. To the deep red dianion was added the iodide **4**, dissolved in anhyd THF (1 mL), whereby the colour changed to yellow. The mixture was stirred for another 5 h at 0 °C, then quenched with aq sat. NH_4Cl solution (5 mL). After evaporation of the solvents, H_2O (10 mL) was added and the suspension was slightly acidified with aq 1 N HCl. Extraction with $CHCl_3$ (3 × 10 mL) afforded 0.931 g of the crude product **18a/b**, after removal of solvents. For analytical purpose, a small sample was purified by column chromatography on silica gel (hexane–EtOAc, 5:5). The ratio of the diastereomers was 66:34, determined by signal integration (ArH and CH_2C$_6$H$_4$OMe) of the ^{1}H NMR spectrum; R_f 0.25 (for both isomers, SiO_2, hexane–EtOAc, 2:8).

18a/b

^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.13 (d, *J* = 8.6 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.76 (d, *J* = 8.6 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.63 (s, 1 H, ArH), 4.28 (s, 2 H, OCH_2C$_6$H$_4$OMe-4), 4.15–4.06 (m, 1 H, ArC*H*CO_2H), 3.73, 3.70, 3.69, 3.60 (4 s, each 3 H, OCH_3), 3.25–3.16 (m, 2 H, CH_2OPMB), 2.12 (s, 3 H, ArCH_3), 1.91–1.82 (m, 1 H, ArCHCH_2), 1.79–1.70 (m, 1 H, ArCHCH_2), 1.62–1.51 (m, 1 H, C*H*Me), 086 (d, *J* = 6.6 Hz, 3 H, CHCH_3). δ (minor isomer) = 7.16 (d, *J* = 8.6 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.77 (d, *J* = 8.6 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.65 (s, 1 H, ArH), 4.32 (s, 2 H, OCH_2C$_6$H$_4$OMe-4), 4.15–4.06 (m, 1 H, ArC*H*CO_2), 3.75, 3.71, 3.69, 3.66 (4 s, each 3 H, OCH_3), 3.25–3.16 (m, 2 H, CH_2OPMB), 2.12 (s, 3 H, ArCH_3), 1.91–1.82 (m, 1 H, ArCHCH_2), 1.70–1.64 (m, 1 H, ArCHCH_2), 1.43–1.35 (m, 1 H, C*H*Me), 0.87 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (major isomer) = 180.2, 159.0, 150.5, 149.4, 147.1, 130.6, 129.1, 126.4, 125.3, 113.6, 108.5, 75.4, 72.5, 61.2, 60.1, 55.9, 55.2, 41.3, 36.9, 31.1, 17.0, 9.7. δ (minor isomer) = 179.9, 159.0, 150.1, 149.3, 147.0, 130.5, 129.0, 127.0, 125.4, 113.7, 108.6, 74.9, 72.3, 61.1, 60.1, 55.8, 55.2, 41.2, 37.2, 31.5, 17.2, 9.7.

MS (EI, 70 eV): *m*/*z* (%) = 432 (10, $[M]^+$), 320 (9, $[M - H - CH_2C_6H_4OMe\text{-}4]^+$), 294 (16), 265 (24), 212 (11), 211 (23), 209 (23), 196 (14), 195 (37), 183 (19), 129 (26), 121 (100, $[CH_2C_6H_4OMe\text{-}4]^+$).

HRMS (100 °C, 70 eV): *m*/*z* calcd for $C_{24}H_{32}O_7$: 432.2148; found: 432.2145.

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.48; H, 7.52.

The crude product (0.904 g, ~2.08 mmol) from the above reaction was dissolved anhyd THF (10 mL) and cooled to –40 °C. DMS·BH_3 (0.2 mL, 3.12 mmol) was added via syringe and the mixture was allowed to warm slowly to r.t. whereby the colour turned from orange into yellow. After stirring for 18 h, a mixture of EtOAc–AcOH (10 mL, 1:1) was added carefully under icebath cooling, then the solution was neutralised with a aq sat. $NaHCO_3$ solution (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were passed through a plug of $MgSO_4$ and the solvents were evaporated. The remaining yellow oil was further purified by column chromatography on silica gel using hexane–EtOAc (6:4) as eluent. The desired alcohols **19a/b** were obtained in 62% (542 mg, clear oil) yield over the two steps; R_f 0.32 (for both isomers, SiO_2, hexane–EtOAc, 1:1).

19a/b

^{1}H NMR (250 MHz, $CDCl_3$): δ (major isomer) = 7.16 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.80 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.56 (s, 1 H, ArH), 4.29 (s, 2 H, OCH_2C$_6$H$_4$OMe-4), 3.73, 3.71, 3.67, 3.62 (4 s, each 3 H, OCH_3), 3.69–3.58 (m, 2 H, CH_2OH), 3.41–3.22 (m, 2 H, CH_2OPMB), 3.22–3.14 (m, 1 H, ArC*H*), 2.59 (br s, 1 H, OH), 2.18 (s, 3 H, ArCH_3), 1.88–1.66 (m, 1 H, ArCHCH_2), 1.66–1.52 (m, 1 H, C*H*Me), 1.49–1.24 (m, 1 H, ArCHCH_2), 0.92 (d, *J* = 6.6 Hz, 3 H, CHCH_3). δ (minor isomer) = 7.20 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.82 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.58 (s, 1 H, ArH), 4.36 (s, 2 H, OCH_2C$_6$H$_4$OMe-4), 3.75, 3.73, 3.71, 3.59 (4 s, each 3 H, OCH_3), 3.69–3.58 (m, 2 H, CH_2OH), 3.41–3.22 (m, 2 H, CH_2OPMB), 3.22–3.14 (m, 1 H, ArCH), 2.59 (br s, 1 H, OH), 2.18 (s, 3 H, ArCH_3), 1.88–1.66 (m, 1 H, ArCHCH_2), 1.66–1.52 (m, 1 H, C*H*Me), 1.49–1.24 (m, 1 H, ArCHCH_2), 0.92 (d, *J* = 6.6 Hz, 3 H, CHCH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (major isomer) = 158.7, 151.0, 149.1, 145.8, 130.4, 129.7, 128.6, 124.6, 113.3, 107.9, 75.6, 72.1, 67.5, 60.7, 59.6, 55.4, 54.7, 37.6, 35.4, 30.5, 16.6, 9.4. δ (minor isomer) = 158.6, 150.6, 149.0, 145.9, 130.7, 129.7, 128.6, 124.7, 113.3, 107.9, 74.7, 72.2, 66.7, 60.7, 59.6, 55.4, 54.7, 37.5, 35.9, 31.0, 17.7, 9.4.

MS (EI, 70 eV): *m*/*z* (%) = 418 (24, $[M]^+$), 282 (18, $[M - O - CH_2C_6H_4OMe\text{-}4]^+$), 279 (13), 267 (14), 251 (23), 222 (16), 195 (43), 137 (15), 122 (15), 121 (100, $[CH_2C_6H_4OMe\text{-}4]^+$), 85 (13).

HRMS (130 °C, 70 eV): *m*/*z* calcd for $C_{24}H_{34}O_6$: 418.2355; found: 418.2362.

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 68.81; H, 8.32.

(2*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-(trimethoxymethylphenyl)pentan-1-ol (20a/b)

To a solution of the alcohols **19a/b** (1.51 g, 3.59 mmol) in anhyd DMF (4 mL) was added imidazole (612 mg, 8.99 mmol) and TBSCl (650 mg, 4.32 mmol). This mixture was stirred at r.t. for 1 d, then diluted with toluene (15 mL) and washed with H_2O (4 × 15 mL). The combined aqueous layers were extracted with toluene–Et_2O (1:1, 2 ×). The organic layers were combined and passed through a plug of $MgSO_4$. Removal of solvents in vacuo gave 1.82 g (95%) of TBS-protected **19a/b** as a brown crude oil; R_f 0.69 (for both isomers, SiO_2, hexane–EtOAc, 6:4).

TBS-Protected 19a/b

^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 7.24 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.87 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.67 (s, 1 H, ArH), 4.37 (s, 2 H, $OCH_2C_6H_4$OMe-4), 3.81, 3.79, 3.75, 3.71 (4 s, each 3 H, OCH_3), 3.81–3.65 (m, 2 H, CH_2OTBS), 3.46–3.32 (m, 2 H, CH_2OPMB), 3.32–3.21 (m, 1 H, ArCH), 2.26 (s, 3 H, ArCH_3), 2.02–1.75 (m, 1 H, ArCHCH_2), 1.70–1.52 (m, 1 H, C*H*Me), 1.49–1.30 (m, 1 H, ArCHCH_2), 0.99 (d, *J* = 6.8 Hz, 3 H, CHCH_3), 0.90 [s, 9 H, $OSiC(CH_3)_3$], 0.03 [s, 6 H, $OSi(CH_3)_2$]. δ (minor isomer) = 7.28 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.88 (d, *J* = 8.4 Hz, 2 H, $CH_2C_6H_4$OMe-4), 6.69 (s, 1 H, ArH), 4.43 (s, 2 H, $OCH_2C_6H_4$OMe-4), 3.84, 3.81, 3.79, 3.66 (4 s, each 3 H, OCH_3), 3.81–3.65 (m, 2 H, CH_2OTBS), 3.46–3.32 (m, 2 H, CH_2OPMB), 3.32–3.21 (m, 1 H, ArCH), 2.26 (s, 3 H, ArCH_3), 2.02–1.75 (m, 1 H, ArCHCH_2), 1.70–1.52 (m, 1 H, C*H*Me), 1.49–1.30 (m, 1 H, ArCHCH_2), 0.99 (d, *J* = 6.8 Hz, 3 H, CHCH_3), 0.88 [s, 9 H, $OSiC(CH_3)_3$], 0.01 [s, 6 H, $OSi(CH_3)_2$].

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (major isomer) = 158.8, 151.1, 148.9, 145.9, 131.5, 130.7, 128.7, 124.5, 113.4, 108.6, 75.9, 72.2, 68.0, 60.8, 59.8, 55.6, 54.8, 37.5, 35.4, 30.7, 25.7, 18.1, 16.8, 9.5, –5.7. δ (minor isomer) = 158.8, 150.7, 148.8, 145.9, 131.5, 130.4, 128.7, 124.6, 113.4, 108.6, 74.9, 72.3, 67.3, 60.7, 59.8, 55.8, 54.8, 37.6, 35.9, 31.2, 25.7, 18.0, 16.8, 9.5, –5.6.

MS (EI, 70 eV): *m*/*z* (%) = 532 (4, $[M]^+$), 135 (23), 121 (100, $[CH_2C_6H_4OMe\text{-}4]^+$), 82 (10), 73 (10).

HRMS (110 °C, 70 eV): *m*/*z* calcd for $C_{30}H_{48}O_6Si$: 532.3220; found: 532.3233.

20a/b

To a solution of TBS-protected alcohols **19a**/**b** (2.23 g, 4.19 mmol) from the above reaction in a mixture of CH_2Cl_2/H_2O (18:1, 19 mL) was added DDQ (1.43 g, 6.29 mmol). The reaction mixture turned into black and the stirring was continued for 3 h at r.t. Then the precipitated DDQH was filtered off, the organic phase was washed with aq sat. NH_4Cl solution (2 × 20 mL) and with H_2O (1 × 20 mL). The aqueous layers were extracted with CH_2Cl_2 (3 × 25 mL), the combined organic phases were passed through a plug of $MgSO_4$ and concentrated in vacuo to give the crude product as a blue-black oil. To remove the anisaldehyde, the crude product was further purified by column chromatography eluting with hexane–EtOAc (8:2). Alcohols **20a**/**b** were obtained in 69% yield (1.19 g) as a colourless oil. It was possible to isolate small quantities of diastereomeric pure material (first and last fractions); R_f 0.44 (major isomer, SiO_2, hexane–EtOAc, 6:4); R_f 0.39 (minor isomer, SiO_2, hexane–EtOAc, 6:4).

^{1}H NMR (250 MHz, $CDCl_3$): δ (major isomer) = 6.62 (s, 1 H, ArH), 3.81, 3.77, 3.68 (3 s, each 3 H, OCH_3), 3.76–3.62 (m, 2 H, CH_2OH), 3.57–3.45 (m, 2 H, CH_2OTBS), 3.41–3.28 (m, 1 H, ArCH), 2.21 (s, 3 H, ArCH_3), 1.91–1.78 (m, 1 H, ArCHCH_2), 1.64–1.47 (m, 1 H, C*H*Me), 1.43–1.32 (m, 1 H, ArCHCH_2), 0.90 (d, *J* = 6.7 Hz, 3 H, CHCH_3), 0.83 [s, 9 H, $SiC(CH_3)_3$], –0.02 [s, 6 H, $Si(CH_3)_2$]. δ (minor isomer) = 6.65 (s, 1 H, ArH), 3.84, 3.80, 3.71 (3 s, each 3 H, OCH_3), 3.76–3.62 (m, 2 H, CH_2OH), 3.57–3.45 (m, 2 H, CH_2OTBS), 3.41–3.28 (m, 1 H, ArCH), 2.24 (s, 3 H, ArCH_3), 1.91–1.78 (m, 1 H, ArCHCH_2), 1.64–1.47 (m, 1 H, C*H*Me), 1.32–1.22 (m, 1 H, ArCHCH_2), 0.92 (d, *J* = 6.7 Hz, 3 H, CHCH_3), 0.86 [s, 9 H, $SiC(CH_3)_3$], –0.01 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ (major isomer) = 150.6, 149.2, 146.2, 131.6, 125.0, 108.5, 68.2, 67.6, 61.2, 60.2, 56.1, 37.6, 36.6, 33.5, 25.8, 18.3, 18.0, 9.7, –5.4, –5.5. δ (minor isomer) = 150.8, 149.1, 146.4, 131.6, 125.5, 108.5, 69.1, 68.4, 61.2, 60.2, 56.1, 37.6, 36.3, 33.5, 26.2, 18.1, 17.8, 9.7, –5.4, –5.5.

MS (EI, 70 eV): *m*/*z* (%) = 412 (8, $[M]^+$), 263 (17), 210 (14), 195 (40), 169 (26), 168 (100), 165 (11), 156 (84), 141 (26), 139 (77), 135 (15), 113 (13), 111 (41), 77 (17), 75 (30).

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_{22}H_{40}O_5Si$: 412.2645; found: 412.2653.

Anal. Calcd for $C_{22}H_{40}O_5Si$: C, 64.04; H, 9.77. Found: C, 64.31; H, 9.59.

(2*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-methyl-4-(trimethoxymethylphenyl)pentanal (21a/b)

To a solution of oxalyl chloride (0.671 g, 5.29 mmol) in anhyd CH_2Cl_2 (6 mL) under argon cooled to –78 °C was added DMSO (0.826 g, 10.6 mmol), dissolved in anhyd CH_2Cl_2 (2.5 mL). After stirring for 30 min, the alcohols **20a**/**b** (1.09 g, 2.64 mmol), dissolved in anhyd CH_2Cl_2 (3 mL), were transferred via syringe into the flask. The stirring was continued for 1 h, then Et_3N (1.61 g, 15.86 mmol) was added to the mixture. After 10 min, the dry-ice Dewar vessel was removed and the cloudy solution was allowed to warm to r.t. The resulting orange solution was washed with H_2O (20 mL), aq sat. NH_4Cl solution (20 mL), H_2O (20 mL), aq sat. $NaHCO_3$ solution (20 mL), H_2O (20 mL) and finally with brine (20 mL). The organic phase was passed through a plug of $MgSO_4$ and the solvent was removed in vacuo to yield 1.07 g (99%) of aldehyde **20** as a light brown oil; R_f 0.56 (for both isomers, SiO_2, hexane–EtOAc, 7:3).

^{1}H NMR (250 MHz, $CDCl_3$): δ (major isomer) = 9.53 (d, *J* = 1.6 Hz, 1 H, CHO), 6.60 (s, 1 H, ArH), 3.81, 3.78, 3.67 (3 s, each 3 H, OCH_3), 3.79–3.65 (m, 2 H, TBSOCH_2), 3.39–3.23 (m, 1 H, ArC*H*), 2.41–2.25 (m, 1 H, C*H*Me), 2.20 (s, 3 H, ArCH_3), 2.07–1.92 (m, 1 H, CH_2CHMe), 1.80–1.67 (m, 1 H, CH_2CHMe), 1.13 (d, *J* = 7.1, 1 H, CHCH_3), 0.85 [s, 9 H, $SiC(CH_3)_3$], –0.01 [s, 6 H, $Si(CH_3)_2$]. δ (minor isomer) = 9.63 (d, *J* = 1.6 Hz, 1 H, CHO), 6.62 (s, 1 H, ArH), 3.82, 3.78, 3.63 (3 s, each 3 H, OCH_3), 3.79–3.65 (m, 2 H, TBSOCH_2), 3.39–3.23 (m, 1 H, ArCH), 2.41–2.25 (m, 1 H, C*H*Me), 2.21 (s, 3 H, ArCH_3), 2.07–1.92 (m, 1 H, CH_2CHMe), 1.80–1.67 (m, 1 H, CH_2CHMe), 1.04 (d, *J* = 6.9 Hz, 3 H, CHCH_3), 0.85 [s, 9 H, $SiC(CH_3)_3$], –0.01 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (62.9 MHz, $CDCl_3$): δ (major isomer) = 205.1, 149.3, 146.8, 145.9, 129.7, 125.2, 108.7, 67.6, 61.2, 60.2, 56.1, 44.3, 37.6, 32.7, 25.8, 18.2, 14.4, 9.7, –5.5. δ (minor isomer) = 204.9, 149.2, 146.6, 145.7, 130.5, 125.2, 108.5, 67.4, 61.1, 60.2, 56.1, 44.3, 37.8, 33.5, 25.8, 18.2, 13.4, 9.7, –5.5.

MS (EI, 70 eV): *m*/*z* (%) = 410 (39, $[M]^+$), 354 (16), 353 (63, $[M - C_3H_5O]^+$), 338 (37), 267 (15), 265 (15), 265 (18), 261 (46), 237 (10), 230 (32), 196 (14), 195 (100), 187 (24), 171 (47).

HRMS (80 °C, 70 eV): *m*/*z* calcd for $C_{22}H_{38}O_5Si$: 410.2489; found: 410.2496.

(4*S*,6*R*)-*(E)*-7-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-(trimethoxymethylphenyl)hept-2-enoic Acid Methoxymethylamide (23a)

The diethyl phosphonate **22** (813 mg, 3.40 mmol) was dissolved in anhyd THF (15 mL) and cooled to 0 °C. NaH (Fluka 60%, 136 mg, 3.40 mmol) was added slowly and the mixture was stirred for 1 h at 0 °C. Then aldehydes **21a**/**b** (1.07 g, 2.62 mmol), dissolved in anhyd THF (11 mL), were transferred via syringe to the solution. The mixture was allowed to warm to r.t. and stirred for another 2.5 h, then quenched with aq sat. NH_4Cl solution (20 mL). After extraction with Et_2O (5 × 20 mL), drying ($MgSO_4$) and evaporation of solvents, a brown crude oil was obtained, which was further purified by column chromatography eluting with hexane–EtOAc (7:3). It was possible to separate the diastereomers; 742 mg (57%, colourless oil) of the desired major isomer **23a** were isolated along with 456 mg (35%, colourless oil) of the minor isomer **23b**, making up a total yield of 92%; R_f 0.22 (minor isomer, SiO_2, hexane–EtOAc, 7:3).

23a

R_f 0.29 (major isomer, SiO_2, hexane–EtOAc, 7:3); $[\alpha]_D^{20}$ +57.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.75 (dd, *J* = 8.4 Hz, 15.5 Hz, 1 H, HC*H*C=CH), 6.51 (s, 1 H, ArH), 6.20 (d, *J* = 15.5 Hz, 1 H, HCHC=C*H*), 3.70, 3.66, 3.57, 3.51 (4 s, each 3 H, OCH_3), 3.62–3.47 (m, 2 H, TBSOCH_2), 3.18–3.08 (m, 1 H, ArC*H*), 3.11 (s, 3 H, NCH_3), 2.22–2.11 (m, 1 H, C*H*Me), 2.08 (s, 3 H, ArCH_3), 1.82–1.68 (m, 1 H, CH_2CHMe), 1.58–1.43 (m, 1 H, CH_2CHMe), 0.92 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 0.72 [s, 9 H, $SiC(CH_3)_3$], –0.15 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 166.8, 152.1, 150.8, 148.7, 145.9, 130.4, 124.5, 117.4, 108.6, 67.2, 61.1, 60.6, 59.7, 55.6, 38.5, 37.8, 34.2, 31.9, 25.5, 20.4, 17.8, 9.3, –5.9.

MS (EI, 70 eV): *m*/*z* = 496 (11, $[M + H]^+$), 495 (34, $[M]^+$), 439 (28), 438 (100), 208 (11), 195 (21), 73 (23).

HRMS (110 °C, 70 eV): *m*/*z* calcd for $C_{26}H_{45}O_6NSi$: 495.3016; found: 495.3002.

Anal. Calcd for $C_{26}H_{45}O_6NSi$: C, 62.99; H, 9.15; N, 2.83; Found: C, 62.87; H, 9.03; N, 3.04.

(6*R*,4*S*)-(*E*)-7-(*tert*-Butyldimethylsilyloxy)-4-methyl-6-(trimethoxymethylphenyl)hept-2-enal (24)

The amid **23a** (323 mg, 0.652 mmol) was dissolved in anhyd THF (5 mL) and cooled to –78 °C. DIBAL-H (1 M in hexane, 1.96 mL, 1.96 mmol) was slowly added via syringe to the solution. The mixture was stirred for 1 h at –78 °C, then carefully quenched with a mixture of aq 1 M tartaric acid and hexane (1:1, 8 mL). The suspension was allowed to warm to r.t. and stirred for 1 h. Finally extraction with Et_2O (4 × 10 mL), drying ($MgSO_4$) and evaporation of solvents furnished 279 mg (98%) of the aldehyde **24** as a pale yellow oil, which was almost pure; R_f 0.54 (SiO_2, hexane–EtOAc, 7:3); $[\alpha]_D^{20}$ +41.2 (*c* 1.10, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.48 (d, *J* = 8.0 Hz, 1 H, CHO), 6.75 (dd, *J* = 7.5 Hz, 15.7 Hz, 1 H, HC=C*H*CHO), 6.58 (s, 1 H, ArH), 6.05 (dd, *J* = 8.0 Hz, 15.7 Hz, 1 H, *H*C=CHCHO), 3.82, 3.78, 3.62, (3 s, each 3 H, OCH_3), 3.77–3.58 (m, 2 H, TBSOCH_2), 3.28–3.14 (m, 1 H, ArC*H*), 2.44–2.29 (m, 1 H, C*H*Me), 2.20 (s, 3 H, ArCH_3), 2.01–1.82 (m, 1 H, CH_2CHMe), 1.71–1.58 (m, 1 H, CH_2CHMe), 1.07 (d, *J* = 6.6 Hz, 3 H, CHCH_3), 0.85 [s, 9 H, $SiC(CH_3)_3$], –0.02 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 193.7, 164.1, 150.9, 149.0, 146.4, 130.5, 130.2, 124.9, 108.5, 67.2, 60.9, 59.9, 55.8, 38.3, 37.7, 34.7, 25.7, 18.9, 18.1, 9.5, –5.6.

MS (EI, 70 eV): *m*/*z* (%) = 437 (13, $[M + H]^+$), 436 (39, $[M]^+$), 479 (17, $[M - C_3H_5O]^+$), 339 (16), 322 (41), 291 (18), 287 (39), 267 (42), 256 (13), 208 (62), 195 (100), 193 (20), 89 (18), 75 (42).

HRMS (100 °C, 70 eV): *m*/*z* calcd for $C_{24}H_{40}O_5Si$: 436.2645; found: 436.2631.

(2*R*,4*S*)-*tert*-Butyldimethyl-[(5*E*,7*Z*)-4-methyl-2-(2,4,5-trimethoxy-3-methylphenyl)nona-5,7-dienyloxy]silane (2)

To a suspension of (ethyl)triphenylphosphonium bromide (897 mg, 2.42 mmol) in anhyd THF (11 mL) was added NaHMDS (1 M in THF, 2.42 mL, 2.42 mmol) at –78 °C, which resulted in the formation of a deep orange-red solution. The mixture was stirred for 0.5 h at –78 °C, then 0.5 h at 0 °C and cooled again to –78 °C, followed by the addition of aldehyde **24** (703 mg, 1.61 mmol), dissolved in anyhd THF (4 mL). The yellow reaction mixture was allowed to warm slowly to r.t. and stirred for 14 h. A solution of aq sat. NH_4Cl (20 mL) was added, extracted with Et_2O (4 × 15 mL) and solvents were removed to give a crude oil, which was further purified by column chromatography eluting with hexane–EtOAc (30:1). After evaporation of solvents in vacuo 525 mg (73%) of the title compound **2** was obtained as a colourless oil; R_f 0.63 (SiO_2, hexane–EtOAc, 8:2); $[\alpha]_D^{20}$ +43.6 (*c* 1.05, $CHCl_3$).

IR (neat): 2953, 2930, 2856, 2378, 1653, 1091 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.62 (s, 1 H, ArH), 6.25 (dd, *J* = 10.6 Hz, 15.2 Hz, 1 H, HC=C*H*CH=CHMe), 5.95 (t, *J* = 10.6 Hz, 1 H, HC=CHC*H*=CHMe), 5.51 (dd, *J* = 8.1 Hz, 15.2 Hz, 1 H, *H*C=CHCH=CHMe), 5.36 (m, 1 H, HC=CHCH=C*H*Me), 3.82, 3.78, 3.64, (3 s, each 3 H, OCH_3), 3.73–3.54 (m, 2 H, TBSOCH_2), 3.29–3.16 (m, 1 H, ArC*H*), 2.22 (s, 3 H, ArCH_3), 2.18–2.06 (m, 1 H, C*H*Me), 1.85–1.72 (m, 1 H, CH_2CHMe), 1.70 (d, *J* = 7.1 Hz, 3 H, CH=CHCH_3), 1.63–1.51 (m, 1 H, CH_2CHMe), 1.01 (d, *J* = 6.1 Hz, 3 H, CHCH_3), 0.85 [s, 9 H, $SiC(CH_3)_3$], –0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.2, 148.9, 146.2, 139.8, 131.0, 129.7, 125.5, 125.0, 124.3, 109.1, 67.6, 61.0, 60.1, 56.0, 38.5, 38.2, 34.8, 26.0, 21.5, 18.0, 13.1, 9.7, –5.3.

MS (EI, 70 eV): *m*/*z* (%) = 449 (27, $[M + H]^+$), 448 (60, $[M]^+$), 393 (11), 392 (35), 391 (84), 377 (16), 376 (40), 339 (12), 316 (12), 268 (12), 267 (36), 194 (67), 155 (19), 95 (100), 85 (26).

HRMS (60 °C, 70 eV): *m*/*z* calcd for $C_{26}H_{44}O_4Si$: 448.3009; found: 448.3021.

Anal. Calcd for $C_{26}H_{44}O_4Si$: C, 69.60; H, 9.88; Found: C, 69.71; H, 9.97.

(3*S*,5*S*)-3-Methyl-5-(2,4,5-trimethoxy-3-methylphenyl)tetrahydropyran-2-ol (26)

The diastereomeric pure **20b** (minor isomer, 19.5 mg, 47.2 μmol), obtained during column chromatography of the diastereomeric mixture of alcohols **20a**/**b**, was oxidised to the aldehyde by Swern oxidation (same procedure as in the step **20a**/**b**→**21a**/**b**). The crude aldehyde (18.6 mg, 45.3 μmol) was dissolved in anhyd THF (1 mL) and TBAF (1 M in hexane, 90.5 μL, 90.5 μmol) was added via a Hamilton syringe at r.t. The mixture was stirred for 1 h, then quenched by the addition of sat. aq NH_4Cl (2 mL) solution. After extraction with Et_2O (3 × 5 mL), the combined organic layers were passed through a plug of $MgSO_4$ and the solvents were removed under reduced pressure to give the hydroxy aldehyde **25** as a crude oil; R_f 0.11 (SiO_2, hexane–EtOAc, 7:3). The above crude product **25** (29.8 mg, ~45 μmol) was dissolved in MeOH (1 mL), then K_2CO_3 (12.3 mg, 89.0 μmol) was added and the resulting suspension was refluxed for 2.5 h. After the addition of H_2O (5 mL), the mixture was extracted with Et_2O (3 × 5 mL), the combined organic layers were concentrated in vacuo and the residue was further purified by column chromatography (hexane–EtOAc, 6:4). The lactol **26** was obtained in 89% (12.5 mg) yield over the three steps as a colourless oil. The ratio of the two anomers came to 45:55 as determined by signal integration (ArH and CHCH_3) of the ^{1}H NMR spectrum; R_f 0.25 (for both anomers, SiO_2, hexane–EtOAc, 6:4).

^{1}H NMR (250 MHz, $CDCl_3$): δ (major anomer) = 6.51 (s, 1 H, ArH), 4.44 (d, *J* = 6.6 Hz, C*H*OH)), 4.11–3.96 (m, 1 H, OCH_2), 3.83, 3.78, 3.68 (3 s, each 3 H, OCH_3), 3.70–3.55 (m, 1 H, OCH_2), 3.41–3.27 (m, 1 H, ArCH), 2.21 (s, 3 H, ArCH_3), 1.98–1.88 (m, 1 H, C*H*Me), 1.79–1.55 (m, 2 H, CH_2CHMe), 1.04 (d, *J* = 6.4 Hz, 3 H, CHCH_3), 0.85 [s, 9 H, $SiC(CH_3)_3$], –0.03 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100.6 MHz, $CDCl_3$): δ (major anomer) = 151.1, 149.2, 143.8, 124.6, 116.7, 112.2, 98.3, 70.2, 61.9, 58.4, 56.2, 42.9, 39.7, 33.5, 17.8, 10.8.

MS (EI, 70 eV): *m*/*z* (%) = 296 (41, $[M]^+$), 247 (28), 201 (64), 182 (100), 167 (18), 139 (27).

HRMS (50 °C, 70 eV): *m*/*z* calcd for $C_{16}H_{24}O_5$: 296.1623; found: 296.1629.

(3*S*,5*S*)-3-Methyl-5-(2,4,5-trimethoxy-3-methylphenyl)tetrahydropyran-2-one (26) and (*S*)-5-Methyl-3-(2,4,5-trimethoxy-3-methylphenyl)-3,4-dihydro-2*H*-pyran (27)

To a slurry made from DMP (89.8 mg, 212 μmol), $NaHCO_3$ (71.2 mg, 847 μmol) and anhyd CH_2Cl_2 (1 mL) was added the lactol **26** (12.5 mg, 42.4 μmol), dissolved in anhyd CH_2Cl_2 (0.5 mL). The mixture was stirred at r.t. for 1 h, then H_2O (3 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were passed through a plug of $MgSO_4$ and the solvents were evaporated under reduced pressure. Further purification by column chromatography gave the desired lactone **27** (6.40 mg, 51%) along with the elimination product **28** (4.80 mg, 41%).

27

R_f 0.30 (SiO_2, hexane–EtOAc, 6:4); $[\alpha]_D^{20}$ –51.7 (*c* 0.28, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.57 (s, 1 H, ArH), 4.50 (dd, *J* = 2.0 Hz, 5.3 Hz, 1 H, OCOCH_2), 4.23 (dd, *J* = 2.0 Hz, 9.7 Hz, 1 H, OCOCH_2), 3.83, 3.79, 3.70 (3 s, each 3 H, OCH_3), 3.68–3.62 (m, 1 H, ArCH), 2.73 (sept, *J* = 6.9 Hz, 1 H, OCC*H*Me), 2.28–2.23 (m, 1 H, CHMeCH_2), 2.22 (s, 3 H, ArCH_3), 1.84–1.76 (q, *J* = 12.7 Hz, 1 H, CHMeCH_2), 1.35 (d, *J* = 6.9 Hz, 1 H, CHCH_3).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 177.6, 149.3, 148.4, 143.8, 124.5, 119.7, 107.7, 73.7, 61.4, 60.2, 56.2, 36.1, 35.6, 33.3, 16.9, 9.8.

MS (EI, 70 eV): *m*/*z* (%) = 295 (18, $[M + H]^+$), 294 (100, $[M]^+$), 208 (18), 193 (11).

HRMS (80 °C, 70 eV): *m*/*z* calcd for $C_{16}H_{22}O_5$: 294.1467; found: 294.1463.

28

R_f 0.48 (SiO_2, hexane–EtOAc, 6:4); $[\alpha]_D^{20}$ –18.1 (*c* 0.15, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.56 (s, 1 H, ArH), 6.06 (d, *J* = 3.2 Hz, 1 H, C*H*=CMe), 3.86, 3.79, 3.69 (3 s, each 3 H, OCH_3), 3.82–3.65 (m, 2 H, OOCH_2), 3.42–3.28 (m, 1 H, ArCH), 2.22 (s, 3 H, ArCH_3), 2.16 (d, *J* = 3.2 Hz, 3 H, CH=CCH_3), 1.34–1.13 (m, 1 H, CH=CMeCH_2).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 152.3, 151.1, 144.7, 138.3, 128.3, 116.2, 114.9, 106.1, 69.7, 61.6, 59.7, 55.9, 36.8, 36.1, 18.5, 9.5.

MS (EI, 70 eV): *m*/*z* (%) = 278 (100, $[M]^+$), 208 (86), 196 (47), 149 (45), 84 (77).

HRMS (40 °C, 70 eV): *m*/*z* calcd for $C_{16}H_{22}O_4$ 278.1518; found 278.1523.

Acknowledgement

The authors would like to thank Dr. Valentin S. Enev for helpful discussions. Thanks are also due to Dr. Hanspeter Kählig for recording two-dimensional NMR spectra. Financial support by the FWF (Project P14729-CNE) is gratefully acknowledged.

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