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Asymmetric synthesis of aldol products derived from unsymmetrical ketones: assignment of the absolute configuration of antibody aldol products

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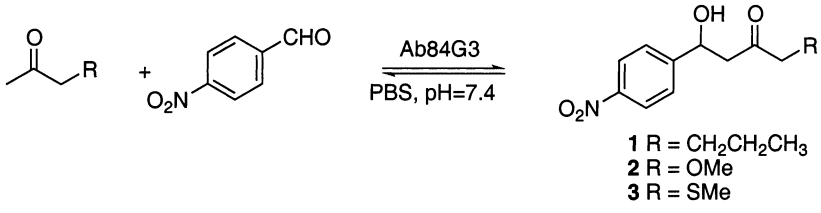
Abstract—Compounds **1**–**7** are the products formed by aldol condensation of *p*-nitrobenzaldehyde with a series of unsymmetrical ketones, the reaction occurring at the less substituted carbon. The asymmetric synthesis of **1**–**7** using the Evans's asymmetric aldol methodology is described in detail. These syntheses were completed to allow us to assign the absolute configuration of products **1**–**3**, obtained in a single step in the presence of the aldolase I antibody 84G3.

1. Introduction

The aldol reaction has emerged as one of the most powerful methods for stereocontrolled carbon–carbon bond formation.[1] An inherent challenge with the use of unmodified unsymmetrical ketones in cross aldol reactions is the simultaneous control of regio- and stereoselectivity and as such, access to enantiomerically pure aldol products derived from unsymmetrical ketones remains difficult. Recently, we have found that, in contrast to other known biocatalysts, the commercially available aldolase type I antibody 84G3 (ab84G3)[2] catalyses the aldol condensations of *p*-nitrobenzaldehyde with a series of unsymmetrical donor ketones by preferential formation of the less substituted enamine. The presence of heteroatoms such as sulfur or oxygen in the donor ketones does not affect the regioselectivity of these antibody-catalysed reactions. The catalyst ab84G3 operates with moderate to high catalytic proficiencies and both enantiomers are accessible using either an antibody-catalysed aldol or retro-aldol reaction. In the presence of antibody 84G3, compounds **1**–**3** are typically obtained with enantiomeric excesses greater than 94% (Scheme 1, Table 1).[3]

Table 1. E.e. for the antibody-catalysed aldol and retro-aldol reactions

Entry	R	Method	Product	e.e. (%)
1	$CH_2CH_2CH_3$	Aldol	(*R*)-**1**	98
2	OMe	Aldol	(*R*)-**2**	98
3	SMe	Aldol	(*R*)-**3**	97
4	$CH_2CH_2CH_3$	Retro-aldol	(*S*)-**1**	94
5	OMe	Retro-aldol	(*S*)-**2**	97
6	SMe	Retro-aldol	(*S*)-**3**	96



Scheme 1. Antibody catalysed aldol and retro-aldol reactions.

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Herein, we report the independent asymmetric synthesis of the aldol products **1**–**3** that allowed us to assign the absolute configuration of the antibody aldol products.[4] In conjunction with our efforts to study the scope and limitation of the biological versus the chemical approach for the preparation of aldol products derived from unsymmetrical methyl ketones, we have also prepared compounds **4**–**7**. A major concern in the planning of the syntheses of **1**–**7** is the potential sensitivity of the *p*-nitrophenyl group to organometallic reagents.[5] It was anticipated that compounds **1**–**7** could be prepared in enantiomerically pure form from a common precursor, **8**, by functional group manipulation of the *N*-methoxy-*N*-methylamide group, although we were somewhat apprehensive as the addition of highly reactive organometallic reagents to compound **8** might be problematic. However, the highly convergent nature of this approach stimulated the exploration of this synthetic strategy as the absolute configuration of compound **8** could be easily secured through use of the Evans's asymmetric aldol methodology (Scheme 2).[6]

2. Results and discussion

The aldol reaction between (4*S*)-4-benzyl-3-acetyl-2-oxazolidinone[7] with *p*-nitrobenzaldehyde was achieved via a boron enolate and gave the expected product in 66% yield as a mixture of two diastereomers (+)-**9a** and (+)-**9b** (d.e. = 45% as assigned by HPLC). These two diastereomers could be cleanly separated by column chromatography. The absolute configuration of the major diastereomer (+)-**9a** was determined unambiguously by X-ray diffraction with reference to the known absolute configuration of the asymmetric carbon atom of the oxazolidinone ring and was found to be (3′*S*,4*S*) (Scheme 3, Fig. 1).[8]

Transamination of compound (+)-**9a** to give the *N*-methoxy-*N*-methylamide (−)-**8**,[9] followed by silylation of the secondary alcohol with *tert*-$BuMe_2SiCl$ in the presence of imidazole provides intermediate (−)-**10** in 78% overall yield. This compound was enantiomerically pure (e.e. >99%) as verified by chiral high performance liquid chromatography (HPLC) analysis. For the preparation of compound (−)-**1**, it was hoped that the addition of *n*-butyllithium or the Grignard reagent derived from *n*-bromobutane to the Weinreb amide (−)-**10** might directly afford the desired protected aldol product (−)-**12**. Unfortunately, model studies showed the addition of organomagnesium, organolithium or organocopper reagents to the Weinreb amide (−)-**10** or its corresponding aldehyde or acyl chloride to be problematic.[5] Analyses of the crude mixtures revealed only products of decomposition with concomitant loss or reduction of the nitro group as well as unwanted substitution of the aromatic ring. It is well known that in some cases, the Pd-catalysed reactions of acyl halides with organometallic reagents give higher yields and selectivities than the non-catalysed reactions. Therefore, we turned to organozinc chemistry in the presence of a palladium-based catalyst.[10] This methodology relies on transmetallation between the acylpalladium complex and the organozinc reagent followed by reductive elimination. Carboxylic acid (−)-**11** was obtained in two

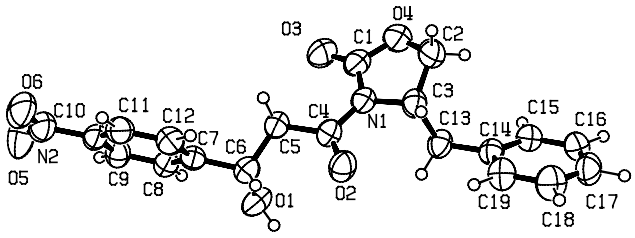
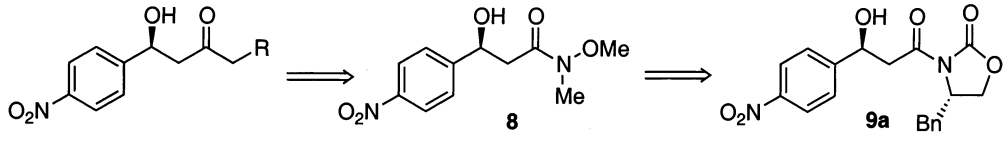
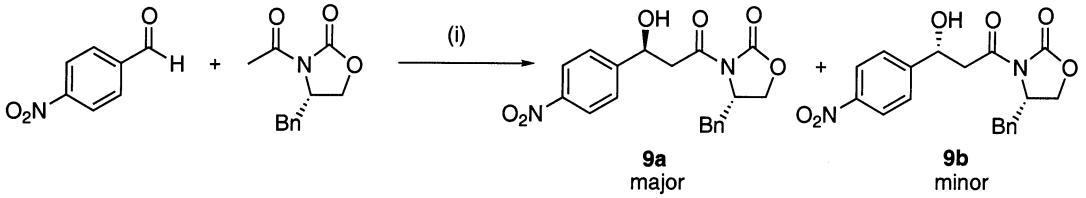


Figure 1. X-Ray crystallography of diastereomer (+)-**9a**.



1 R = $CH_2CH_2CH_3$ **5** R = Cl
2 R = OCH_3 **6** R = CH_2OCH_3
3 R = SCH_3 **7** R = CH_2SCH_3
4 R = OH

Scheme 2. Retrosynthetic approach for the preparation of compounds **1**–**7**.



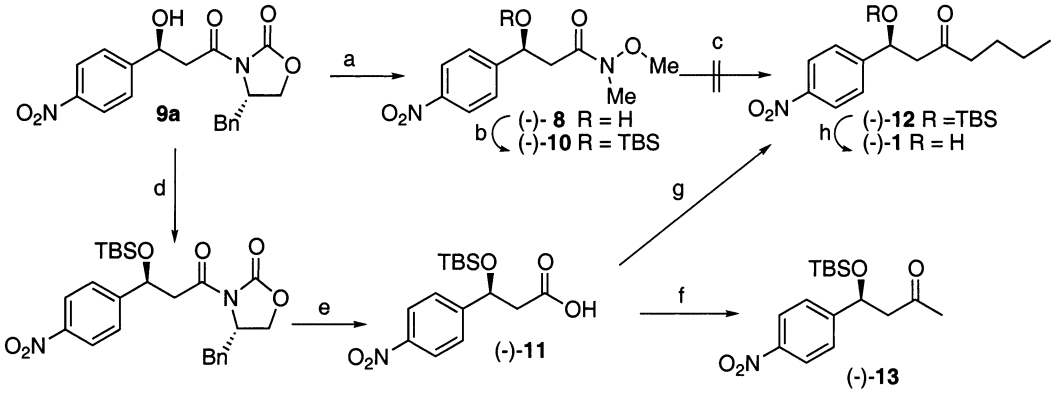
d.e. (crude) = 45%
d.e. (purified) >99%

Scheme 3. Synthesis of compounds (+)-**9a** and (+)-**9b**. *Reagents and conditions*: (i) Et_3N, *n*-Bu_2BOTf, DCM, −78°C then rt, 66%.

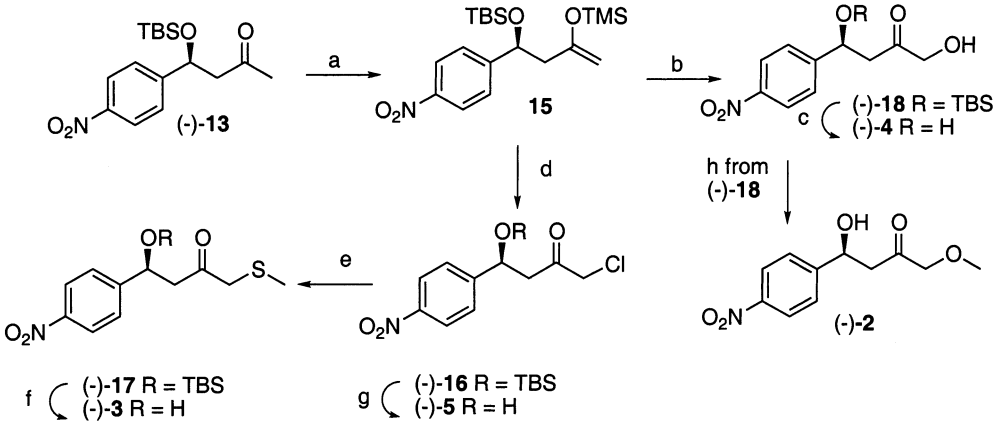
steps from (+)-**9a** by silylation followed by the hydrolytic removal of the chiral auxiliary.[11] The ketones (−)-**12** and (−)-**13** were obtained in an overall yield of 45 and 51%, respectively, by treatment of (−)-**11** with oxalyl chloride followed by addition of dimethyl- or di-*n*-butylzinc on the crude acyl chloride in the presence of 4 mol% of $Pd(PPh_3)_4$ in benzene. The cleavage of the *tert*-butyldimethylsilyloxy group of ketone (−)-**12** was best achieved using TBAF in the presence of acetic acid to afford compound (−)-**1** in a chemical yield of 87%.[12] Other common reagents such as $BF_3{\cdot}OEt_2$, TFA or TBAF in the absence of acetic acid, failed to afford the deprotected product (−)-**1** with an acceptable yield (Scheme 4).[13]

The protected ketone (−)-**13** via its corresponding less substituted silyl enol ether **15** is an obvious precursor of compounds **2**–**5** (Scheme 5). Ketone (−)-**13** was therefore converted into the corresponding kinetic enolate by treatment with 2,6-lutidine in dichloromethane at −78°C, and then to the silyl enol ether **15** by trimethylsilylation of the enolate oxygen with trimethylsilyltriflate. Oxidation of compound **15** with 3 mol% OsO_4 and 2 equiv. of *N*-methylmorpholine-*N*-oxide (the Upjohn process) introduces the requisite hydroxyl group alpha to the carbonyl, affording compound (−)-**4** after a final deprotection step, with an overall yield of 41% from ketone (−)-**13**.[14] Exposure of the silyl enol ether **15** to *N*-chlorosuccinimide in wet acetonitrile at room temperature yielded the chlorinated compound (−)-**16**. The nucleophilic substitution of the chlorine group of **16** with sodium thiomethoxide in toluene at 0°C proceeded smoothly to afford compound **17** in 79% yield. Cleavage of the *tert*-butyldimethylsilyl group of both compounds **16** and **17** afforded our targets (−)-**3** and (−)-**5** with respective yields of 98 and 75%. Finally, the methylation of (−)-**18** followed by deprotection of the corresponding ether afforded compound (−)-**2** in an acceptable overall yield of 50%.

It was anticipated that compounds **6** and **7** could conceivably be prepared from the same enone intermediate (−)-**19** using a Michael addition reaction. Unfortunately, the addition of the vinyl Grignard to the



Scheme 4. Asymmetric synthesis of compound (−)-**1** and intermediate (−)-**13**. *Reagents and conditions*: (a) HN(OMe)Me·HCl, $AlMe_3$ (2 M in toluene), THF, 0°C, 4 h, 78%; (b) TBSCl, imidazole, DMF, rt, 12 h, 100%; (c) *n*-BuMgBr or *n*-BuLi, several conditions; (d) same conditions as b, 84%; (e) 6 equiv. H_2O_2, 6 equiv. LiOH, THF, 0°C then rt, 91%; (f) 1.8 equiv. $(COCl)_2$, cat. DMF, DCM then Me_2Zn, $Pd(PPh_3)_4$, benzene, rt, 51%; (g) 1.8 equiv. $(COCl)_2$, cat. DMF, DCM then *n*-Bu_2Zn, $Pd(PPh_3)_4$, benzene, rt, 45%; h: 10 equiv. TBAF, 10 equiv. AcOH, 15 h, 87%.



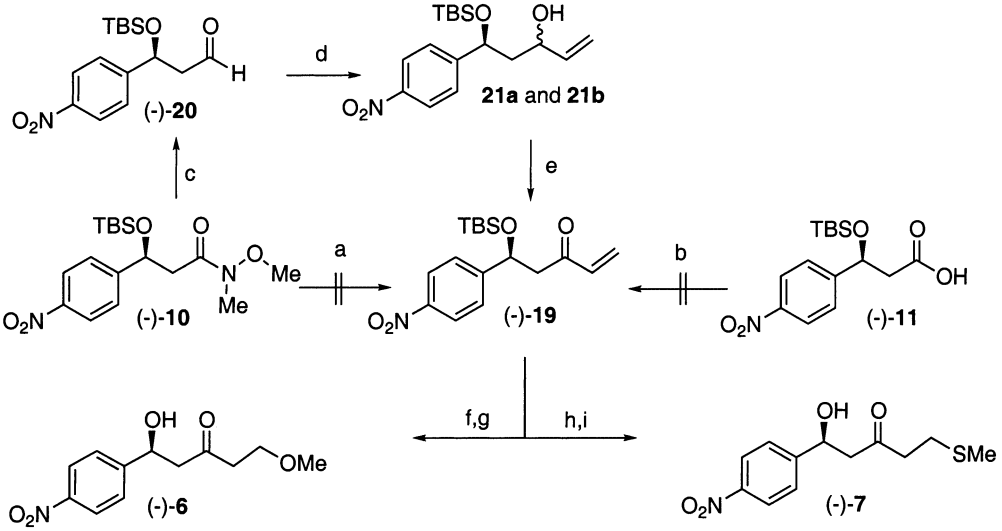
Scheme 5. Asymmetric synthesis of compounds (−)-**2**, (−)-**3**, (−)-**4** and (−)-**5**. *Reagents and conditions*: (a) 2 equiv. TMSOTf, 4 equiv. 2,6-lutidine, DCM, −78°C then 0°C; (b) 2 equiv. NMO, 3 mol% OsO_4, DCM/H_2O, rt, 53%; (c) 10 equiv. TBAF, 10 equiv. AcOH, rt, 15 h, 78%; (d) 1 equiv. NCS, CH_3CN, rt, 35%; (e) 1 equiv. NaSMe, toluene, 0°C, 79%; (f) as in c, 100%; (g) as in c, 75%; (h) 4 equiv. Ag_2O, 8 equiv. MeI, CH_3CN, reflux, 62% then same conditions as in c, 81%.

Weinreb amide (–)-**10** to form the enone (–)-**19** proved to be problematic. All our attempts to isolate the enone from the Weinreb amide (–)-**10** failed. The use of organozinc chemistry as described above was not successful, as the addition of divinylzinc[15] to the acyl chloride prepared in situ from the carboxylic acid (–)-**11** afforded only decomposition products. We found that the enone (–)-**19** could be obtained from the protected Weinreb amide (–)-**10** in three steps. The reductive removal of the *N*-methoxy-*N*-methylamide with diisobutylaluminium hydride followed by the addition of vinyl Grignard to the resulting aldehyde (–)-**20** furnished the diols **21a** and **21b** as a mixture of the *syn* and *anti* stereoisomers with a chemical yield of 53% (d.e. = 25%). Subjecting the mixture of the two diastereomers to oxidation using PDC in the presence of 3 Å molecular sieves afforded the desired enone (–)-**19** in 85% yield. The overall yield from the Weinreb amide (–)-**10** is 42%. The Michael addition of sodium thiomethoxide in toluene or sodium methoxide in methanol to the enone (–)-**19** afforded the desired products in 76 and 60% yields, respectively. For these Michael additions, it is important to carry out the reactions at 0°C to avoid product decomposition. For both Michael adducts, the cleavage of the *tert*-butyldimethylsilyl group was accomplished in quantitative yield in the presence of TBAF and acetic acid to afford compounds (–)-**6** and (–)-**7** as single enantiomers (Scheme 6).

For compounds **1**–**3**, an authentic racemic mixture was prepared and both enantiomers were in each case separated by HPLC. Comparison of the retention times of the antibody-products and the products obtained by independent asymmetric syntheses established the (*R*)-configuration of the stereogenic center of the antibody aldol products, which is consistent with addition of the ketone to the *si* face of the aldehyde, as was previously observed by Lerner et al. for other substrates.[2] For the retro-aldol reactions, HPLC analysis confirmed that at approximately 50% conversion, the isolated unconverted aldol substrates **1**–**3** are of (*S*)-configuration.

3. Conclusions

In conclusion, we have prepared compounds **1**–**7** by independent asymmetric synthesis. This work has revealed that the presence of the *p*-nitrophenyl group can cause problems if these products are to be prepared using a chemical method based on an asymmetric aldol reaction followed by functional group manipulation involving highly reactive organometallic reagents. Indeed, the use of alkyl Grignard or alkyllithium reagents is not always compatible with compounds possessing a *p*-nitrophenyl group within their structure. For the preparation of alkyl ketones, the best route relies on the addition of the corresponding organozinc reagents to the acyl chloride in the presence of a palladium catalyst. If an alkenyl ketone or enone such as (–)-**19** has to be generated, our three-step sequence via the aldehyde is the best approach, since the one-step process based on the addition of divinylzinc to the acyl chloride did not afford the desired product. Interestingly, we have found previously that in contrast to the chemical approach, products (*R*)-**1**–**3** could be readily prepared in one step with enantiomeric excesses of greater than 97%, from the corresponding unmodified ketones and *p*-nitrobenzaldehyde in the presence of the commercially available aldolase antibody 84G3. Both enantiomers are accessible using either the forward or reverse aldol reaction. Indeed, compounds (*S*)-**1**–**3** were obtained by kinetic resolution of the corresponding racemic aldol products via a retroaldolisation process. With the enantiomerically pure compounds **4**–**7** in hand, further studies are now in progress including the



Scheme 6. Asymmetric synthesis of compounds (–)-**6** and (–)-**7**. *Reagents and conditions*: (a) CH_2=CHMgBr, several conditions; (b) 1.8 equiv. $(COCl)_2$, cat. DMF, DCM then $(CH_2{=}CH)_2Zn$, Pd $(PPh_3)_4$, benzene, rt, 0%; (c) 1.2 equiv. DIBAL-H (1 M in hexane), –78°C, 45 min, 94%; (d) 1.1 equiv. CH_2=CHMgBr (0.55 M in THF), –78°C then 0°C then rt, 53%; (e) 1.2 equiv. PDC, 3 Å MS, DCM, rt, 3 h, 85%; (f) Na, MeOH, 0°C, 30 min, 60%; (g) 10 equiv. TBAF, 10 equiv. AcOH, 100%; (h) MeSNa, toluene, 0°C, 5 h, 76%; (i) 10 equiv. TBAF, 10 equiv. AcOH, 100%.

use of antibody 84G3-catalysed reactions for the preparation of natural products.

4. Experimental

Melting points were determined in a capillary and are uncorrected. NMR spectra were recorded on a Bruker DPX-400 or Bruker AMX-500 spectrometer. The experiments were performed at 400 MHz for ^{1}H and 100 MHz for ^{13}C, except when otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in hertz. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. Principal absorption bands are reported in wavenumbers (cm^{-1}). Mass spectra (m/z) and HRMS were recorded on a Micromass GCT in Chemical Ionisation (NH_3, CI), Electronic Impact (EI+) or Field Ionization (FI) modes. Optical rotations were determined on a Perkin–Elmer 241 polarimeter in a 1 dm cell. Concentrations are given in g/100 mL. Microanalyses were performed by 'Elemental Microanalysis Limited', Devon. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel $60F_{254}$. Column chromatography was carried out on Merck Silica gel C60 (40–60 μM). All R_f values are given for the solvent system used for the preparative chromatography.

4.1. (3′*S*,4*S*)-4-Benzyl-3-[3′-hydroxy-3′-(4-nitrophenyl)-propionyl]oxazolidin-2-one 9a and (3′*R*,4*S*)-4-benzyl-3-[3′-hydroxy-3′-(4-nitrophenyl)propionyl]oxazolidin-2-one 9b

To a solution of (4*S*)-3-acetyl-4-benzyl oxazolidin-2-one (3.5 g, 16 mmol) in DCM (25 mL) cooled at −78°C were successively added di-*n*-butylboron triflate in DCM (1 M, 17.6 mL, 17.6 mmol) and triethylamine (2.7 mL, 19.2 mmol). The mixture was stirred at −78°C for 30 min then at 0°C for 1 h. After cooling the mixture to −78°C, a solution of *p*-nitrobenzaldehyde (2.4 g, 16 mmol) in DCM (30 mL) was added dropwise. The solution was quenched after 30 min at −78°C and 1 h at rt by addition of saturated NH_4Cl (20 mL). The aqueous layer was washed with DCM (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography on silica (DCM/hexane/AcOEt, 70/25/5) afforded two diastereomers **9a** and **9b** (d.e. = 45%) as white solids (2.95 g, 66%). Analytical data for **9a**: R_f 0.15; mp 133°C; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, J = 8.8, 2H), 7.61 (d, J = 8.4, 2H), 7.37–7.19 (m, 5H), 5.34 (m, 1H), 4.73 (m, 1H), 4.26 (dd, J = 9.2 and 7.2, 1H), 4.23 (dd, J = 9.2 and 3.2, 1H), 3.68 (d, J = 4, 1H), 3.37 (m, 2H), 3.29 (dd, J = 13.6 and 3.4, 1H), 2.82 (dd, J = 13.6 and 9.2, 1H); ^{13}C NMR ($CDCl_3$): δ 171.7, 153.3, 149.6, 147.4, 134.7, 129.4, 129.0, 127.5, 126.6, 123.8, 69.2, 66.5, 55.1, 44.2, 37.7; IR (neat): ν 3446br, 1760, 1702, 1516, 1392, 1346, 1211, 1115, 1071; MS (CI+): m/z 403.2 ($M+NH_4^+$), 388.2 ($M+H^+$), 353.2 (M^+-OH), 237.2 ($M^+-C_9H_{10}O$), 220.1 ($M^+-C_9H_{10}O-OH$), 195.2 ($M+H^+$−oxazolidinone), 178.1 (oxazolidinone+H^+). Anal calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.27; H, 4.83; N, 7.54%; $[\alpha]_D^{25} = +29.5$ (c 1, DCM). Analytical data for **9b**: R_f 0.1; mp 116°C; ^{1}H NMR ($CDCl_3$): δ 8.23 (d, J = 9.2, 2H), 7.62 (d, J = 8.4, 2H), 7.38–7.21 (m, 5H), 5.38 (m, 1H), 4.72 (m, 1H), 4.24 (m, 2H), 3.58 (d, J = 4.4, 1H), 3.45 (dd, J = 18 and 2.8, 1H), 3.33 (dd, J = 14 and 3.6, 1H), 3.28 (dd, J = 18 and 9.4, 1H), 2.82 (dd, J = 14 and 9.6, 1H); ^{13}C NMR ($CDCl_3$): δ 171.5, 153.3, 149.6, 147.4, 134.8, 129.3, 129.1, 127.6, 126.6, 123.8, 69.2, 66.6, 55.1, 44.3, 37.7; IR (neat): ν 3506br, 1780, 1694, 1520, 1391, 1348, 1212, 1111, 1072; MS (CI+): m/z 403.2 ($M+NH_4^+$), 388.2 ($M+H^+$), 195.2 ($M+H^+$−oxazolidinone), 178.1 (oxazolidinone+H^+). Anal calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.14; H, 4.82; N, 7.55%; HRMS: $[C_{19}H_{18}N_2O_6+H]^+$ requires 388.1509. Found 388.1508; $[\alpha]_D^{25} = +90.5$ (c 1, DCM).

4.2. (3*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-3-(4-nitrophenyl)propionamide (−)-8

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.75 g, 17.8 mmol) in THF (60 mL) at 0°C was added a solution of trimethylaluminium in toluene (2 M, 8.9 mL, 17.8 mmol). After 30 min at 0°C and 20 min at rt, the solution was cooled to −15°C and a solution of **9a** (2.2 g, 5.9 mmol) in THF (40 mL) was added dropwise. The cloudy mixture was warmed to 0°C and stirred for 4 h. The solution was quenched by addition of saturated 0.5 M HCl (100 mL). The aqueous layer was washed three times with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification by column chromatography on silica (AcOEt/hexane, 55/45) afforded (−)-**8** as a white solid (1.18 g, 78%); R_f 0.25; mp 81°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, J = 8.7, 2H), 7.60 (d, J = 8.6, 2H), 5.25 (dt, J = 9.6 and 3.0, 1H), 4.53 (d, J = 3.1, 1H), 3.66 (s, 3H), 3.23 (s, 3H), 2.93 (dd, J = 17.0 and 2.2, 1H), 2.75 (dd, J = 17.0 and 9.7, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 150.7, 147.8, 127.0, 124.2, 69.9, 61.8, 40.5, 32.4; IR (neat): ν 3414br, 1640, 1520, 1348, 1070; MS (CI+): m/z 255.1 ($M+H^+$). Anal calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.83; H, 5.70; N, 10.91%; HRMS: $[C_{11}H_{14}N_2O_5+H]^+$ requires 255.0981. Found 255.0988; $[\alpha]_D^{25} = -57.5$ (c 1, DCM).

4.3. (3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-*N*-methoxy-*N*-methyl-3-(4-nitrophenyl)propionamide (−)-10

Imidazole (1.45 g, 21 mmol) and TBSCl (1.6 g, 10.6 mmol) were added to a solution of (−)-**8** (1.12 g, 4.4 mmol) in DMF (15 mL) at room temperature. The mixture was stirred overnight and quenched with NH_4Cl (pH 6), extracted with DCM and the combined organic layers were washed with brine and dried over $MgSO_4$. Purification by chromatography on silica (DCM/hexane/EtOAc, 20/70/10) afforded (−)-**10** as a white solid (1.7 g, 100%) R_f 0.2; mp 45°C; ^{1}H NMR ($CDCl_3$): δ 8.19 (d, J = 8.7, 2H), 7.57 (d, J = 8.6, 2H), 5.36 (dd, J = 8.3 and 4.8, 1H), 3.64 (s, 3H), 3.17 (s, 3H), 3.02 (dd, J = 14.9 and 8.3, 1H), 2.53 (dd, J = 14.9 and 4.6, 1H), 0.85 (s, 9H), 0.05 (s, 3H), −0.11 (s, 3H); ^{13}C

NMR ($CDCl_3$): δ 170.7, 152.3, 147.2, 126.7, 123.6, 71.1, 61.3, 42.9, 31.9, 25.6, 18.0, –4.9, –5.1; IR (neat, cm^{-1}): ν 2930, 2857, 1662, 1607, 1523, 1472, 1388, 1348, 1089, 831; MS (CI+): m/z 369.2 ($M+H^+$), 237.2 ($M^+-OSiC_6H_{15}$), 195.2 ($M+H^+-SiC_6H_{15}-NOC_2H_6$). Anal. calcd for $C_{17}H_{28}N_2O_5Si$: C, 55.41; H, 7.66; N, 7.60. Found: C, 55.04; H, 7.70; N, 7.52%; HRMS: $[C_{17}H_{28}N_2O_5Si+H]^+$ requires 369.1846. Found 369.1848; $[\alpha]_D^{25}=-69.6$ (c 1, DCM).

4.4. (3′*S*,4*S*)-4-Benzyl-3-[3′-(*tert*-butyldimethylsilanyloxy)-3′-(4-nitrophenyl)propionyl]oxazolidin-2-one

Imidazole (3.5 g, 51.8 mmol) and TBSCl (3.9 g, 25.9 mmol) was added to a solution of **9a** (4 g, 10.8 mmol) in DMF (40 mL) at room temperature. The reaction was stirred overnight. The product was filtered off and washed with Et_2O to afford a white solid (4.4 g, 84%). Mp 173°C; ^1H NMR ($CDCl_3$): δ 8.21 (d, $J=9.2$, 2H), 7.61 (d, $J=8.8$, 2H), 7.38–7.22 (m, 5H), 5.40 (dd, $J=8.4$ and 4.8, 1H), 4.66 (m, 1H), 4.18 (m, 2H), 3.46 (dd, $J=15.6$ and 8.0, 1H), 3.31 (dd, $J=14.0$ and 3.6, 1H), 3.23 (dd, $J=15.6$ and 4.4, 1H), 2.79 (dd, $J=13.6$ and 9.6, 1H), 0.88 (s, 9H), 0.09 (s, 3H), –0.12 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 169.5, 153.4, 151.5, 147.4, 135.0, 129.4, 129.0, 127.5, 126.9, 123.7, 70.4, 66.2, 55.1, 46.5, 37.7, 25.7, 18.0, –4.8, –5.1; IR (neat, cm^{-1}): ν 2926, 2852, 1789, 1695, 1598, 1518, 1476, 1390, 1347, 1248, 1201, 1048; MS (CI+): m/z 502.2 ($M+NH_4^+$), 485.2 ($M+H^+$), 323.1 ($M^+-SiC_6H_{15}-NO_2$), 195.1 ($M+H^+-SiC_6H_{15}$–oxazolidinone). Anal calcd for $C_{25}H_{32}N_2O_6Si$: C, 61.96; H, 6.66; N, 5.78. Found: C, 61.79; H, 6.91; N, 6.12%; HRMS: $[C_{25}H_{32}N_2O_6Si+H]^+$ requires 485.2108. Found 485.2109; $[\alpha]_D^{25}=+24.0$ (c 1, $CHCl_3$).

4.5. (3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(4-nitrophenyl)propionic acid (–)-11

To a solution of (3′*S*,4*S*)-4-benzyl-3-[3′-(*tert*-butyldimethylsilanyloxy)-3′-(4-nitrophenyl)propionyl]-oxazolidin-2-one (2 g, 4.1 mmol) in THF (40 mL) at 0°C were added aqueous hydrogen peroxide (27.5% wt, 3.1 mL, 24.8 mmol) and aqueous lithium hydroxide (0.8 M, 31 mL, 24.8 mmol). After stirring at 0°C for 1 h, the solution was allowed to warm to rt and was stirred for an additional 3 h. Then $Na_2S_2O_3{\cdot}5H_2O$ was added (5.1 g, 20.7 mmol), the solution was extracted with EtOAc, then acidified to pH 3 and extracted again with EtOAc. The combined organic layers were dried over $MgSO_4$. Purification by chromatography on silica (EtOAc/hexane, 50/50) afforded (–)-**11** as a white solid (1.2 g, 91%) (a few drops of acetic acid were added before the column to dissolve completely the product); R_f 0.32; mp 142°C; ^1H NMR ($CDCl_3$): δ 8.22 (d, $J=8.4$, 2H), 7.55 (d, $J=8.8$, 2H), 5.26 (dd, $J=8.8$ and 4.4, 1H), 2.78 (dd, $J=15.6$ and 8.4, 1H), 2.65 (dd, $J=15.6$ and 4.4, 1H), 0.87 (s, 9H), 0.07 (s, 3H), –0.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.4, 150.9, 147.5, 126.6, 123.8, 70.9, 45.6, 25.6, 18.0, –4.7, –5.3; IR (neat): ν 3434br, 1645, 1520, 1345, 1101; MS (CI+): m/z 343.1 ($M+NH_4^+$), 326.1 ($M+H^+$), 164.0 ($M^+-NO_2-SiC_6H_{15}$), 120.4 ($M^+-NO_2-SiC_6H_{15}-COOH$). Anal calcd for $C_{15}H_{23}NO_5Si$: C, 55.36; H, 7.12; N, 4.30. Found: C, 54.94; H, 7.41; N, 4.28%; HRMS: $[C_{15}H_{23}NO_5Si+NH_4]^+$ requires 343.1689. Found 343.1693; $[\alpha]_D^{25}=-49.8$ (c 1, DCM).

4.6. (1*S*)-1-(*tert*-Butyldimethylsilanyloxy)-1-(4-nitrophenyl)heptan-3-one (–)-12

Oxalyl chloride (75 μL, 0.86 mmol) was added at 0°C to a solution of (–)-**11** (165 mg, 0.51 mmol) in DCM (3 mL). The reaction was initiated by addition of two drops of DMF. After 30 min at 0°C, the mixture was allowed to warm to rt and stirred for an additional hour. Solvents were evaporated. The solid residue was dissolved in benzene (2.5 mL) and palladium tetrakis (25 mg, 0.02 mmol) was added. After cooling to 0°C, di-*n*-butylzinc (1 M in heptane, 0.5 mL, 0.5 mmol) was added dropwise, the mixture was stirred at rt for 1 h and quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$. Purification by chromatography on silica (DCM/hexane, 50/50) afforded (–)-**12** as a white solid (82 mg, 45%). R_f 0.16; mp decomposition; ^1H NMR ($CDCl_3$): δ 8.19 (d, $J=9.2$, 2H), 7.52 (d, $J=8.4$, 2H), 5.30 (dd, $J=8.4$ and 4.4, 1H), 2.91 (dd, $J=15.6$ and 8.4, 1H), 2.52 (dd, $J=15.6$ and 4.4, 1H), 2.44 (dt, $J=17.6$ and 7.5, 1H), 2.37 (dt, $J=17.6$ and 7.6, 1H), 1.51 (m, 2H), 1.30 (m, 2H), 0.89 (t, $J=7.4$, 3H), 0.85 (s, 9H), 0.03 (s, 3H), –0.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 208.3, 152.2, 147.2, 126.6, 123.7, 70.7, 53.0, 44.4, 25.6, 25.4, 22.2, 18.0, 13.8, –4.8, –5.2; IR (neat): ν 2931, 2858, 1717, 1608, 1524, 1347, 1258, 1095; MS (CI+): m/z 366.3 ($M+H^+$), 308.2 ($M^+-C_4H_9$); HRMS: $[C_{19}H_{31}NO_4Si+H]^+$ requires 366.2101. Found 366.2115; $[\alpha]_D^{25}=-64.4$ (c 1, DCM).

4.7. (4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-4-(4-nitrophenyl)butan-2-one (–)-13

Oxalyl chloride (595 μL, 6.8 mmol) was added at 0°C to a solution of (–)-**11** (1.23 g, 3.8 mmol) in DCM (20 mL). The reaction was initiated by addition of three drops of DMF. After 30 min at 0°C, the mixture was allowed to warm to rt and was stirred for an additional hour. The solvents were evaporated under anhydrous conditions. The solid residue was dissolved in benzene (20 mL) and palladium tetrakis(triphenylphosphine) (150 mg, 0.13 mmol) was added. After cooling to 0°C, dimethylzinc (2 M in toluene, 1.6 mL, 3.3 mmol) was added dropwise, the mixture was stirred at rt for 1 h and quenched by addition of water. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$. Purification by chromatography on silica (DCM/hexane, 50/50) afforded (–)-**13** as a white solid (626 mg, 51% for both steps). R_f 0.26; mp 36°C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, $J=9.0$, 2H), 7.52 (d, $J=9.0$, 2H), 5.28 (dd, $J=8.5$ and 4.5, 1H), 2.94 (dd, $J=15.5$ and 8.5, 1H), 2.58 (dd, $J=15.5$ and 4.5, 1H), 2.16 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), –0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.0, 151.9, 147.2, 126.6, 123.7, 70.7, 53.8, 31.7, 25.6, 18.0, –4.8, –5.3; IR (neat): ν 2990, 1720, 1608, 1523, 1347, 1257, 1090; MS (CI+): m/z 341.2 ($M+NH_4^+$),

324.2 ($M+H^+$), 266.1 ($M^+-C_4H_9$), 162.1 ($M^+-NO_2-SiC_6H_{15}$); Anal calcd for $C_{16}H_{25}NO_4Si$: C, 59.41; H, 8.27; N, 4.40. Found: C, 59.70; H, 8.27; N, 4.40%; HRMS: $[C_{16}H_{25}NO_4Si+H]^+$ requires 324.1631. Found 324.1643; $[\alpha]_D^{25}=-70.0$ (*c* 1, DCM).

4.8. (4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-chloro-4-(4-nitrophenyl)butan-2-one (−)-16

Trimethylsilyl triflate (434 μL, 2.4 mmol) was added to a solution of (−)-**13** (385 mg, 1.2 mmol) and lutidine (560 μL, 4.8 mmol) in 4 mL of DCM at −78°C. The reaction mixture was stirred for 2 h at −78°C, 30 min at 0°C and then diluted with cold DCM and washed with cold sat. $NaHCO_3$. The aqueous layer was extracted three times with cold DCM. The combined organic layers were washed with cold sat. NaCl, dried over Na_2SO_4 and concentrated to give the corresponding silyl enol ether **15** which was used in the next step without purification. A solution of the residue in CH_3CN (4 mL) at 0°C was successively treated with *N*-chlorosuccinimide (160 mg, 1.2 mmol) and water (0.5 mL). The mixture was warmed to rt and stirred for 3 h. Water was added, and the solution was extracted with EtOAc, washed with brine and dried over Na_2SO_4. Purification by chromatography on silica (hexane/Et_2O, 80/20) afforded (−)-**16** as a white solid (150 mg, 35% for both steps). R_f 0.13; mp 54°C; ^1H NMR ($CDCl_3$): δ 8.22 (d, $J=8.4$, 2H), 7.54 (d, $J=8.8$, 2H), 5.30 (dd, $J=8.4$ and 4.0, 1H), 4.15 (d, $J=15.8$, 1H), 4.11 (d, $J=15.8$, 1H), 3.06 (dd, $J=15.6$ and 8.6, 1H), 2.70 (dd, $J=15.6$ and 4.2, 1H), 0.86 (s, 9H), 0.04 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.5, 151.0, 147.4, 126.5, 123.8, 70.8, 50.0, 49.4, 25.6, 17.9, −4.8, −5.4; IR (neat): *v* 2990, 1738, 1608, 1523, 1348, 1254, 1093; MS (CI+): *m*/*z* 375.0 ($M+NH_4^+$), 358.0 ($M+H^+$), 195.9 ($M^+-NO_2-SiC_6H_{15}$), 162.0 ($M+H^+-NO_2-SiC_6H_{15}-Cl$); HRMS: $[C_{16}H_{24}ClNO_4Si+H]^+$ requires 358.1241. Found 358.1235 $[\alpha]_D^{25}=-101.2$ (*c* 1, DCM).

4.9. (4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-methylsulfanyl-4-(4-nitrophenyl)butan-2-one (−)-17

To a solution of (−)-**16** (100 mg, 0.27 mmol) in toluene (3 mL) was added sodium thiomethoxide (20 mg, 0.27 mmol) at 0°C. After stirring at 0°C for 3 h, the solution was quenched by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc and the combined organic layers were dried over $MgSO_4$. Removal of solvents and purification by chromatography on silica (hexane/Et_2O, 80/20) afforded (−)-**17** as a pale yellow oil (78 mg, 79%). R_f 0.22; ^1H NMR ($CDCl_3$): δ 8.20 (d, $J=8.8$, 2H), 7.54 (d, $J=8.4$, 2H), 5.30 (dd, $J=8.2$ and 4.5, 1H), 3.20 (d, $J=13.6$, 1H), 3.14 (d, $J=13.6$, 1H), 3.14 (dd, $J=15.9$ and 8.1, 1H), 2.77 (dd, $J=15.9$ and 4.5, 1H), 1.99 (s, 3H), 0.86 (s, 9H), 0.05 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.2, 151.7, 147.2, 126.6, 123.6, 70.8, 50.4, 44.1, 25.6, 17.9, 15.4, −4.9, −5.3; IR (neat): *v* 2929, 2857, 1711, 1608, 1523, 1347, 1258, 1094; MS (CI+): *m*/*z* 387.1 ($M+NH_4^+$), 370.2 ($M+H^+$), 208.1 ($M^+-NO_2-SiC_6H_{15}$), 162.1 ($M+H^+-NO_2-SiC_6H_{15}-SCH_3$); HRMS: $[C_{17}H_{27}NO_4SSi+H]^+$ requires 370.1508. Found 370.1513; $[\alpha]_D^{25}=-81.3$ (*c* 1, DCM).

4.10. (4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-hydroxy-4-(4-nitrophenyl)butan-2-one (−)-18

Trimethylsilyl triflate (112 μL, 0.62 mmol) was added to a solution of (−)-**13** (100 mg, 0.31 mmol) and lutidine (144 μL, 1.24 mmol) in 1 mL of DCM at −78°C. The reaction mixture was stirred for 2 h at −78°C, 30 min at 0°C and then diluted with cold DCM and washed with cold sat. $NaHCO_3$. The aqueous layer was extracted three times with cold DCM. The combined organic layers were washed with cold sat. NaCl, dried over Na_2SO_4 and concentrated to give the corresponding silyl enol ether **15** (128 mg) which was used in the next step without purification. Osmium tetroxide (0.2 M in toluene, 51 μL, 0.01 mmol) and aqueous NMO (50% (w/w), 180 μL, 0.77 mmol) was added sequentially to a solution of the crude silyl enol ether in DCM (1.5 mL) and the mixture was stirred at rt for 2 h. Then a 50% (w/w) solution of $Na_2S_2O_5$ (1 mL) was added and the reaction was stirred for 15 min. The mixture was extracted with DCM, washed with brine and dried over Na_2SO_4. Removal of solvents and purification by chromatography on silica (EtOAc/hexane, 15/85) afforded (−)-**18** as a colourless oil (56 mg, 53% for both steps). R_f 0.19; ^1H NMR ($CDCl_3$): δ 8.22 (d, $J=9.2$, 2H), 7.54 (d, $J=8.7$, 2H), 5.32 (dd, $J=8.9$ and 3.8, 1H), 4.32 (dd, $J=19.5$ and 4.8, 1H), 4.16 (dd, $J=19.5$ and 4.8, 1H), 3.06 (t, $J=4.8$, 1H), 2.87 (dd, $J=14.7$ and 8.9, 1H), 2.56 (dd, $J=14.8$ and 3.8, 1H), 0.86 (s, 9H), 0.02 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 207.3, 151.0, 147.4, 126.5, 123.9, 70.9, 69.9, 49.0, 25.6, 18.0, −4.8, −5.4; IR (neat): *v* 3416, 2923, 1723, 1606, 1518, 1349, 1074; MS (CI+): *m*/*z* 357.1 ($M+NH_4^+$), 340.1 ($M+H^+$), 178.0 ($M^+-NO_2-SiC_6H_{15}$); HRMS: $[C_{16}H_{25}NO_5Si+NH_4]^+$ requires 357.1846. Found 357.1849 $[\alpha]_D^{25}=-94.7$ (*c* 1, DCM).

4.11. (4*S*)-4-(*tert*-Butyldimethylsilanyloxy)-1-methoxy-4-(4-nitrophenyl)butan-2-one

A mixture of (−)-**18** (50 mg, 0.15 mmol), silver(I) oxide (140 mg, 0.6 mmol) and methyl iodide (75 μL, 1.2 mmol) in CH_3CN (1 mL) was heated under reflux for 20 h in the dark. After cooling, the solution was diluted with EtOAc and filtered through Celite. Removal of solvents and purification by chromatography on silica (EtOAc/hexane, 20/80) afforded a white solid (33 mg, 62%). R_f 0.22; mp 56°C; ^1H NMR ($CDCl_3$): δ 8.20 (d, $J=8.8$, 2H), 7.53 (d, $J=8.4$, 2H), 5.33 (dd, $J=8.4$ and 3.6, 1H), 4.04 (d, $J=17.4$, 1H), 3.98 (d, $J=17.4$, 1H), 3.41 (s, 3H), 2.93 (dd, $J=15.6$ and 8.4, 1H), 2.54 (dd, $J=15.6$ and 4.0, 1H), 0.86 (s, 9H), 0.04 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 205.6, 151.7, 147.3, 126.6, 123.7, 78.6, 70.4, 59.3, 49.3, 25.6, 18.0, −4.8, −5.3; IR (neat): *v* 2955, 2930, 1731, 1523, 1347, 1092; MS (CI+): *m*/*z* 371.2 ($M+NH_4^+$), 354.2 ($M+H^+$), 239.1 ($M+H^+-SiC_6H_{15}$) 222.1 ($M^+-OSiC_6H_{15}$), 192.1 ($M^+-NO_2-SiC_6H_{15}$); HRMS: $[C_{17}H_{27}NO_5Si+H]^+$ requires 354.1737. Found 354.1726; $[\alpha]_D^{25}=-61.2$ (*c* 0.5, DCM).

4.12. (3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(4-nitrophenyl)propionaldehyde (−)-20

To a solution of (−)-**10** (2.5 g, 6.8 mmol) in THF (80 mL) at −78°C was added a solution of DIBAL-H in hexane (1 M, 8.2 mL, 8.2 mmol). The reaction was stirred at −78°C for 45 min and then quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of solvents and purification by chromatography on silica (hexane/EtOAc, 90/10) afforded (−)-**20** as a white solid (1.98 g, 94%); R_f 0.27; mp 47°C; ^{1}H NMR ($CDCl_3$): δ 9.79 (t, $J=2.0$, 1H), 8.22 (d, $J=8.4$, 2H), 7.54 (d, $J=8.8$, 2H), 5.34 (dd, $J=7.7$ and 4.4, 1H), 2.90 (ddd, $J=16.0$, 7.6 and 2.0, 1H), 2.68 (ddd, $J=16.0$, 4.4 and 1.6, 1H), 0.88 (s, 9H), 0.08 (s, 3H), −0.10 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.7, 151.2, 147.4, 126.5, 123.8, 69.6, 53.6, 25.6, 18.0, −4.7, −5.2; IR (neat, cm^{-1}): ν 2956, 2858, 1727, 1608, 1523, 1472, 1348, 1095, 838; MS (CI+): m/z 327.3 ($M+NH_4^+$), 310.3 ($M+H^+$), 252.2 ($M+NH_4^+-NO_2-CH_2CHO$). Anal calcd for $C_{15}H_{23}NO_4Si$: C, 58.22; H, 7.46; N, 4.53. Found: C, 57.84; H, 7.58; N, 4.58%; HRMS: $[C_{15}H_{23}NO_4Si+NH_4]^+$ requires 327.1740. Found 327,1743; $[\alpha]_D^{25}=-50.2$ (c 1, DCM).

4.13. (5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-5-(4-nitrophenyl)pent-1-en-3-ol 21a and 21b

A solution of vinyl-magnesium bromide in THF (0.55 M, 10 mL, 5.5 mmol) was added at −78°C to a solution of (−)-**20** (1.7 g, 5 mmol) in THF (50 mL). After 1 h at −78°C, the solution was stirred at rt for 2 h and quenched by addition of sat. aqueous NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvents and purification by chromatography on silica (DCM/hexane, 75/25) afforded a mixture of **21a** and **21b** as a colourless oil (892 mg, 53%, d.e=25%); Noesy and Goesy experiments suggest that the major diastereomer **21a** is the *syn* and the minor diastereomer **21b** is the *anti*. R_f 0.20; ^{1}H NMR ($CDCl_3$): **21a** δ 8.14 (d, $J=8.4$, 2H), 7.45 (d, $J=8.8$, 2H), 5.85 (ddd, $J=16.8$, 10.4 and 6.0, 1H), 5.18 (dt, $J=16.8$ and 1.5, 1H), 5.05 (dt, $J=10.4$ and 1.5, 1H), 4.92 (dd, $J=8.8$ and 6.2, 1H), 4.13 (m, 1H), 2.63 (d, $J=2.0$, 1H), 1.90 (dt, $J=13.0$ and 8.8, 1H), 1.78 (ddd, $J=13.0$, 6.8 and 3.2, 1H), 0.91 (s, 9H), 0.09 (s, 3H), −0.18 (s, 3H); **21b** (deduced from the mixture *syn* and *anti*) δ 8.14 (d, $J=8.4$, 2H), 7.52 (d, $J=8.8$, 2H), 5.85 (m, 1H), 5.18 (dm, $J=16.8$, 1H), 5.05 (m, 2H), 4.23 (m, 1H), 2.44 (d, $J=3.2$, 1H), 1.90 (dt, $J=13.0$ and 8.8, 1H), 1.74 (m, 1H), 0.93 (s, 9H), 0.11 (s, 3H), −0.12 (s, 3H); IR from the mixture (neat): ν 3428br, 1522, 1348, 1086, 838; ^{13}C NMR ($CDCl_3$, 125 MHz): **21a** δ 152.0, 147.2, 140.0, 126.7, 123.6, 114.9, 73.7, 71.1, 47.0, 25.6, 17.9, −4.6, −5.1; **21b** δ 152.3, 147.0, 140.5, 126.4, 123.6, 114.4, 71.7, 69.0, 46.5, 25.6, 18.0, −4.8, −5.3; IR (neat, cm^{-1}): ν 3428, 2954, 2858, 1607, 1523, 1348, 1086, 838; MS (CI+): m/z 338.2 ($M+H^+$), 266.1 ($M^+-CH_2CH(OH)CHCH_2$), 188.1 ($M^+-OH-OSiC_6H_{15}$), 176.1 ($M^+-NO_2-SiC_6H_{15}$), 95 (81). HRMS: $[C_{17}H_{27}NO_4Si+H]^+$ requires 338.1788. Found 327.1783.

4.14. (5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-5-(4-nitrophenyl)pent-1-en-3-one (−)-19

To a solution of **21a** and **21b** (674 mg, 2 mmol) in DCM (13 mL) was added 3 Å molecular sieves (2.7 g) and PDC (908 mg, 2.4 mmol). After stirring for 3 h, Et_2O was added and the precipitate was filtered and washed with Et_2O. Removal of solvents and purification by chromatography on silica (hexane/DCM, 50/50) afforded (−)-**19** as a colourless oil (570 mg, 85%). R_f 0.32; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, $J=8.8$, 2H), 7.55 (d, $J=8.4$, 2H), 6.35 (dd, $J=17.6$ and 10.4, 1H), 6.21 (dd, $J=17.6$ and 1, 1H), 5.88 (dd, $J=10.6$ and 1, 1H), 5.35 (dd, $J=8.2$ and 4.6, 1H), 3.15 (dd, $J=15.6$ and 8, 1H), 2.69 (dd, $J=15.6$ and 4.4, 1H), 0.84 (s, 9H), 0.03 (s, 3H), −0.13 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 197.8, 152.1, 147.2, 137.1, 129.2, 126.6, 123.7, 70.8, 49.9, 25.7, 18.0, −4.8, −5.2; IR (neat, cm^{-1}): ν 2930, 2857, 1662, 1607, 1523, 1472, 1388, 1348, 1089, 831; MS (CI+): m/z 336.2 ($M+H^+$), 278.1 ($M^+-C_4H_9$), 266.1 ($M^+-CH_2CH(O)-CHCH_2$), 174.0 ($M^+-NO_2-SiC_6H_{15}$); HRMS: $[C_{17}H_{25}NO_4Si+H]^+$ requires 336.1631. Found 336.1635; $[\alpha]_D^{25}=-73.4$ (c 1, DCM).

4.15. (1*S*)-1-(*tert*-Butyldimethylsilanyloxy)-5-methylsulfanyl-1-(4-nitrophenyl)pentan-3-one

To a solution of (−)-**19** (175 mg, 0.52 mmol) in toluene (6 mL) was added small portions of sodium thiomethoxide (40.2 mg in total, 0.57 mmol) at 0°C. The reaction mixture was stirred for 5 h at 0°C and then quenched with NH_4Cl, extracted with DCM and the combined organic layers washed with brine and dried over $MgSO_4$. Removal of solvents and purification by chromatography on silica (hexane/DCM, 20/80) afforded a yellow oil (150 mg, 76%). R_f 0.23; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, $J=8.8$, 2H), 7.53 (d, $J=8.8$, 2H), 5.30 (dd, $J=8.4$ and 4.4, 1H), 2.94 (dd, $J=16.0$ and 8.4, 1H), 2.82–2.65 (m, 4H), 2.58 (dd, $J=15.6$ and 4.0, 1H), 2.10 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), −0.15 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 206.2, 151.8, 147.3, 126.6, 123.7, 70.7, 53.2, 44.3, 27.5, 25.7, 18.0, 15.8, −4.8, −5.2; IR (neat, cm^{-1}): ν 2955, 2929, 2857, 1717, 1608, 1523, 1472, 1408, 1347, 1094, 839. MS (CI+): m/z 384.2 ($M+NH_4^+$), 384.2 ($M+H^+$); HRMS: $[C_{18}H_{29}NO_4SSi+NH_4]^+$ requires 401.1930. Found 401.1932. $[\alpha]_D^{25}=-71.4$ (c 1, DCM).

4.16. (1*S*)-1-(*tert*-Butyldimethylsilanyloxy)-5-methoxy-1-(4-nitrophenyl)pentan-3-one

To a solution of sodium methoxide (formed by dissolving sodium (12 mg, 0.52 mmol) in MeOH (6 ml)) at 0°C was added (−)-**19** (85 mg, 0.25 mmol) in MeOH (2.8 mL). After stirring for 30 min at 0°C, the reaction was acidified to pH 6–7 by addition of HCl (1N in MeOH). Removal of solvents and purification by chromatography on silica (DCM/hexane, 70/30) afforded a colourless oil (54 mg, 60%). R_f 0.13; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, $J=8.8$, 2H), 7.53 (d, $J=8.4$, 2H), 5.31 (dd, $J=8.0$ and 4.4, 1H), 3.62 (m, 2H), 3.30 (s, 3H), 2.97 (dd, $J=16.1$ and 8.0, 1H), 2.65 (m, 3H), 0.85 (s, 9H), 0.04 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (125

MHz, $CDCl_3$): δ 206.2, 151.9, 147.1, 126.5, 123.6, 70.3, 67.0, 58.7, 53.5, 44.2, 25.5, 17.9, −4.9, −5.2; IR (neat, cm^{-1}): ν 2957, 2955, 2857, 1717, 1608, 1523, 1347, 1259, 1093, 835; MS (FI): m/z 368.2 ($M+H^+$); HRMS: $[C_{18}H_{29}NO_5Si+H]^+$ requires 368.1893. Found 368.1895; $[\alpha]_D^{25}=-56.1$ (c 1.04, DCM).

4.17. General procedure for the deprotection of the aldol compounds

A stock solution was prepared by addition of AcOH (0.15 mL) to a solution of tetrabutylammonium fluoride in THF (1 M, 2.5 mL). The TBDMS ether (1 equiv.) was dissolved in THF (0.1 M) and treated by a portion of stock solution (10 equiv.). After 15 h at rt, the reaction mixture was quenched by addition of sat. aqueous $NaHCO_3$ (pH 8). The aqueous layer was extracted with EtOAc and the combined organic layers were washed once with sat. NH_4Cl and dried over $MgSO_4$. Removal of solvent and purification by chromatography on silica gave the corresponding alcohol.

4.17.1. (1*S*)-1-Hydroxy-1-(4-nitrophenyl)heptan-3-one (−)-1. Column chromatography (EtOAc/hexane, 30/70) afforded (−)-**1** as a colourless oil (87%); R_f 0.28; ^1H NMR ($CDCl_3$): δ 8.16 (d, $J=8.8$, 2H), 7.52 (d, $J=8.8$, 2H), 5.25 (m, 1H), 3.80 (d, $J=2.4$, 1H), 2.81 (m, 2H), 2.44 (t, $J=7.6$, 2H), 1.55 (m, 2H), 1.28 (m, 2H), 0.88 (t, $J=7.6$, 3H); ^{13}C NMR ($CDCl_3$): δ 211.1, 150.2, 147.2, 126.4, 123.7, 69.0, 50.5, 43.3, 25.5, 22.2, 13.8; IR (neat, cm^{-1}): ν 3466br, 2959, 1709, 1605, 1520, 1347, 1081, 856; MS (EI+): m/z 251.1 (M^+), 194.0 ($M^+-C_4H_9$), 152.0 ($M^+-CH_2C(O)C_4H_9$), 57.4 ($C_4H_9^+$); HRMS: $[C_{13}H_{17}NO_4]^+$ requires 251.1158. Found 251.1162; $[\alpha]_D^{25}=-55.3$ (c 1, DCM).

4.17.2. (4*S*)-4-Hydroxy-1-methoxy-4-(4-nitrophenyl)-butan-2-one (−)-2. Column chromatography (DCM/Et_2O, 90/10) afforded (−)-**2** as a white solid (81%). R_f 0.20; mp 78°C; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.21 (d, $J=7.2$, 2H), 7.55 (d, $J=6.8$, 2H), 5.31 (t, $J=4.8$, 1H), 4.05 (d, $J=13.8$, 1H), 4.01 (d, $J=13.8$, 1H), 3.48 (s, 1H), 3.42 (s, 3H), 2.90 (d, $J=5.2$, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 208.5, 149.9, 147.2, 126.3, 123.7, 77.7, 68.7, 59.3, 47.2; IR (neat, cm^{-1}): ν 3436br, 2936, 1726, 1606, 1519, 1348, 1088; MS (FI): m/z 239.1 (M^+), 207.1 (M^+-MeOH). Anal calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.01; H, 5.57; N, 5.83%; HRMS: $[C_{11}H_{13}NO_5]^+$ requires 239.0794. Found 239.0789; $[\alpha]_D^{25}=-37.5$ (c 0.5, DCM).

4.17.3. (4*S*)-4-Hydroxy-1-methylsulfanyl-4-(4-nitrophenyl)butan-2-one, (−)-3. Column chromatography (DCM/Et_2O, 98/2) afforded **(−)-3** as a pale yellow solid (98%). R_f 0.19; mp 86°C; ^1H NMR ($CDCl_3$): δ 8.21 (d, $J=8.8$, 2H), 7.57 (d, $J=8.5$, 2H), 5.28 (t, $J=6.3$, 1H), 3.57 (s, 1H), 3.19 (s, 2H), 3.05 (d, $J=6.4$, 2H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 204.7, 149.9, 147.3, 126.5, 123.7, 69.3, 48.0, 43.4, 15.6; IR (neat, cm^{-1}): ν 3468br, 2921, 1706, 1605, 1519, 1348, 1063; MS (CI+): m/z 273.1 ($M+NH_4^+$), 255.1 ($M+H^+$), 122.1 (NO_2-Ph^+). Anal calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.96; H, 5.19; N, 5.49%; $[\alpha]_D^{25}=-32.2$ (c 1, DCM).

4.17.4. (4*S*)-4-Dihydroxy-4-(4-nitrophenyl)butan-2-one (−)-4. Column chromatography (DCM/EtOAc, 80/20) afforded (−)-**4** as a colourless oil (78%). R_f 0.12; ^1H NMR (CD_3OD): δ 8.21 (d, $J=8.4$, 2H), 7.63 (d, $J=8.4$, 2H), 5.28 (dd, $J=8.9$ and 4.2, 1H), 4.26 (d, $J=18.7$, 1H), 4.22 (d, $J=18.7$, 1H), 2.88 (dd, $J=15.8$ and 8.9, 1H), 2.75 (dd, $J=15.8$ and 4.2, 1H); ^{13}C NMR (CD_3OD): δ 208.5, 152.2, 147.5, 126.8, 123.4, 68.9, 68.5; IR (neat, cm^{-1}): ν 3413br, 2913, 1703, 1605, 1512, 1348, 1035; MS (FI): m/z 225.1 (M^+), 207.1 (M^+-H_2O), 151.0 (p-nitrobenzaldehyde); HRMS: $[C_{10}H_{11}NO_5]^+$ requires 225.0637. Found 225.0638; $[\alpha]_D^{25}=-38.7$ (c 0.5, DCM).

4.17.5. (4*S*)-1-Chloro-4-hydroxy-4-(4-nitrophenyl)butan-2-one (−)-5. Column chromatography (hexane/EtOAc, 65/35) afforded (−)-**5** as a white solid (75%). R_f 0.21; mp 94°C; ^1H NMR ($CDCl_3$): δ 8.23 (d, $J=8.0$, 2H), 7.57 (d, $J=8.0$, 2H), 5.34 (m, 1H), 4.14 (s, 2H), 3.15 (d, $J=3.6$, 1H), 3.03 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 202.1, 149.4, 147.5, 126.4, 123.9, 68.9, 48.4, 48.2; IR (neat, cm^{-1}): ν 3390br, 2912, 1726, 1601, 1509, 1344; MS (CI+): m/z 261.1 ($M+NH_4^+$), 150.0 (M^+-COCH_2Cl-OH), 122.1 (NO_2-Ph^+); HRMS: $[C_{10}H_{10}ClNO_4+NH_4]^+$ requires 261.0642. Found 261.0645; $[\alpha]_D^{25}=-30.4$ (c 0.5, DCM).

4.17.6. (1*S*)-1-Hydroxy-5-methoxy-1-(4-nitrophenyl)-pentan-3-one (−)-6. Column chromatography (DCM/EtOAc, 80/20) afforded (−)-**6** as a colourless oil (quant.). R_f 0.27; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, $J=8.7$, 2H), 7.55 (d, $J=8.9$, 2H), 5.29 (m, 1H), 3.67 (m, 3H), 3.35 (s, 3H), 2.88 (d, $J=7.2$, 2H), 2.71 and 2.72 (2t, $J=6.0$, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.7, 150.4, 147.8, 126.9, 124.2, 69.4, 67.9, 59.4, 52.1, 43.9; IR (neat, cm^{-1}): ν 3470, 2857, 1710, 1600, 1516, 1345, 1260, 1106, 854; MS (FI): m/z 253.1 (M^+), 221.1 (M^+-MeOH); HRMS: $[C_{12}H_{15}NO_5]^+$ requires 253.0950. Found 253.0955; $[\alpha]_D^{25}=-42.6$ (c 1, DCM).

4.17.7. (1*S*)-1-Hydroxy-5-methylsulfanyl-1-(4-nitrophenyl)pentan-3-one (−)-7. Column chromatography (hexane/Et_2O, 40/60) afforded (−)-**7** as a yellow solid (quant.); R_f 0.21; mp 47°C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, $J=7.7$, 2H), 7.56 (d, $J=8.1$, 2H), 5.31 (m, 1H), 3.48 (d, $J=3.3$, 1H), 2.87 (d, $J=6.5$, 2H), 2.77 (m, 4H), 2.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 149.7, 147.3, 126.3, 123.7, 68.8, 51.0, 43.0, 27.6, 15.7; IR (neat, cm^{-1}): ν 3423br, 2919, 1710, 1603, 1519, 1347, 1077; MS (FI): m/z 269.1 (M^+), 151.0 (p-nitrobenzaldehyde); HRMS: $[C_{12}H_{15}NO_4S]^+$ requires 269.0722. Found 269.0719; $[\alpha]_D^{25}=-47.2$ (c 1, DCM).

4.18. Determination of enantiomeric purity for compounds 1, 2, 3, 5, 6 and 10

Determination of enantiomeric purity was performed by high performance liquid chromatography (HPLC) at 270 nm using a waters HPLC system (626 pump, 600S controller, 996 photodiode array detector, millennium[32] software). Chiralcel OD or OD-R Daicel column (10 μm particle size, 4.6×50 mm, flow rate 0.5, 1 or 1.5 mL/min, solvent A: hexane, solvent B: *iso*-propanol,

solvent C: water, solvent D: MeOH) was used as chiral stationary phase. The different retention times of the racemic mixture are for compound **1**: on OD column (1.5 mL/min), Isocratic 96% A/4% B, t_R ((*R*)-**1**) = 18.0 min, t_R ((*S*)-**1**) = 19.3 min; for compound **2**: on OD column (1.0 mL/min), Isocratic 80% A/20% B, t_R ((*S*)-**2**) = 13.9 min, t_R ((*R*)-**2**) = 17.2 min; for compound **3**: on OD column (1.0 mL/min), Isocratic 88% A/12% B, t_R ((*S*)-**3**) = 17.2 min, t_R ((*R*)-**3**) = 19.1 min; for compound **6**: on OD-R column (0.5 mL/min), Isocratic 15% C/85% D, t_R ((*S*)-**6**) = 10.0 min, t_R ((*R*)-**6**) = 11.0 min; for compound **7**: on OD column (1.0 mL/min), Isocratic 85% A/15% B, t_R ((*S*)-**7**) = 15.7 min, t_R ((*R*)-**7**) = 16.8 min; for compound **10** on OD column (1.0 mL/min), Isocratic 99.5% A/0.5% B, t_R ((*S*)-**10**) = 14.5 min, t_R ((*R*)-**10**) = 15.6 min; in all cases, the *R* enantiomer in the independent synthesis was not observed.

4.19. X-Ray crystallography

Crystals of **9a** suitable for X-ray analysis were grown from methylene chloride. A single crystal of **9a** was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 220 K in a stream of cold N_2 using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf–Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package. The structure was solved using the direct-methods program SIR92, which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atom was located in a difference Fourier map and subsequently its coordinates and isotropic thermal parameter were refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0268$, $wR = 0.0278$. Crystal data: colourless orthorhombic crystal (0.20×0.20×0.40 mm) in space group $P2_122_1$; $a = 6.8117(1)$, $b = 7.1052(1)$, $c = 37.3863(6)$ Å, $\alpha = \beta = \gamma = 90°$C; $V = 1809.4$ Å^3; $Z = 4$; $D_{calad} = 1.359$ Mg/m^3; $F(000) = 776.254$; absorption coefficient = 0.103 mm^{-1}; reflections measured = 7558, unique reflections = 1529 ($R_{int} = 0.031$); observations [$I > 3\sigma(I)$] = 1232; parameters = 248; goodness-of-fit = 1.0665; $R = 0.0268$; $Rw = 0.0278$.

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