Stereospecific Syntheses of 2-Alkyl and 2-Phenyl Substituted 3-(2,6-Dimethyl-4-hydroxyphenyl)propanoic Acids

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Abstract: Stereospecific syntheses of 2-methyl-, 2-ethyl-, 2-cyclohexyl- and 2-phenyl- substituted 3-(2,6-dimethyl-4-hydroxyphenyl)propanoic acids were developed. The key steps for the formation of the stereogenic centers involved the utilization of Evans' 4-benzyl-2-oxazolidinone chiral auxiliary. These compounds were designed to replace the N-terminal tyrosine residue in opioid peptides.

Key words: amino acids, tyrosine analogues, asymmetric synthesis, chiral auxiliaries, Heck reaction

For decades it has been assumed that a positively charged nitrogen in opioid compounds is a necessary requirement for binding to their receptors. The quaternary ammonium group on the ligand was assumed to engage either in an ionic interaction with a negatively charged receptor moiety[2] (e.g., side chain of an Asp residue) or in chelation by multiple aromatic receptor residues.[3] In a recent study, both somatostatin-derived cyclic hexapeptides lacking a positive charge and a neutral des-amino analogue of a cyclic β-casomorphin analogue were shown to be δ opioid antagonists with moderate δ receptor binding affinity.[4] Subsequently, we prepared an analogue of the potent enkephalin-derived peptide H-Dmt-D-Ala-Gly-Phe-Leu-NH_2 (Dmt = 2',6'-dimethyltyrosine) in which the N-terminal amino group was replaced with the neutral and almost isosteric methyl group.[5] A Dmt[1]-containing enkephalin analogue was chosen as parent peptide because substitution of Dmt for Tyr[1] in opioid peptides is known to generally result in significantly enhanced μ and δ opioid receptor binding affinities.[6] The substitution of the amino group in this enkephalin analogue with a methyl group was achieved by replacing L-Dmt[1] with (2*S*)-2-methyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic acid [(2*S*)-Mdp], for which a stereospecific synthesis was developed and described in a preliminary publication.[5] The resulting compound, (2*S*)-Mdp-D-Ala-Gly-Phe-Leu-NH_2, turned out to be a quite potent δ opioid antagonist and a somewhat less potent μ antagonist, indicating that a positively charged N-terminal amino group is not an absolute requirement for the binding of this opioid peptide to δ and μ receptors, but it is required for signal transduction.

In view of this remarkable result, it was of interest to replace the amino group of the N-terminal L-Dmt residue in opioid peptides with other, somewhat larger aliphatic or aromatic groups (ethyl, cyclohexyl and phenyl) to probe the receptor-binding site. Stereospecific syntheses of (2*S*)-2-ethyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic acid (Edp), (2*R*)-2-cyclohexyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic acid (Cdp) and (2*R*)-2-phenyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic acid (Pdp) were therefore developed, and are described in the present paper.

The syntheses of (2*S*)-Mdp **10a** and (2*S*)-Edp **10b** are shown in Scheme 1. 3,5-Dimethylphenol **1** was iodinated using a literature procedure[7] to give 3,5-dimethyl-4-iodophenol **2**, which was protected as the Boc derivative **3**. Heck coupling[8] of **3** with methyl acrylate then afforded alkene **4**. The *trans* configuration of **4** was established by measurement of the coupling constant (16.4 Hz) of the two alkene protons. Subsequent catalytic hydrogenation, followed by basic hydrolysis afforded acid **6**. Incorporation of Evans' chiral auxiliary (*S*)-(–)-4-benzyl-2-oxazolidinone was performed in the standard manner[9] to yield **7**. Asymmetric methylation[10] or ethylation then furnished **8a** or **8b** as single diastereomers after purification by flash chromatography. Removal of the chiral oxazilidinone auxiliary and Boc group then gave (2*S*)-Mdp **10a** or (2*S*)-Edp **10b**.

We initially attempted to prepare (2*R*)-Cdp by a synthetic route analogous to that used for the preparation of (2*S*)-Mdp and (2*S*)-Edp. Oxazolidinone **7** in THF was treated with NaHMDS at –78 °C for an hour, followed by treatment with cyclohexyl iodide at –78 °C. The mixture was allowed to warm up to –25 °C for 3 hours. No desired incorporation product was obtained. It had previously been shown that 3-bromocyclohexene reacted smoothly with lithium enolate, while bromo- or iodocyclohexane failed to give any desired product.[11] Preparation of the sodium enolate of **7** by treatment with NaHMDS at –78 °C and subsequent reaction with bromocyclohexene did give the desired product **11**, which can be transformed to (2*R*)-Cdp by catalytic hydrogenation and subsequent removal of the chiral auxiliary and Boc group (Scheme 2). However, the yield of **11** was very low (15%), probably due to steric hindrance and lack of reactivity of bromocyclohexene towards the enolate. Therefore, it is not practical to synthesize Cdp by this approach.

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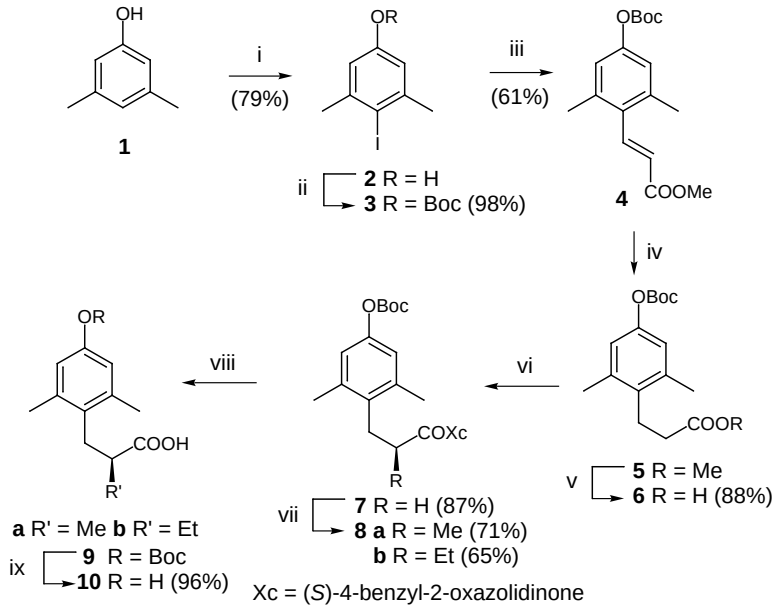


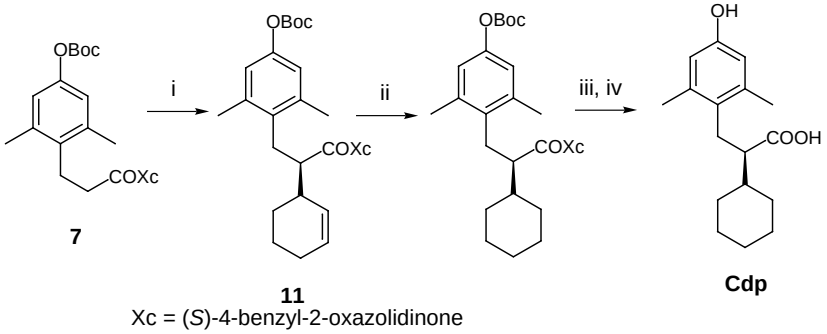
Scheme 1 Reagents and conditions: i. KI, KIO_3, MeOH, HCl; ii. $(Boc)_2O$, Et_3N, DMAP, H_2O–THF, r.t.; iii. CH_2=CHCOOMe, $Pd(OAc)_2$, Et_3N, (*o*-MePh)$_3$P, CH_3CN, reflux; iv.H_2, Pd/C, 70 psi, 60 °C, EtOAc; v. 1 N NaOH–THF; vi.Et_3N, PvCl, Et_2O, –78 °C to 0 °C, then treated with *n*-BuLi, Xc, THF, –78 °C to 0 °C; vii. NaHMDS, THF, MeI or EtI, –78 °C to –25 °C; viii. LiOH, H_2O_2, THF–H_2O; ix. TFA, CH_2Cl_2, r.t.

An alternative approach for the synthesis of Cdp is depicted in Scheme 3. 3,5-Dimethyl-4-iodophenol **2** was protected as its TBDMS derivative **12**. Subsequent metal-halogen exchange with *n*-butyllithium, followed by the addition of DMF afforded aldehyde **13**. Reduction of **13** with sodium borohydride yielded alcohol **14**. The attempted transformation of the alcohol to bromide **15** using Ph_3P/CBr_4 did not occur in satisfactory yield. However, the reaction proceeded smoothly and cleanly with PBr_3 and pyridine in ether to give the desired bromide **15**. Evans' 4-benzyl-2-oxazolidinone chiral auxiliary was incorporated into commercially available cyclohexyl acetic acid **16a** in the usual manner to afford **17a**. Oxazolidinone **17a** in THF was treated with NaHMDS at –78 °C for half an hour, followed by the addition of bromide **15** at –78 °C, and subsequent warming up to –25 °C. To our delight, the desired product **18a** was obtained in 75% yield. The oxazolidinone chiral auxiliary and TBDMS protecting group were removed to afford Cdp **20a**.

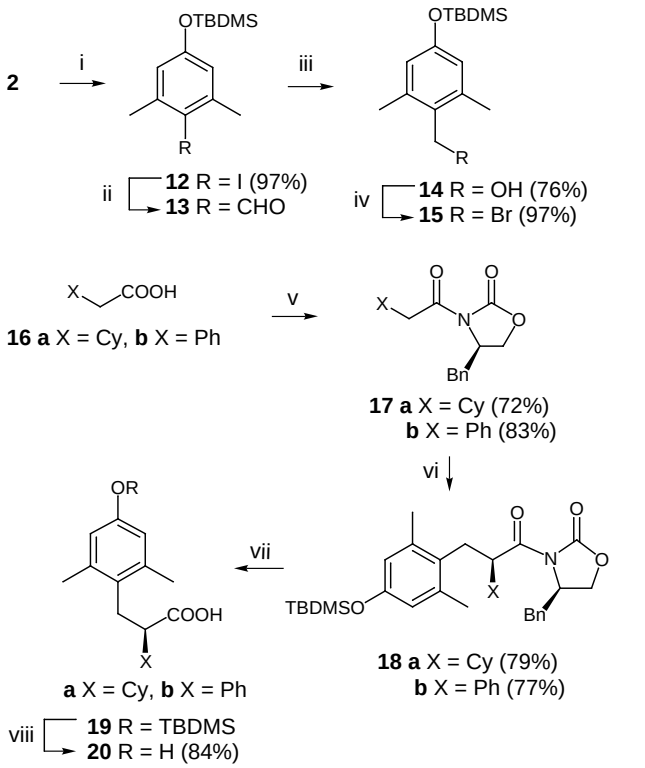
The performed synthesis of (2*R*)-Pdp **20b** was analogous to that of (2*R*)-Cdp, using phenylacetic acid instead of cyclohexylacetic acid (Scheme 3). The compound was easily prepared with reaction yields similar to those obtained in the synthesis of (2*R*)-Cdp.

A non-stereospecific synthesis of (*R*,*S*)-Mdp has been reported.[12] However, the substitution of such a racemic compound for Tyr[1] in opioid peptides is unsatisfactory for two reasons. Firstly, it may not be possible to separate the resulting diastereomeric peptides and, therefore, a conclusive biological activity determination in terms of agonist or antagonist properties would not be possible. Secondly, even in cases where the diastereomeric peptides could be separated, it would still be necessary to make the stereochemical assignments, which would obviously require a stereospecific synthesis of (2*S*)- or (2*R*)-Mdp.

In conclusion, convenient asymmetric syntheses of the Dmt analogues (2*S*)-Mdp, (2*S*)-Edp, (2*R*)-Cdp and (2*R*)-



Scheme 2 Reagents and conditions: i. NaHMDS, THF, 3-bromocyclohexene, –78 °C to –25 °C; ii. H_2, Pd/C; iii. LiOH, H_2O_2, THF–H_2O; iv. TFA, CH_2Cl_2, r.t.



Scheme 3 Reagents and conditions: i. TBDMSCl, imidazole, DMF; ii. *n*-BuLi, THF, DMF, –78 °C to r.t.; iii. $NaBH_4$, MeOH; iv. PBr_3, pyridine, Et_2O; v. Et_3N, PvCl, Et_2O, –78 °C to 0 °C, then treated with *n*-BuLi, Xc, THF, –78 °C to 0 °C; vi. NaHMDS, THF, **15**, –78 °C to –25 °C; vii. LiOH, H_2O_2, THF–H_2O; viii. 1 N HCl/MeOH; Cy = Cyclohexyl, Ph = Phenyl

Pdp were developed. The incorporation of these Dmt analogues into opioid peptides is under way. It is expected that the substitution of the N-terminal amino function with the various alkyl- and phenyl groups will not only affect the opioid activity profile of the resulting peptides but may also improve their bio-availability due to their increased lipophilic character.

Mass spectra were recorded on a Micromass Autospec TOF mass spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer and referenced with respect to the residual signals of the solvent. THF and Et_2O were distilled from sodium benzophenone ketyl, and Et_3N from CaH_2. Anhyd CH_2Cl_2 and DMF were purchased from Aldrich and were used without further drying. All other reagents were purchased from Aldrich. Products were purified by flash chromatography on silica gel (40 μm; Baker). A Varian HPLC system consisting of a programmable solvent delivery system 9010 and a variable wavelength detector 9050 was used for the diastereomeric purity determinations.

4-Iodo-3,5-dimethyl-*O*-*tert*-butoxycarbonyl-phenol (3)

Et_3N (0.35 mL, 2.5 mmol) was added to 3,5-dimethyl-4-iodophenol (248 mg, 1.0 mmol) in a mixture of H_2O and THF (10 mL/10 mL) at r.t. Di-*tert*-butyl dicarbonate [$(Boc)_2O$] (262 mg, 1.2 mmol) was then introduced, followed by 4-(dimethylamino)pyridine (DMAP) (12 mg, 0.1 mmol). The mixture was stirred at r.t. for 30 min. THF was removed under reduced pressure. The residue was partitioned between EtOAc, 1 N HCl and brine. The organic layer was separated, washed, and dried. The solvent was removed in vacuo to afford **3** as a white solid (328 mg, 98%).

^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (s, 2 H), 2.45 (s, 6 H), 1.53 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.7, 150.5, 143.3, 119.7, 83.7, 29.7, 27.7, 19.7.

HRMS (EI): *m/z* calcd for $C_{13}H_{17}IO_3$ $[M]^+$: 348.0222. Found: 348.0209.

Methyl (*E*)-3-(4-*tert*-Butoxycarbonyloxy-2,6-dimethylphenyl)-2-propenoate (4)

A mixture of **3** (3.48 g, 10 mmol), methyl acrylate (2.70 mL, 30 mmol), tri-*o*-tolylphosphine (161 mg, 0.53 mmol), Et_3N (2.79 mL, 20 mmol) and palladium(II) acetate (45 mg, 0.20 mmol) in MeCN (50 mL) was refluxed for 24 h. The mixture was then cooled down to r.t. and filtered through Celite. The solvent was removed in vacuo and the residue was diluted with H_2O (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash chromatography (EtOAc–hexanes, 1:15) afforded **4** as a colorless oil (1.9 g, 61%).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, 1 H, *J* = 16.4 Hz), 6.87 (s, 2 H), 6.03 (d, 1 H, *J* = 16.4 Hz), 3.80 (s, 3 H), 2.32 (s, 6 H), 1.54 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 167.1, 151.9, 150.3, 142.7, 138.4, 131.7, 123.8, 120.9, 83.7, 51.7, 27.7, 21.2.

HRMS (EI): *m/z* calcd for $C_{17}H_{22}O_5$ $[M]^+$: 306.1467. Found: 306.1471.

Methyl 3-(4-*tert*-Butoxycarbonyloxy-2,6-dimethyl-phenyl)-propanoate (5)

An argon purged reaction vessel was charged with **4** (1.0 g, 3.3 mmol) and Pd/C (10%, 0.2 g) in EtOAc (50 mL). The reaction vessel was then carefully pressurized to 70 psi with H_2 and heated at 60 °C for 5 h. The mixture was cooled down to r.t., vented with Ar, and filtered through Celite. The filtrate was collected and concentrated to yield **5** as a white solid, which was used directly without further purification.

3-(4-*tert*-Butoxycarbonyloxy-2,6-dimethylphenyl)propanoic Acid (6)

Crude **5** (0.62 g, 2 mmol) was dissolved in a mixture of 1 N NaOH and THF (5 mL/5 mL) and stirred at r.t. until TLC showed the disappearance of the starting material. THF was removed in vacuo. The pH of the aqueous layer was adjusted to 2–3 by adding 1 N HCl, and then extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). The solvent was removed to furnish **6** as a white solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.81 (s, 2 H), 2.92–2.98 (m, 2 H), 2.45–2.51 (m, 2 H), 2.31 (s, 6 H), 1.53 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 179.2, 152.2, 148.8, 137.6, 134.4, 120.8, 83.4, 33.1, 27.7, 24.3, 19.8.

HRMS (EI): *m/z* calcd for $C_{16}H_{22}O_5$ $[M]^+$: 294.1467. Found: 294.1464.

(4*S*)-4-Benzyl-3-[3-(4-*tert*-butoxycarbonyloxy-2,6-dimethylphenyl)propanoyl]-1,3-oxazolan-2-one (7)

To a stirred solution of **6** (0.59 g, 2 mmol) in anhyd Et_2O (20 mL) at –78 °C was added Et_3N (0.29 mL, 2.1 mmol), followed by pivaloyl chloride (0.26 mL, 2.1 mmol). The resulting solution was stirred at 0 °C for 1 h and then re-cooled to –78 °C. Meanwhile, a solution of (4*S*)-4-(benzyl)-2-oxazolidinone (354 mg, 2 mmol) in freshly distilled THF (10 mL) was cooled to –78 °C and treated slowly with a 1.6 M solution of *n*-BuLi in hexanes (1.37 mL, 2.2

mmol). The resulting solution was stirred at –78 °C for 15 min and then added via cannula into the solution of the mixed anhydride. The mixture was stirred at –78 °C for 15 min, and at 0 °C for 30 min. Sat. NH_4Cl (5 mL) was added to quench the reaction. THF was removed in vacuo and the residue was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$). Purification by flash chromatography (EtOAc–hexanes, 1:5) furnished **7** as a white solid (733 mg, 81%).

$[\alpha]_D^{20}$ +46.2° (*c* 1.03, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.33 (m, 5 H), 6.81 (s, 2 H), 4.67–4.70 (m, 1 H), 4.15–4.23 (m, 2 H), 3.30–3.34 (dd, 1 H, *J* = 3.2, 13.2 Hz), 2.94–3.07 (m, 4 H), 2.75–2.81 (dd, 1 H, *J* = 9.6, 13.2 Hz), 2.34 (s, 6 H), 1.53 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 153.4, 152.3, 148.9, 137.8, 135.3, 134.6, 129.5, 129.1, 127.4, 120.8, 83.4, 66.3, 55.3, 37.9, 34.5, 27.7, 24.1, 20.0.

HRMS (EI): *m/z* calcd for $C_{26}H_{31}NO_6$ $[M]^+$: 453.2151. Found: 453.2153.

(2*S*)-1-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-3-(4-*tert*-butoxycarbonyloxy-2,6-dimethylphenyl)-2-methylpropan-1-one (8a)

To a solution of **7** (590 mg, 1.3 mmol) in anhyd THF (10 mL) at –78 °C was added slowly 1.0 M sodium bistrimethylamide in THF (1.44 mL, 1.44 mmol). The resulting mixture was stirred at –78 °C for 1 h. MeI (0.40 mL, 6.5 mmol) in THF (5 mL) was introduced slowly at –78 °C, and the mixture was stirred at –25 °C for 3 h. Sat. NH_4Cl (5 mL) was then added to quench the reaction. The volatiles were removed under reduced pressure and the residue was taken up in CH_2Cl_2. The combined organic extracts were washed with aq. potassium bisulfate solution (10%) and dried ($MgSO_4$). Purification by flash chromatography (EtOAc–hexanes, 1:10) afforded **8a** as a white foamy solid (0.43 g, 71%).

HPLC diastereomeric analysis (4.6 mm × 25.0 cm Vydac 218TP54 column, 50–95% gradient of MeOH, 1 mL/min, 220 nm) showed >99:1 diastereomeric purity (t_R 23.90 min).

$[\alpha]_D^{20}$ +110.1° (*c* 1.12, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.31 (m, 5 H), 6.77 (s, 2 H), 4.43–4.49 (m, 1 H), 4.17–4.22 (m, 1 H), 3.93–4.04 (m, 2 H), 3.19–3.24 (dd, 1 H, *J* = 3.2, 13.6 Hz), 2.99–3.05 (dd, 1 H, *J* = 8.0, 14.0 Hz), 2.80–2.85 (dd, 1 H, *J* = 7.2, 14.0 Hz), 2.67–2.73 (dd, 1 H, *J* = 10.0, 13.6 Hz), 2.32 (s, 6 H), 1.51 (s, 9 H), 1.24 (d, 3 H, *J* = 6.8 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.1, 152.9, 152.1, 148.9, 138.7, 135.4, 133.4, 129.5, 128.9, 127.3, 120.7, 83.3, 65.9, 55.8, 37.8, 36.4, 32.9, 27.7, 20.5, 17.3.

HRMS (FAB): *m/z* calcd for $C_{27}H_{34}NO_6$ $[M+H]^+$: 468.2386. Found: 468.2384.

(2*S*)-2-Methyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic Acid [(2*S*)-Mdp] (10a)

The oxazolidinone chiral auxiliary of **8a** (468 mg, 1 mmol) was removed in the standard manner,[13] except that Et_2O was used instead of CH_2Cl_2 to extract the oxazolidinone chiral auxiliary, to give **9a**. The crude **9a** was dissolved in a mixture of TFA–CH_2Cl_2 (5 mL/5 mL) at 0 °C and the solution was then stirred at r.t. until TLC indicated the disappearance of the starting material. The solvent was removed in vacuo, and the residue was purified by flash chromatography (EtOAc–hexanes, 1:1) to give **10a** as a white solid (200 mg, 96%).

$[\alpha]_D^{20}$ +45.9° (*c* 0.93, CH_2Cl_2).

^{1}H NMR (400 MHz, CD_3COCD_3): δ = 6.5 (s, 2 H), 2.94–3.00 (m, 1 H), 2.61–2.68 (m, 2 H), 2.24 (s, 6 H), 1.08 (d, 3 H, *J* = 6.8 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 177.7, 155.9, 138.6, 128.1, 115.8, 40.2, 33.0, 20.5, 16.8.

HRMS (FAB): *m/z* calcd for $C_{12}H_{16}O_3$ $[M]^+$: 208.1099. Found: 208.1095.

(2*S*)-1-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-3-(4-*tert*-butoxycarbonyloxy-2,6-dimethylbenzyl)-2-ethylpropan-1-one (8b)

The synthesis of **8b** (65% yield) was analogous to that of **8a** except that EtI was used instead of MeI.

HPLC diastereomeric analysis (4.6 mm × 25.0 cm Vydac 218TP54 column, 50–95% gradient of MeOH, 1 mL/min, 220 nm) showed >99:1 diastereomeric purity (t_R 25.85 min).

$[\alpha]_D^{20}$ +114.0° (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.32 (m, 5 H), 6.75 (s, 2 H), 4.34–4.39 (m, 1 H), 4.20–4.28 (m, 1 H), 3.93–3.96 (m, 1 H), 3.80–3.84 (m, 1 H), 3.22–3.26 (dd, 1 H, *J* = 3.6, 13.2 Hz), 2.98–3.03 (dd, 1 H, *J* = 9.6, 13.6 Hz), 2.81–2.86 (dd, 1 H, *J* = 6.4, 13.6 Hz), 2.61–2.67 (dd, 1 H, *J* = 10.0, 13.2 Hz), 2.32 (s, 6 H), 1.87–1.90 (m, 1 H), 1.57–1.65 (m, 1 H), 1.51 (s, 9 H), 0.98 (t, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 176.7, 152.9, 152.0, 148.8, 138.6, 135.4, 133.3, 129.4, 128.9, 127.2, 120.6, 83.2, 65.8, 56.0, 42.7, 37.9, 32.1, 27.7, 25.7, 20.4, 11.7.

HRMS (FAB): *m/z* calcd for $C_{28}H_{36}NO_6$ $[M+H]^+$: 482.2542. Found: 482.2531.

(2*S*)-2-Ethyl-3-(4-hydroxy-2,6-dimethylphenyl)propanoic Acid [(2*S*)-Edp] (10b)

The preparation of **10b** (96% yield) from **8b** was analogous to that of **10a** from **8a**.

$[\alpha]_D^{20}$ +55.6° (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, CD_3COCD_3): δ = 6.50 (s, 2 H), 2.88–2.94 (m, 1 H), 2.66–2.71 (m, 1 H), 2.44–2.51 (m, 1 H), 2.23 (s, 6 H), 1.61–1.70 (m, 1 H), 1.44–1.52 (m, 1 H), 0.89 (t, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 181.0, 153.3, 138.4, 128.3, 115.0, 47.4, 31.4, 24.8, 20.4, 12.2.

HRMS (EI): *m/z* calcd for $C_{13}H_{18}O_3$ $[M]^+$: 222.1256. Found: 222.1263.

4-Iodo-3,5-dimethyl-*O*-*tert*-butyldimethylsilyl-phenol (12)

To a solution of **2** (2.48 g, 10.0 mmol) and imidazole (1.7 g, 25 mmol) in anhyd DMF (5 mL) at r.t. was added *tert*-butyldimethylsilyl chloride (1.96 g, 13 mmol). The solution was stirred at r.t. for 1 h and H_2O (5 mL) was then added to the reaction mixture. The solvent was removed under high vacuum and the residue was taken up in CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine and dried ($MgSO_4$). The solvent was removed to provide **12** as a white sticky solid (3.51 g, 97%), which was used directly in the next reaction without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 2 H), 2.41 (s, 6 H), 0.98 (s, 9 H), 0.19 (s, 6 H).

MS (FAB, NBA): *m/z* = 362 (M^+, 100%).

4-*tert*-Butyldimethylsilyloxy-2,6-dimethylphenyl)methanol (14)

n-BuLi (2.1 mL, 3.3 mmol) was added dropwise into a solution of crude **12** (1.09 g, 3.0 mmol) in THF (15 mL) at –78 °C, and the mixture was stirred for 1 h. DMF (1.16 mL, 15 mmol) was introduced slowly, and the mixture was then warmed up slowly to r.t. After 30 min at r.t., a few drops of H_2O were added to quench the reaction. The solvent was removed and the residue was taken up in EtOAc. The organic extracts were washed with H_2O and brine, and dried ($MgSO_4$). Removal of the solvent provided in quantitative yield the

crude aldehyde **13** as a yellow oil, which was used directly in the subsequent reduction step.

$NaBH_4$ (110 mg, 3 mmol) was added to a solution of crude **13** in MeOH (20 mL) at 0 °C. The mixture was allowed to warm up to r.t., and was stirred for 30 min. Sat. NH_4Cl was then added to the reaction mixture. The solvent was removed and the residue was taken up in EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Purification by flash chromatography (EtOAc–hexanes, 1:10) afforded the desired product as a light yellow solid (606 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (s, 2 H), 4.63 (s, 2 H), 2.35 (s, 6 H), 0.96 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.9, 138.8, 129.7, 119.7, 58.9, 25.6, 19.5, 18.1, –4.4.

HRMS (EI): *m/z* calcd for $C_{15}H_{26}O_2Si$ $[M]^+$: 266.1702. Found: 266.1709.

4-(Bromomethyl)-3,5-dimethyl-*tert*-butyldimethyl-silyloxyphenol (15)

To a solution (–5 °C) of **14** (1.6 g, 6 mmol) in Et_2O (8 mL) containing pyridine (97 μL, 1.2 mmol) was added dropwise a solution of PBr_3 (0.57 mL, 6 mmol) in Et_2O. The mixture was stirred at 0 °C for 30 min, warmed up slowly to r.t., and then poured into a mixture of ice and brine. The layers were separated and the aqueous layer was washed with Et_2O. The combined Et_2O extracts were washed with sat. $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent provided the desired bromide as a colorless oil (1.91 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.49 (s, 2 H), 4.55 (s, 2 H), 2.34 (s, 6 H), 0.95 (s, 9 H), 0.18 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 155.7, 138.2, 126.8, 119.8, 30.3, 25.6, 19.4, 18.2, –4.4.

HRMS (EI): *m/z* calcd for $C_{15}H_{25}OSiBr$ $[M]^+$: 328.0858. Found: 328.0850.

(4*R*)-4-Benzyl-3-(2-cyclohexylacetyl)-1,3-oxazolan-2-one (17a)

The incorporation of the oxazolidinone chiral auxiliary into **16a** (2.5 g, 17.6 mmol) was done using a procedure analogous to that described for the preparation of **7**. Recrystallization of the crude product from EtOAc–hexanes gave **17a** as a white solid (3.8 g, 72%).

$[\alpha]_D^{20}$ –62.7° (*c* 1.00, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.33 (m, 5 H), 4.63–4.69 (m, 1 H), 4.11–4.19 (m, 2 H), 3.20–3.31 (dd, 1 H, *J* = 3.2, 13.2 Hz), 2.70–2.89 (m, 3 H), 1.62–1.91 (m, 6 H), 0.96–1.33 (m, 5 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 153.4, 135.3, 129.4, 128.9, 127.3, 66.0, 55.2, 42.7, 38.0, 34.3, 33.10, 33.05, 27.6, 26.18, 26.11, 26.10.

MS (FAB, NBA): *m/z* calcd for $C_{18}H_{24}NO_3$ $[M+1]^+$: 302.17563. Found: 302.17510.

(2*R*)-1-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-2-cyclohexyl-3-(4-*tert*-butyldimethylsilyloxy-2,6-dimethylphenyl)propan-1-one (18a)

To a solution of **17** (1.39 g, 4.63 mmol) in freshly distilled THF (20 mL) at –78 °C was added sodium bis(trimethylsilyl)amide in THF (1.0 M, 5.1 mL, 5.1 mmol) and the mixture was stirred at –78 °C for 30 min. A solution of bromide **15** (1.6 g, 4.86 mmol) in THF (5 mL) was then added dropwise. The mixture was allowed to warm up to –25 °C, and then stirred for 30 min. The reaction was quenched by the addition of sat. NH_4Cl. The volatiles were removed and the residue was taken up in CH_2Cl_2, washed with a 10% $NaHSO_4$ and dried ($MgSO_4$). Purification by flash chromatography (EtOAc–hexanes, 1:10) afforded **18a** as a white solid (2.01 g, 79%).

HPLC diastereomeric analysis (4.6 mm × 25.0 cm Vydac 218TP54 column, 50–95% gradient of MeOH, followed by 95% MeOH under isocratic conditions, 1 mL/min, 220 nm) showed >99:1 diastereomeric purity (t_R 34.79 min).

$[\alpha]_D^{20}$ –23.5° (*c* 0.98, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.25 (m, 3 H), 6.91–6.93 (m, 2 H), 6.43 (s, 2 H), 4.53–4.58 (m, 1 H), 4.33–4.39 (m, 1 H), 3.97–4.01 (m, 1 H), 3.87–3.90 (dd, 1 H, *J* = 2.8, 9.2 Hz), 3.05–3.12 (m, 1 H), 2.85–2.90 (dd, 1 H, *J* = 4.0, 13.6 Hz), 2.78–2.82 (dd, 1 H, *J* = 3.2, 13.6 Hz), 2.33 (s, 6 H), 2.06–2.11 (m, 1 H), 1.60–1.76 (m, 5 H), 1.11–1.26 (m, 5 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 176.7, 153.4, 153.0, 138.4, 135.4, 129.2, 128.8, 128.7, 127.0, 119.7, 65.2, 54.7, 46.6, 41.8, 37.5, 30.9, 30.1, 29.3, 26.3, 25.7, 20.4, 18.1, –4.41, –4.45.

HRMS (FAB, NBA): *m/z* calcd for $C_{33}H_{48}NO_4Si$ $[M+1]^+$: 550.3353. Found: 550.3374.

(2*R*)-2-Cyclohexyl-3-(4-*tert*-butyldimethylsilyloxy-2,6-dimethylphenyl)propanoic Acid (19a)

The removal of the oxazolidinone chiral auxiliary of **18a** (550 mg, 1.0 mmol) was performed using the same procedure as for **9a**. Crude **19a** was used in the next reaction without further purification.

(2*R*)-2-Cyclohexyl-3-(4-hydroxy-2,6-dimethylphenyl)-propanoic Acid [(2*R*)-Cdp] (20a)

Crude **19a** was dissolved in 1 N HCl/MeOH and the resulting clear solution was stirred at r.t. for 2 h. After removal of MeOH, the residue was taken up in EtOAc and the solution was washed with H_2O and brine, and dried ($MgSO_4$). The solvent was removed and the desired product was obtained as a white solid (230 mg, 84%).

$[\alpha]_D^{20}$ +33.7° (*c* 0.97, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.46 (s, 2 H), 2.78–2.92 (m, 2 H), 2.43–2.47 (m, 1 H), 2.19 (m, 6 H), 1.07–1.99 (m, 11 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 181.8, 153.1, 138.2, 128.1, 115.1, 51.5, 40.5, 30.9, 30.6, 28.8, 26.3, 26.2, 20.2.

HRMS (FAB, NBA): *m/z* calcd for $C_{17}H_{25}O_3$ $[M + 1]^+$: 277.18036. Found: 277.18010.

(4*R*)-4-Benzyl-3-(2-phenylacetyl)-1,3-oxazolan-2-one (17b)

The incorporation of the oxazolidinone chiral auxiliary into **16b** (2.04 g, 15 mmol) was performed using a procedure analogous to that described for **17a**. Compound **17b** was obtained as a white solid (3.6 g, 83%)

$[\alpha]_D^{20}$ –104.4° (*c* 1.06, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.36 (m, 10 H), 4.66–4.70 (m, 1 H), 4.16–4.25 (m, 4 H), 3.26–3.30 (dd, 1 H, *J* = 3.2, 13.2 Hz), 2.73–2.79 (dd, 1 H, *J* = 9.2, 13.2 Hz).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.03, 153.3, 134.98, 133.4, 129.7, 129.3, 128.8, 128.4, 127.2, 127.1, 65.9, 55.1, 41.4, 37.5.

HRMS (EI): *m/z* calcd for $C_{18}H_{17}NO_3$ $[M]^+$: 295.1208. Found: 295.1203.

(2*R*)-1-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-3-(4-*tert*-butyldimethylsilyloxy-2,6-dimethylphenyl)-2-phenylpropan-1-one (18b)

Using the procedure analogous to that described for **18a**, compound **18b** was obtained as a white solid (5.1 g, 77%).

HPLC diastereomeric analysis (4.6 mm × 25.0 cm Vydac 218TP54 column, 50–95% gradient of MeOH, followed by 95% MeOH under isocratic conditions, 1 mL/min, 220 nm) showed >99:1 diastereomeric purity (t_R 32.57 min).

$[\alpha]_D^{20}$ –169.1° (*c* 1.26, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.36 (m, 8 H), 7.05–7.07 (m, 2 H), 6.50 (s, 2 H), 5.46 (t, 1 H, *J* = 7.6 Hz), 4.60–4.65 (m, 1 H), 3.99–4.06 (m, 2 H), 3.53 (dd, 1 H, *J* = 7.6, 14.0 Hz), 3.03–3.11 (m, 2 H), 2.69–2.74 (dd, 1 H, *J* = 8.4, 13.2 Hz), 2.23 (s, 6 H), 0.99 (s, 9 H), 0.18 (s, 3 H), 0.17 (s, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.9, 153.5, 152.7, 138.39, 138.37, 135.0, 129.4, 128.9, 128.6, 128.5, 128.4, 127.4, 127.2, 119.7, 65.4, 55.2, 47.9, 37.6, 33.7, 31.6, 25.7, 22.6, 20.2, 18.1, 14.1, –4.41, –4.44.

HRMS (FAB, NBA): *m/z* calcd for $C_{33}H_{42}NO_4Si$ $[M+1]^+$: 544.28832. Found: 544.28660.

(2*R*)-3-(4-*tert*-Butyldimethylsilyloxy-2,6-dimethylphenyl)-2-phenylpropanoic Acid (19b)

The oxazolidinone chiral auxiliary of **18b** (460 mg, 0.85 mmol) was removed using the procedure described for **9a**. Crude **19b** was used in the next reaction without further purification.

(2*R*)-2-Phenyl -3-(4-hydroxy-2,6-dimethylphenyl)propanoic Acid [(2*R*)-Pdp] (20b)

Using the procedure described for **20a**, compound **20b** was obtained as a white solid (192 mg, 84%).

$[\alpha]_D^{20}$ –146.2° (*c* 0.91, EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.29 (m, 5 H), 6.45 (s, 2 H), 3.73–3.76 (t, 1 H), 3.38–3.43 (dd, 1 H, *J* = 6.4, 14.4 Hz), 2.95–3.01 (dd, 1 H, *J* = 8.0, 14.4 Hz), 2.07 (s, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 179.5, 153.4, 138.5, 138.3, 128.5, 128.1, 127.7, 127.5, 114.9, 51.5, 33.2, 20.1.

HRMS (FAB, NBA): *m/z* calcd for $C_{17}H_{19}O_3$ $[M+1]^+$: 271.13342. Found: 271.13300.

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