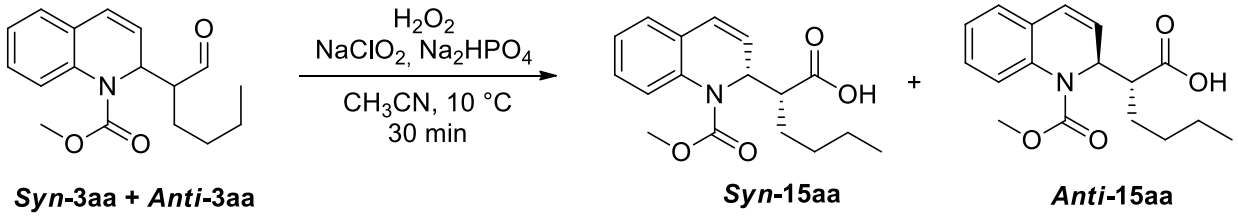
Determination of relative stereochemistry of 3aa

The relative configuration of **3aa**-*syn* and **3aa**-anti were determined by chemical transformation and subsequent comparison with a known compound of similar structure.[7]



***Syn*-3aa + *Anti*-3aa** ***Syn*-15aa** ***Anti*-15aa**

Procedure of oxidation:

An oven-dried 10 mL pyrex vial was loaded with **3aa** (136.0 mg, 0.5 mmol) followed by acetonitrile (2.5 mL). The resulting colourless solution was added with a 1 M solution of NaH_2PO_4 (0.66 mmol, 1.0 mL), a 50% aqueous solution of H_2O_2 (0.50 mmol, 35 μL) and a 1M solution of $NaClO_2$ (0.70 mmol, 0.70 mL) keeping the temperature at 10 °C. The reaction mixture was allowed to react for 30 minutes when saturated aqueous solution of Na_2SO_3 was added. The aqueous solution was extracted with AcOEt (3x10 mL) and Et_2O (2x10mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The reaction crude was purified by preparative TLC (5 hexanes/ 5 Et_2O, 3 runs) to afford:

15aa-*syn* as a colourless oil (54 mg, 36%)

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.55 (br, 1H, *OH*), 7.53 (d, 1H, *J* = 7.3 Hz), 7.26 (dd, 1H, *J* = 8.0, 4.4 Hz), 7.10 (d, 2H, *J* = 4.3 Hz), 6.57 (d, 1H, *J* = 9.5 Hz), 6.09 (dd, 1H, *J* = 9.5, 6.0 Hz), 5.26 (dd, 1H, *J* = 8.9, 6.3 Hz), 3.76 (s, 3H), 2.53 – 2.36 (m, 1H), 1.80 –1.38 (m, 2H), 1.37 – 1.06 (m, 4H), 0.83 (t, 3H, *J* = 6.5 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.6, 154.7, 134.3, 127.8, 127.1, 126.4, 126.1, 125.5, 124.7, 53.4, 53.1, 49.1, 29.5, 27.5, 22.5, 13.7.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{21}NO_4Na$ 326.1368, found 326.1365.

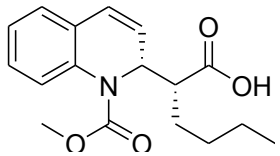
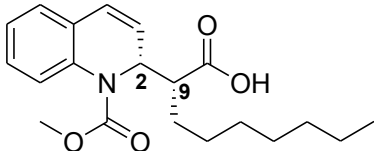
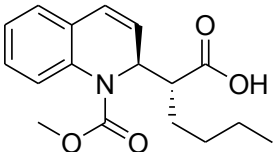
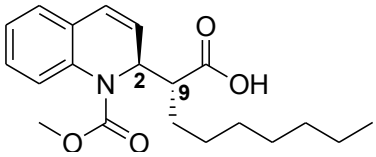
15aa-*anti* as a colourless oil (10 mg, 6%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (bs, 1H), 7.30 – 7.02 (m, 4H), 6.56 (d, 1H, *J* = 9.5 Hz), 6.11 (dd, 1H, *J* = 9.3, 6.0 Hz), 5.34 – 5.16 (m, 1H), 3.92 – 3.73 (m, 3H), 2.49 – 2.29 (m, 1H), 1.69 – 1.52 (m, 2H), 1.41 – 1.10 (m, 4H), 1.01 – 0.75 (m, 3H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.6, 155.1, 134.1, 127.7, 127.3, 126.4, 125.0, 124.8, 53.2, 53.0, 48.5, 28.8, 28.2, 22.4, 13.7.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{21}NO_4Na$ 326.1368, found 326.1373.

Table 4. Determination of relative configuration of **3aa**

15aa-*syn* and **15aa**-*anti*	Reference Compound[7]
	
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 53.4, 53.1, 49.1	^{13}C NMR (126 MHz, $CDCl_3$) δ 53.5 (C-2); 53.1 (OMe); 49.2 (C-9)
	
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 53.2, 53.0, 48.5	^{13}C NMR (126 MHz, $CDCl_3$) δ 53.2 (OMe); 53.0 (C-2); 48.4 (C-9)

X-ray crystallography: Determination of absolute stereochemistry of 5dc-*syn*

Crystal of suitable size was selected from a solid sample of compound **5dc**-*syn* in Et_2O by a slow evaporation of the solvent. An X-ray diffraction study on a single crystal of **5dc**-*syn* led to the molecular structure shown in Figure 1.

In the measurement, performed at room temperature, a certain degree of conformational disorder was present in the ethoxyl group. The conformation of the rest of the molecule is affected by the hydrogen interaction between O(3) and O(1), the O(3)···O(1) distance being 2.911(4) Å. The absolute configuration *R*,*R* of the chiral centers C(5) and C(13) was established on the basis of the Flack's parameter (0.017(11)) [Flack, H. D. *Acta Cryst*. **1983,** *A39*, 876-881].

The CIF file has also been deposited with the Cambridge Crystallographic Data Centre, deposition number CCDC 1057075.These data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif

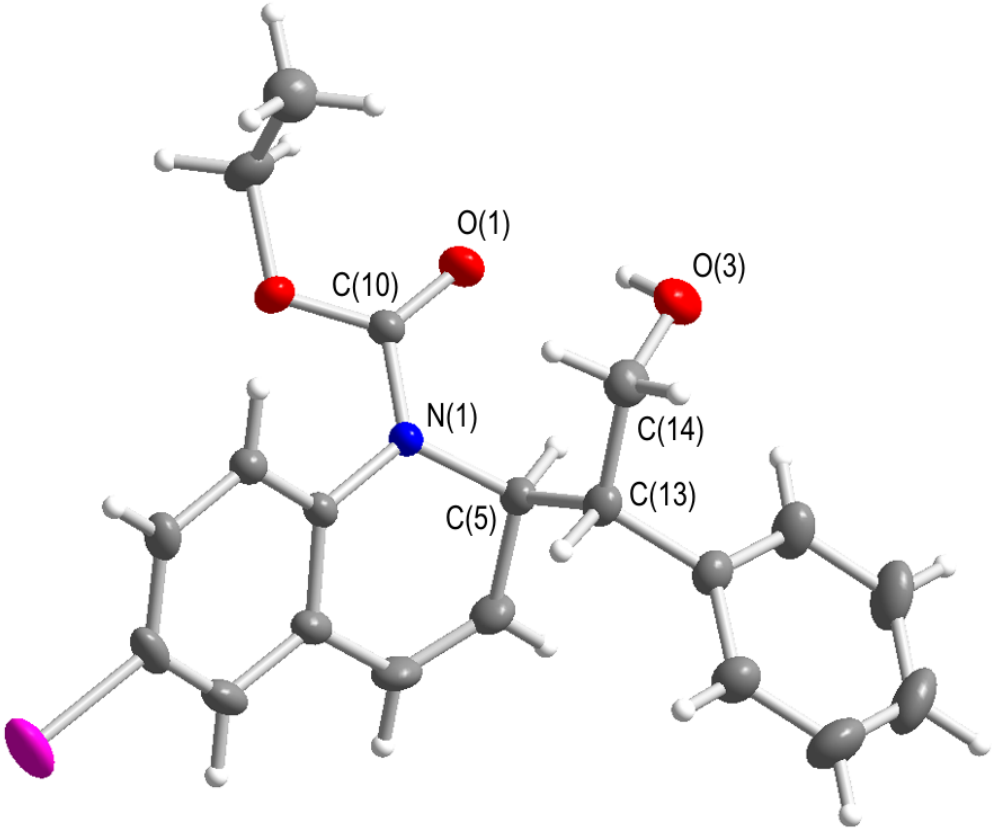


Figure 1. ORTEP diagram of compound **5dc**-*syn* Ellipsoids are at 30% probability.

Table 5 Bond lengths [Å] and angles [°] for **5dc**-*syn*

Br(1)-C(1)	1.896(3)
C(1)-C(9)	1.376(6)
C(1)-C(2)	1.380(6)
C(2)-C(3)	1.382(5)
C(2)-H(2)	0.9300
C(3)-C(4)	1.383(4)
C(3)-H(3)	0.9300
C(4)-C(8)	1.394(4)
C(4)-N(1)	1.423(4)
N(1)-C(10)	1.359(4)
N(1)-C(5)	1.482(4)
C(5)-C(6)	1.500(5)
C(5)-C(13)	1.544(5)
C(5)-H(5)	0.9800
C(6)-C(7)	1.312(5)
C(6)-H(6)	0.9300
C(7)-C(8)	1.463(5)
C(7)-H(7)	0.9300
C(8)-C(9)	1.391(5)
C(9)-H(9)	0.9300
C(10)-O(1)	1.209(4)
C(10)-O(2)	1.329(4)
O(2)-C(11)	1.457(4)
C(11)-C(12B)	1.397(14)
C(11)-C(12A)	1.542(12)
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12A)-H(12A)	0.9600
C(12A)-H(12B)	0.9600
C(12A)-H(12C)	0.9600
C(12B)-H(12D)	0.9600
C(12B)-H(12E)	0.9600
C(12B)-H(12F)	0.9600
C(13)-C(15)	1.514(5)
C(13)-C(14)	1.539(5)
C(13)-H(13)	0.9800
C(14)-O(3)	1.402(5)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700

O(3)-H(3A)	0.8200
C(15)-C(20)	1.373(5)
C(15)-C(16)	1.393(5)
C(16)-C(17)	1.381(6)
C(16)-H(16)	0.9300
C(17)-C(18)	1.361(8)
C(17)-H(17)	0.9300
C(18)-C(19)	1.367(8)
C(18)-H(18)	0.9300
C(19)-C(20)	1.385(6)
C(19)-H(19)	0.9300
C(20)-H(20)	0.9300

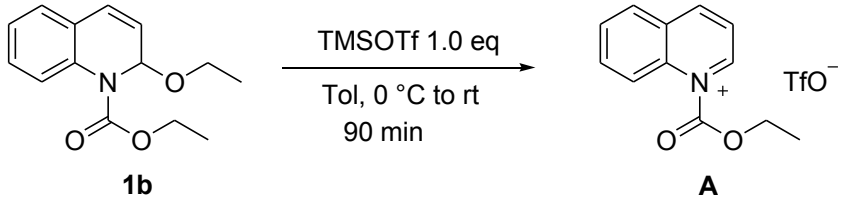
C(9)-C(1)-C(2)	121.5(3)
C(9)-C(1)-Br(1)	118.2(3)
C(2)-C(1)-Br(1)	120.3(3)
C(1)-C(2)-C(3)	119.1(3)
C(1)-C(2)-H(2)	120.5
C(3)-C(2)-H(2)	120.5
C(2)-C(3)-C(4)	120.2(3)
C(2)-C(3)-H(3)	119.9
C(4)-C(3)-H(3)	119.9
C(3)-C(4)-C(8)	120.5(3)
C(3)-C(4)-N(1)	122.4(3)
C(8)-C(4)-N(1)	117.2(3)
C(10)-N(1)-C(4)	124.3(2)
C(10)-N(1)-C(5)	117.7(3)
C(4)-N(1)-C(5)	117.5(2)
N(1)-C(5)-C(6)	109.0(3)
N(1)-C(5)-C(13)	111.0(3)
C(6)-C(5)-C(13)	112.6(3)
N(1)-C(5)-H(5)	108.0
C(6)-C(5)-H(5)	108.0
C(13)-C(5)-H(5)	108.0
C(7)-C(6)-C(5)	122.0(3)
C(7)-C(6)-H(6)	119.0
C(5)-C(6)-H(6)	119.0
C(6)-C(7)-C(8)	120.7(3)
C(6)-C(7)-H(7)	119.7
C(8)-C(7)-H(7)	119.7
C(9)-C(8)-C(4)	119.0(3)

C(9)-C(8)-C(7)	122.1(3)
C(4)-C(8)-C(7)	118.9(3)
C(1)-C(9)-C(8)	119.6(3)
C(1)-C(9)-H(9)	120.2
C(8)-C(9)-H(9)	120.2
O(1)-C(10)-O(2)	123.6(3)
O(1)-C(10)-N(1)	123.5(3)
O(2)-C(10)-N(1)	112.9(3)
C(10)-O(2)-C(11)	116.5(3)
C(12B)-C(11)-O(2)	110.8(7)
O(2)-C(11)-C(12A)	110.4(5)
O(2)-C(11)-H(11A)	109.6
C(12A)-C(11)-H(11A)	109.6
O(2)-C(11)-H(11B)	109.6
C(12A)-C(11)-H(11B)	109.6
H(11A)-C(11)-H(11B)	108.1
C(11)-C(12A)-H(12A)	109.5
C(11)-C(12A)-H(12B)	109.5
H(12A)-C(12A)-H(12B)	109.5
C(11)-C(12A)-H(12C)	109.5
H(12A)-C(12A)-H(12C)	109.5
H(12B)-C(12A)-H(12C)	109.5
C(11)-C(12B)-H(12D)	109.5
C(11)-C(12B)-H(12E)	109.5
H(12D)-C(12B)-H(12E)	109.5
C(11)-C(12B)-H(12F)	109.5
H(12D)-C(12B)-H(12F)	109.5
H(12E)-C(12B)-H(12F)	109.5
C(15)-C(13)-C(14)	113.7(3)
C(15)-C(13)-C(5)	111.0(3)
C(14)-C(13)-C(5)	111.9(3)
C(15)-C(13)-H(13)	106.6
C(14)-C(13)-H(13)	106.6
C(5)-C(13)-H(13)	106.6
O(3)-C(14)-C(13)	114.5(3)
O(3)-C(14)-H(14A)	108.6
C(13)-C(14)-H(14A)	108.6
O(3)-C(14)-H(14B)	108.6
C(13)-C(14)-H(14B)	108.6
H(14A)-C(14)-H(14B)	107.6
C(14)-O(3)-H(3A)	109.5

C(20)-C(15)-C(16)	117.5(3)
C(20)-C(15)-C(13)	120.7(3)
C(16)-C(15)-C(13)	121.9(3)
C(17)-C(16)-C(15)	120.8(4)
C(17)-C(16)-H(16)	119.6
C(15)-C(16)-H(16)	119.6
C(18)-C(17)-C(16)	120.6(5)
C(18)-C(17)-H(17)	119.7
C(16)-C(17)-H(17)	119.7
C(17)-C(18)-C(19)	119.6(4)
C(17)-C(18)-H(18)	120.2
C(19)-C(18)-H(18)	120.2
C(18)-C(19)-C(20)	120.0(5)
C(18)-C(19)-H(19)	120.0
C(20)-C(19)-H(19)	120.0
C(15)-C(20)-C(19)	121.5(4)
C(15)-C(20)-H(20)	119.3
C(19)-C(20)-H(20)	119.3

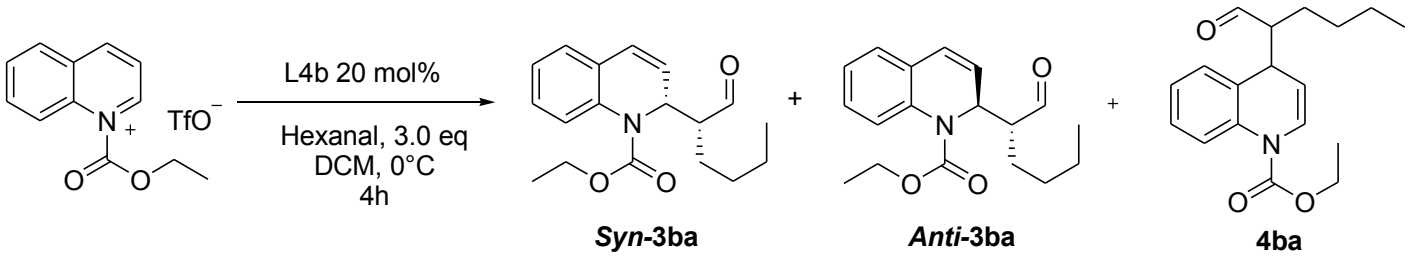
Mechanistic Insights: Replacing the *N,O*-acetal 1b with a preformed quinolinium ion

Synthesis of quinolinium triflate A



The ethoxycarbonylquinolinium triflate **A** was synthesized following a previously reported procedure.[8] A 25 mL oven-dried Schlenk tube, under Argon protection, was charged with **1b** (742 mg, 3.0 mmol) and toluene. The resulting colourless solution was cooled at 0 °C and trimethylsilyl trifluoromethanesulfonate (667 mg, 0.54 mL, 3.0 mmol) was added dropewise over 15 minutes. Upon addition of TMSOTf, a fine white solid is formed. The reaction mixture was allowed to stir for 30 min at 0 °C and 45 min at rt then it was filtered. The resulting solid was washed with Et_2O and dried 3 hours under vacuum to afford the title compound **A** (917 mg, 87%). Spectral data are consistent with the literature.[8]

Orgacatalyzed alkylation using isolated quinolinium triflate

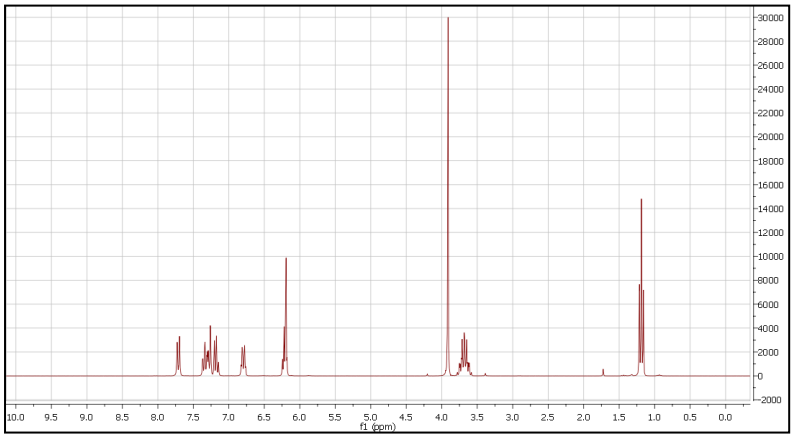


A flame-dried 10 mL Schlenk tube was charged with **A** (57 mg, 0.15 mmol) followed by DCM (0.60 mL) under argon atmosphere. The resulting solution was cooled at 0 °C and **L3b** (0.03 mmol, 19 mg) and distilled hexanal (45μL, 0.45 mmol) were added. The reaction mixture was allowed to react at the same temperature for 4 hour. The reaction was quenched by adding water (5 mL) and the aqueous phase was extracted with ether (3x10 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated under vaccum to afford a yellowish oil. The analysis of the reaction crude by ^1H NMR showed a regioisomeric ratio of **4ba/3ba** = 7/93, a diasteroisomeric ratio of **3ba**-*syn*/**3ba**-*anti* = 65/35 and 38% of quinoline (with respect to the products). Subsequent flash chromatography (7 hexanes/3 Et_2O, R_f= 0.25) gave a colourless oil as mixture of **3ba**-*syn*+*anti* (23

mg, 50%). The ee was determined by Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 98:2) flow rate 1.0 ml/min; 220 nm; **3ba-***syn* t_R (minor) = 11.2 min, t_R (major)= 13.2 min; 44 %ee; **3ba-***anti* t_R (minor) = 10.3 min, t_R (major)= 10.9 min; 54% ee.

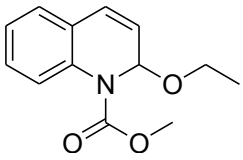
Mechanistic Insights: Optimized reaction condition analyzed by ^{1}H NMR

A dried NMR tube was loaded with *N-O* acetal **1a** (23 mg, 0.1 mmol), propionaldehyde (17 mg, 0.30 mmol), **L3b** (12 mg, 0.02 mmol) and toluene-d_8 (0.40 mL). After 5 minutes a ^{1}H NMR was recorded (t_0) and *p*-toluensulfonic acid was added at room temperature. The subsequent ^{1}H NMR spectra were recorded according to the indicated time. Signals of the corresponding enamine (6.31 and 4.10 ppm) cannot be detected (see, M. B. Schmid, K. Zeitler, and R. M. Gschwind, R., *J. Am. Chem. Soc*. 2011, **133,** 7065).



N-O Acetal **1a**

^{1}H NMR (250 MHz, $CDCl_3$)



N,O-acetal **1a,** propionaldehyde, **L3b**, Tol-d_8, *t*=0 min

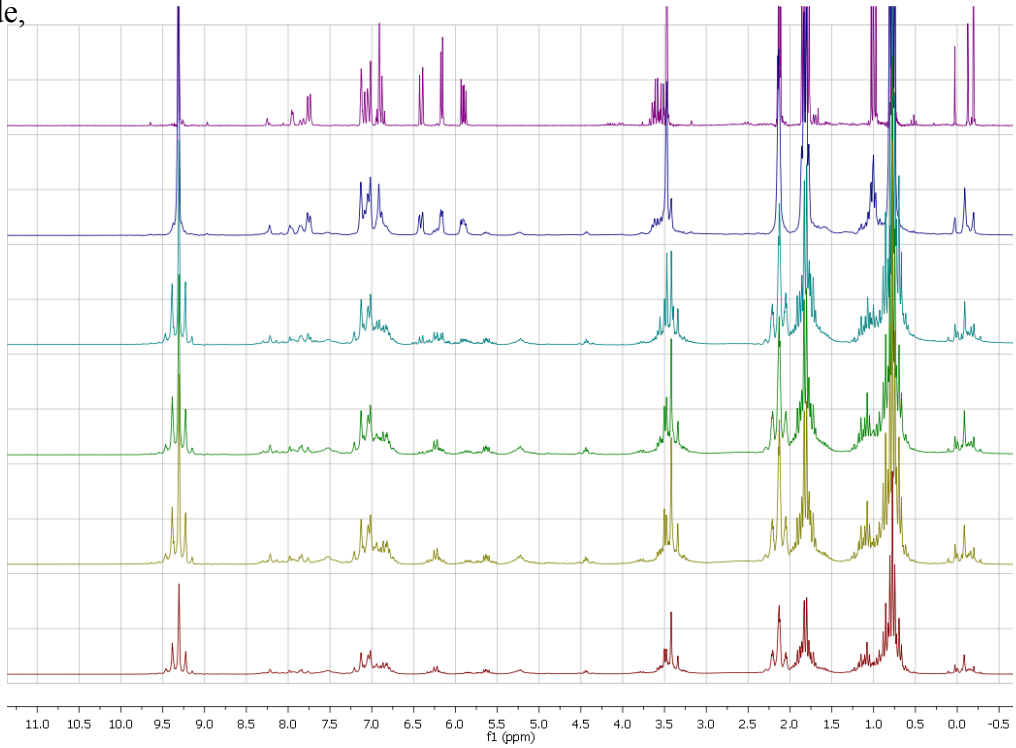
+TsOH, *t*=5 min

t=15 min

t=30 min

t=1 h

t=1.5 h



General Procedure for the enantioselective alkylation of quinolines with aldehydes.

General Procedure A (without in situ reduction)

An oven-dried 10 mL pyrex vial was charged with the specified *N,O*-acetal **1a-f** (1.0 eq) in toluene (0.25 M) and **L3b** (20 mol%) and the appropriate aldehyde (3.0 eq). The resulting solution was cooled to the specified temperature and added with anhydrous *p*-toluensulfonic acid (20 mol%). The mixture was allowed to react until no *N,O*-acetal was detected by TLC (pre-treated with 10% triethylamine in hexanes), quenched with water (5 ml per 0.20 mmol of *N,O*-acetal), extracted three times with Et_2O and the combined organic phases were dried over $MgSO_4$. Removal of solvents afforded a crude which was purified by flash chromatography or/and preparative TLC.

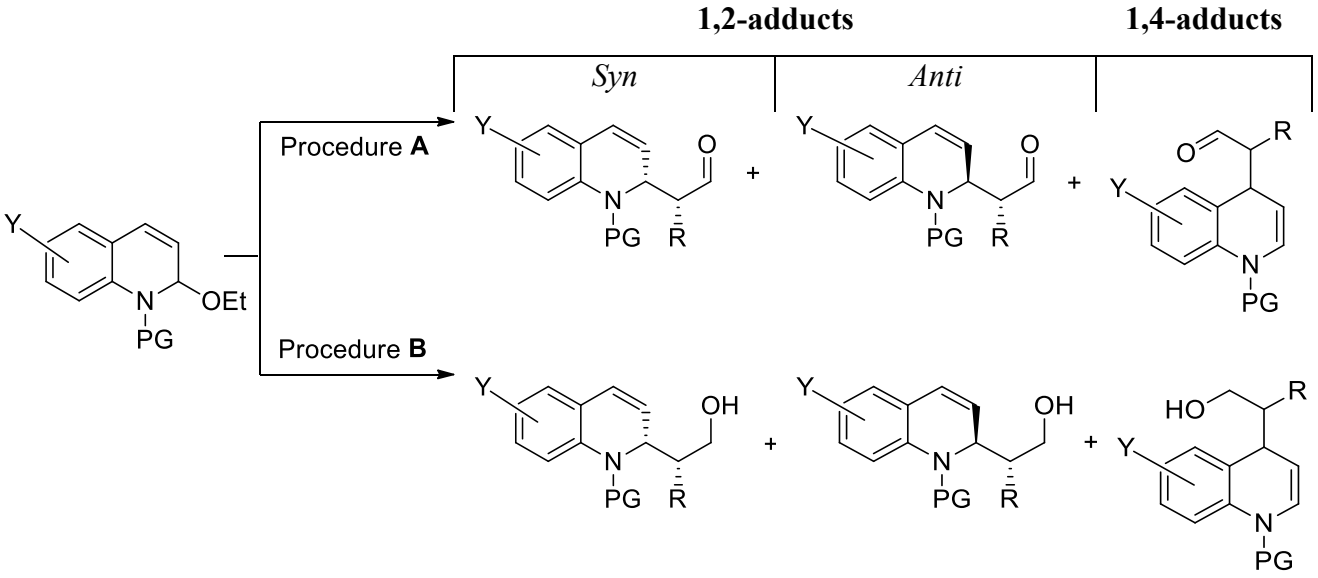
General Procedure B (with in situ reduction)

An oven-dried 10 mL pyrex vial was loaded with the specified *N-O* acetal **1a-f** (1.0 eq) in toluene (0.25 M) and **L3b** (20 mol%) and the appropriate aldehyde (3.0 eq). The resulting solution was cooled to the specified temperature and added with anhydrous *p*-toluensulfonic acid (20 mol%). The mixture was allowed to react until no *N,O*-acetal was detected by TLC (pre-treated with 10% triethylamine in hexanes). The solution was then cooled at 0 °C, diluted with methanol (0.40 mL per 0.20 mmol of *N,O*-acetal) and additioned with sodium borohydride (6.0 eq). Upon disappearance of aldehyde **3**, the reaction mixture was quenched with water (5 ml per 0.20 mmol of *N,O*-acetal) and the resulting aqueous layer was extracted with Et_2O four times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a residue which was purified by flash chromatography or/and preparative TLC.

The racemic products were prepared following the general procedure A or B:
- **3aa**, **3ad**, **3ba**, **3cd**, **3ga**, **5ad**, **5cd**, **5ha**, replacing **L3b** with pyrrolidine (20 mol%);
- **3ab**, **3da**, **3ed**, **3ef**, **5ab**, **5ac**, **5cc**, **5dc**, **5ec**, **5ed**, replacing **L3b** with *(R)*-**L1** (10 mol%) and *(S)*-**L1** (10 mol%) and replacing *p*-toluensulfonic acid with $In(OTf)_3$ (20 mol%).

Note: the 1,4-adducts of both type **4** and **6** were in some cases not isolated in a pure state and the corresponding NMR spectra have not been reported.

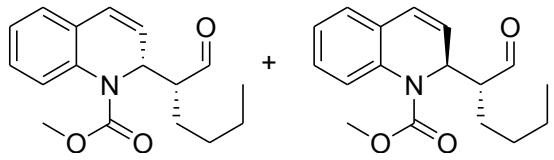
Table 6: Overview of Products



Expanded Table 6

Entry	Y	PG	R	General Procedure	Q[a] (%)	1,2/1,4 add.[b]	1,2:Syn /Anti [b]
1	H	CO_2Me	H	A	6%	95/5	-
2	H	CO_2Me	H	B	8%	95/5	-
3	H	CO_2Me	Ph	B	<1%	81/19	77/33
4	H	CO_2Me	CH_3	A	4%	90/10	82/18
5	H	CO_2Me	CH_3	B	2%	91/9	83/17
6	H	CO_2Et	C_4H_9	A	5%	92/8	78/22
7	H	Cbz	H	A	<1%	96/4	-
8	H	Cbz	H	B	<1%	96/4	-
9	H	Cbz	Ph	B	<1%	n.d.	77/33
10	H	Cbz	CH_3	A	<1%	89/11	80/20
11	6-Br	CO_2Et	Ph	B	<1%	n.d.	73/27
12	6-Br	CO_2Et	C_4H_9	A	2%	88/12	71/29
13	6-NO_2	CO_2Et	CH_3	B	<1%	81/19	65/35
14	6-NO_2	CO_2Et	CH_3	B	<1%	81/19	65/35
15	6-NO_2	CO_2Et	Ph	B	<1%	80/20	70/30
16	6-OMe	CO_2Et	C_4H_9	A	3%	91/9	65/35
17	6-Me	CO_2Et	C_4H_9	A	<1%	88/12	71/29
18	4-Me	CO_2Et	C_4H_9	B	5%	Na	63/37

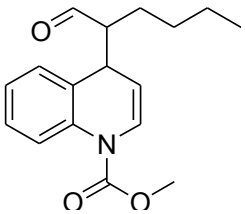
[a] Q=corresponding quinoline; [b] Regio- and diastereoselectivity determined by ^{1}H NMR of the reaction crude.



(*R*)-Methyl 2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-methyl 2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate (3aa-*syn* + *anti*)

According the general procedure A, *N,O*-acetal **1a** (34 mg, 0.15 mmol), **L3b** (18 mg, 0.03 mmol), freshly distilled hexanal (45 mg, 0.45 mmol), anhydrous *p*-toluensulfonic acid (5 mg, 0.03 mmol), toluene (0.60 mL) was allowed to react at 0 °C for 15h. Subsequent flash chromatography (8 hexanes /2 Et_2O, R_f=0.29) afforded a colourless oil (38 mg, 89%) as inseparable mixture of **3aa**-*syn(I)* and **3aa**-*anti(II)*. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.54 (d, 1H, *J* = 2.9 Hz, $H_{(II)}$), 9.44 (d, $1H_{(I)}$, *J* = 4.5 Hz), 7.54 –7.04 (m, $4H_{(II+I)}$), 6.65-6.49 (m, $1H_{(II+I)}$), 6.08 (dd, $1H_{(II+I)}$, *J* = 9.5, 6.0 Hz), 5.39 – 5.24 ($m_{(II+I)}$, 1H), 3.80 (s, $3H_{(II)}$), 3.77 (s, $3H_{(I)}$), 2.54 – 2.40 (m, $1H_{(II)}$) 2.38 – 2.24 (m, $1H_{(I)}$), 1.80 – 1.62 (m, $1H_{(II+I)}$), 1.62 – 1.47 (m, $1H_{(II+I)}$), 1.37-1.10 (m, $4H_{(II+I)}$), 0.83 (t, $3H_{(II+I)}$, J = 6.8 Hz,). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ $202.7_{(II+I)}$, $154.9_{(II+I)}$, 134.2, 128.2, 128.1, 127.2, 126.7, 126.5, 126.4, 125.2, 125.0, 124.8, $56.6_{(I)}$, $55.9_{(II)}$, $53.4_{(II+I)}$, $52.2_{(II+I)}$, $29.8_{(I)}$, $29.4_{(II)}$, $25.3_{(II+I)}$, $22.7_{(II+I)}$, $13.8_{(II+I)}$.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 97:3) flow rate 1.0 ml/min; 220 nm; **3aa**-*syn* t_R (minor) = 10.3 min, t_R (major)= 11.8 min, 95.6%; **3aa**-*anti* t_R (minor) = 9.2 min, t_R (major)= 9.7 min, 77.6%ee.



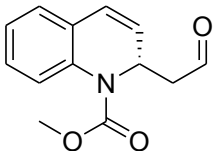
Methyl 4-(1-oxohexan-2-yl)quinoline-1(4H)-carboxylate (4aa-*syn* +*anti*)

The faster eluting fraction of the above flash chromatography (8 hexanes /2 Et_2O, R_f=0.46) gave the title compound as inseparable mixture of **4aa**-*syn* and **4aa**-*anti* (3 mg, 7%). Major diastereomer (I), minor diastereomer (II).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.69 – 9.60 (m, $1H_{(II+I)}$), 8.01 (d, *J* = 8.4 Hz, $1H_{(II+I)}$), 7.32 – 7.04 (m, $4H_{(II+I)}$), 5.39 (dd, $1H_{(II)}$, *J* = 7.6, 6.1 Hz), 5.29 (dd, $1H_{(I)}$, *J* = 7.6, 6.0 Hz), 3.91 (s, $3H_{(II+I)}$), 3.86 – 3.80 (m, $1H_{(I)}$), 3.74 (t, $1H_{(II)}$, *J* = 6.2 Hz), 2.57 – 2.43 (m, $1H_{(I+II)}$), 1.80 – 1.67 (m, $1H_{(II+I)}$), 1.55 – 1.40 (m, $1H_{(II+I)}$), 1.36 – 1.04 (m, $4H_{(II+I)}$), 0.93-0.78 (m, $3H_{(II+I)}$).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 204.6, 204.4, 153.0, 137.2, 137.1, 129.5, 128.9, 128.6, 128.4, 128.4, 128.3, 128.1, 127.2, 127.1, 125.3, 125.2, 121.7, 110.6, 110.0, 58.8, 58.7, 53.6, 38.9, 38.7, 29.8, 29.7, 26.2, 25.4, 22.9, 22.8, 13.9, 13.9.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 97:3); flow rate 1.0 mL/min; 220 nm; (I) t_R (major) = 8.0 min, t_R (minor) = 8.5 min 95%ee; (II) t_R (minor) = 9.7 min, t_R (major) = 11.2 min, 99% ee.



(*S*)-Methyl 2-(2-oxoethyl)quinoline-1(2*H*)-carboxylate (3ab)

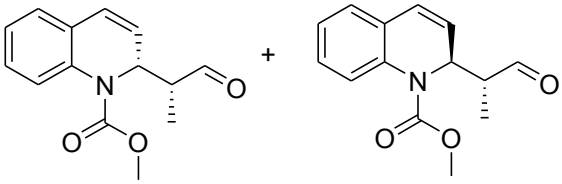
Following the general procedure A, *N,O*-acetal **1a** (47 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), acetaldehyde (26 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) were allowed to react at 0 °C for 2h. Subsequent flash chromatography (7 hexanes/3 Et_2O, R_f=0.20) afforded an orange oil (29 mg, 62%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.52 (d, 1H, *J* = 7.2 Hz), 7.24–7.03 (m, 3H), 6.52 (d, 1H, *J* = 9.5 Hz), 6.11 (dd, 1H, *J* = 9.4, 6.0 Hz), 5.56 (dd, 1H, *J* = 13.3, 6.5 Hz), 3.80 (s, 3H), 2.58 (d, 2H, *J* = 6.9 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.8, 154.7, 133.9, 128.1, 128.0, 126.9, 126.6, 126.0, 124.9, 124.8, 53.4, 48.4, 47.5.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{13}H_{13}NO_3Na$ 254.0793, found 254.0792.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; t_R (major) = 13.8 min, t_R (minor)= 18.9 min; 1.6% ee.

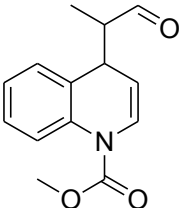


(*R*)-Methyl 2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-methyl 2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-carboxylate (3ad-*syn* + *anti*)

Following the general procedure A, *N-O* acetal **1a** (47 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), propionaldehyde (35 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol) and toluene (0.80 mL) were allowed to react at 0 °C for 5.5h. Subsequent flash chromatography (8 hexanes/2 Et_2O, R_f= 0.17) gave a colourless oil as mixture of **3ad**-*syn*(I) and **3ad**-*anti*(II) (42 mg, 85%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.65 (d, 1H $_{(II)}$, *J* = 1.6 Hz), 9.53 (d, 1H$_{(I)}$, *J* = 2.9 Hz), 7.57 – 7.41 (m, 1H$_{(I+II)}$), 7.29 – 7.19 (m, 1H$_{(I+II)}$), 7.09 (d, 2H$_{(I+II)}$, *J* = 4.2 Hz), 6.64 – 6.51 (m, 1H$_{(I+II)}$), 6.14 (dd, 1H$_{(II)}$ *J* = 9.6, 5.9 Hz), 6.06 (dd, 1H$_{(I)}$, *J* = 9.5, 6.0 Hz), 5.36– 5.26 (m, 1H$_{(I+II)}$), 3.80 (s, 3H$_{(II)}$), 3.79 (s, 3H$_{(I)}$), 2.63 – 2.44 (m, 1H$_{(I+II)}$), 1.05 (d, 3H$_{(II)}$, *J* = 7.3 Hz,), 1.05 (d, 3H$_{(I)}$, *J* = 7.3 Hz).

^{13}CNMR (62.5 MHz, $CDCl_3$) δ 203.2, 202.8, 128.7, 128.6, 128.1, 127.5, 127.1, 127.0, 126.9, 125.5, 125.5, 125.6, 54.8, 54.0, 53.9, 53.8, 53.6, 52.3, 50.5, 34.7, 31.0, 31.0, 30.4, 24.0, 23.3, 10.8, 10.7, 10.5.

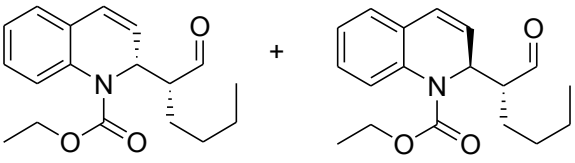


Methyl 4-(1-oxopropan-2-yl)quinoline-1(4*H*)-carboxylate (4ad-s*yn*+*anti*)

The faster eluting fraction of the above flash chromatography (8Hex/2Et_2O, Rf= 0.21) the title compound was recovered as a colourless oil (3 mg, 7%). Major diastereomer (I), minor diastereomer (II).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.72 (d, $1H_{(I+II)}$, J = 1.2 Hz), 8.06 – 7.98 (m, $1H_{(I+II)}$), 7.33 – 7.05 (m, $4H_{(I+II)}$) , 5.44 (dd, $1H_{(II)}$, J = 7.6, 6.1 Hz), 5.22 (dd, $1H_{(I)}$, J = 7.8, 5.8 Hz), 3.99 (t, $1H_{(I)}$), 3.91 (s, $3H_{(I+II)}$), 3.77 (t, $1H_{(II)}$, J = 6.1 Hz), 2.75 – 2.54 (m, $1H_{(I+II)}$), 1.05 (m, $3H_{(I+II)}$).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.7, 202.3, 152.4, 134.6, 134.6, 128.2, 128.1, 127.6, 127.0, 126.6, 126.5, 126.3, 125.0, 124.9, 124.7, 53.5, 53.4, 53.3, 53.0, 51.8, 49.9, 10.2, 10.0.



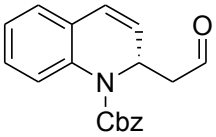
(*R*)-Ethyl 2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-ethyl 2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate (3ba-*syn* + *anti)*

Following the general procedure A, *N,O*-acetal **1b** (49 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), freshly distilled hexanal (60 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) were allowed to react at 0 °C for 16h. Subsequent flash chromatography (7 hexanes/3 Et_2O, R_f= 0.25) gave colourless oil (51 mg, 85%) as inseparable mixture of **3ba-***syn(I)* and **3ba-***anti(II)*.

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.54 (d, $1H_{(II)}$, J = 2.9 Hz), 9.44 (d, $1H_{(I)}$, J = 4.6 Hz), 7.58–7.37 (m, $1H_{(I+II)}$), 7.29–7.16 (m, $1H_{(I+II)}$), 7.09 (d, $2H_{(I+II)}$, J = 4.0 Hz), 6.65-6.50 (m, $1H_{(I+II)}$), 6.08 (dd, $1H_{(I+II)}$, J = 9.5, 6.0 Hz,), 5.31 (dd, $1H_{(I+II)}$, J = 7.9, 6.0 Hz), 4.36–4.10 ($m_{(I+II)}$, 2H), 2.53–2.39 ($m_{(II)}$, 1H), 2.39–2.22 ($m_{(I)}$, 1H), 1.81–1.46 ($m_{(I+II)}$, 2H), 1.39–1.05 ($m_{(I+II)}$, 7H), 0.84 ($3H_{(I+II)}$, t, J = 6.8 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ $202.8_{(I+II)}$, $154.4_{(I+II)}$, 134.4, 128.1, 128.0, 127.2, 126.8, 126.5, 126.4, 125.3, 124.8, 124.8, 62.6, 62.5, $56.7_{(II)}$, $56.0_{(I)}$, $52.1_{(II)}$, $52.1_{(I)}$, $29.5_{(I+II)}$, $25.3_{(I)}$, $25.3_{(II)}$, $22.8_{(I+II)}$, $14.5_{(I+II)}$, $13.9_{(I+II)}$.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 98:2) flow rate 1.0 ml/min; 220 nm; **3ba**-*syn* t_R (minor) = 11.2 min, t_R (major)= 13.2 min; 83%ee; **3ba**-*anti* t_R (minor) = 10.3 min, t_R (major)= 10.9 min; 76% ee



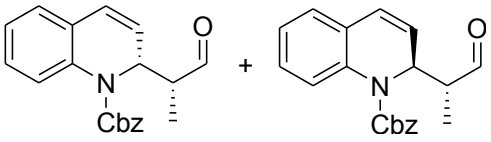
(*S*)-Benzyl 2-(2-oxoethyl)quinoline-1(2*H*)-carboxylate (3cb)

Following the general procedure A, *N,O*-acetal **1c** (62 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), acetaldehyde (26 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) were allowed to react at 0 °C for 16h. Subsequent flash chromatography (7 hexanes/3 Et_2O, R_f=0.18) gave a colourless oil (44 mg, 72%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.67 (t, 1H, *J* = 2.0 Hz,), 7.55 (d, 1H, *J* = 5.9 Hz), 7.42 – 7.31 (m, 5H), 7.26 – 7.17 (m, 1H), 7.09 (d, 2H, *J* = 4.2 Hz), 6.52 (d, *J* = 9.5 Hz, 1H), 6.10 (dd, 1H, *J* = 9.5, 6.0 Hz), 5.58 (dd, 1H, *J* = 6.5, 6.5 Hz), 5.30 (d, 1H, *J* = 12.3 Hz), 5.20 (d, 1H, *J* = 12.3 Hz), 2.61 – 2.54 (m, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 199.7, 154.0, 136.0, 133.9, 128.7, 128.4, 128.2, 128.1, 127.9, 126.9, 126.6, 126.0, 124.9, 124.8, 68.2, 48.5, 47.5.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{17}NO_3Na$ 330.1106, found 330.1105.

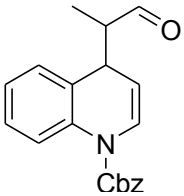


(*R*)-Benzyl 2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-benzyl 2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-carboxylate (3cd-*syn* +*anti*)

Following the general procedure A, *N,O*-acetal **1c** (62 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), propionaldehyde (35 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol) and toluene (0.80 mL) were allowed to react at 0 °C for 13h. Subsequent preparative TLC (7 hexanes/3 Et_2O, 4 runs, R_f= 0.67) afforded a colourless oil as a mixture of **3cd-***syn*(*I*) and **3cd-***anti*(*II*) (55mg, 85%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.63 (d, $1H_{(II)}$, *J* = 1.5 Hz), 9.52 (d, $1H_{(I)}$, *J* = 2.8 Hz), 7.62 – 7.46 (m, $1H_{(I+II)}$), 7.43 – 7.17 (m, $6H_{(I+II)}$), 7.09 (d, $2H_{(I+II)}$, *J* = 4.9 Hz), 6.64 – 6.51 (m, $1H_{(I+II)}$), 6.13 (dd, $1H_{(II)}$, *J* = 9.6, 5.9 Hz), 6.04 (dd, $1H_{(I)}$, *J* = 9.6, 6.0 Hz), 5.38 – 5.14 (m, $3H_{(I+II)}$), 2.62 – 2.45 (m, $1H_{(I+II)}$), 1.07 (d, $3H_{(I)}$, *J* = 7.1 Hz), 1.04 (d, $3H_{(II)}$, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.5, 202.2, 154.5, 154.3, 136.0, 135.9, 134.6, 128.7, 128.4, 128.1, 128.0, 127.4, 127.3, 127.2, 127.0, 126.6, 126.5, 126.3, 126.0, 125.0, 124.9, 124.8, 68.3, 68.2, 53.3, 53.0, 51.8, 49.9, 10.2, 10.0.



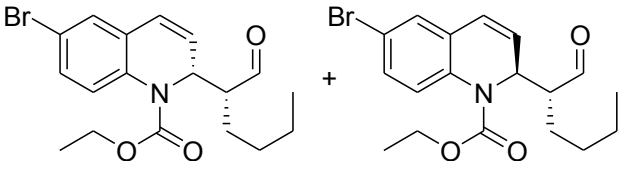
Benzyl 4-(1-oxopropan-2-yl)quinoline-1(4*H*)-carboxylate (4cd-*syn* +*anti*)

From the above preparative TLC (R_f=0.75) was collected a colourless oil as mixture of **4cd-***syn* and **4cd-***anti* (5 mg, 7%). Major diastereomer (I), minor diastereomer

(II).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.69 (s, 1H$_{(I+II)}$), 8.05 – 7.96 (m, 1H$_{(I+II)}$), 7.46 – 7.02 (m, 9H$_{(I+II)}$), 5.41 (dd, 1H$_{(II)}$, J = 7.6, 6.1 Hz), 5.31 (s, 2H$_{(I+II)}$), 5.19 (dd, 1H$_{(I)}$, J = 7.8, 5.8 Hz), 4.01 – 3.94 (m, 1H$_{(I)}$), 3.76 (t, 1H$_{(II)}$, J = 6.0 Hz), 2.72 – 2.55 (m, 1H$_{(I+II)}$), 1.01 (d, 3H$_{(I+II)}$, J = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.9, 203.8, 152.4, 137.2, 135.9, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 128.3, 128.3, 128.1, 127.9, 127.2, 127.0, 125.4, 125.2, 121.8, 111.4, 109.2, 68.3, 68.3, 53.7, 53.3, 39.4, 38.3, 31.1, 29.8, 10.9, 8.9.



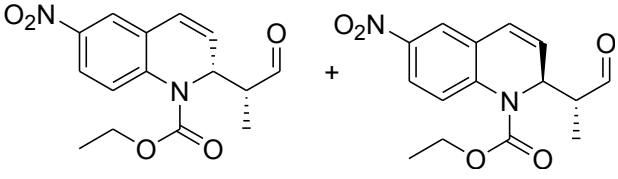
(*R*)-Ethyl 6-bromo-2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-ethyl 6-bromo-2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate (3da-*syn* + *anti*)

Following the general procedure A, *N,O*-acetal **1d** (65 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), freshly distilled hexanal (60 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) were allowed to react at room temperature for 3 days. Subsequent flash chromatography (8 hexanes/2 Et_2O, R_f= 0.21) gave amorphous white solid (61 mg, 80%) as a mixture of **3da-***syn(I)* and **3da**-*anti(II)*.

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.56 (d, 1H$_{(I)}$, J = 2.7 Hz), 9.45 (d, 1H$_{(II)}$, J = 4.6 Hz), 7.48 – 7.29 (m, 2H$_{(I+II)}$), 7.25 – 7.20 (m, 1H$_{(I+II)}$), 6.56 – 6.42 (m, 1H$_{(I+II)}$), 6.14 (dd, 1H$_{(II)}$, J = 9.5, 6.0 Hz), 6.13 (dd, 1H$_{(I)}$, J = 9.5, 6.0 Hz), 5.35 – 5.25 (m, 1H$_{(I+II)}$), 4.38 – 4.10 (m, 2H$_{(I+II)}$), 2.51 – 2.41 (m, 1H$_{(II)}$), 2.36 – 2.22 (m, 1H$_{(II)}$), 1.82 – 1.62 (m, 1H$_{(I+II)}$), 1.58 – 1.44 (m, 1H$_{(I+II)}$), 1.35 – 1.04 (m$_{(I+II)}$, 7H), 0.84 (t, J = 6.9 Hz, 3H$_{(I+II)}$).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ (202.5, 154.0, 133.4, 130.8, 130.7, 129.1, 129.0, 128.9, 128.6, 127.8, 126.8, 126.4, 125.7, 125.3, 117.73, 117.68) $_{(I+II)}$, 62.82$_{(I)}$, 62.77$_{(II)}$, 56.6$_{(II)}$, 56.0$_{(I)}$, 52.1$_{(II)}$, 52.0$_{(I)}$, 29.5$_{(I+II)}$, 25.3$_{(I+II)}$, 22.7$_{(I+II)}$, 14.51$_{(II)}$, 14.46$_{(I)}$, 13.4$_{(I+II)}$.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 97:3) flow rate 1.0 ml/min; 220 nm; **3da-***syn* t_R (major) = 7.8 min, *t*R (minor)= 8.8 min; 99.2%; **3da-***anti* t_R (major) = 7.0 min, t_R (minor)= 8.2 min; 91.0%.



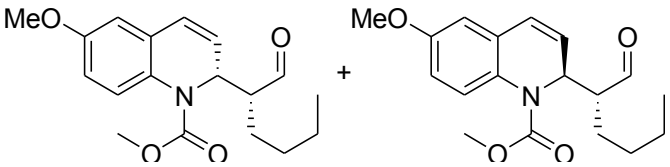
(*R*)-Ethyl 6-nitro-2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-carboxylate and (*S*)-ethyl 6-nitro-2-((*R*)-1-oxopropan-2-yl)quinoline-1(2*H*)-

carboxylate (3ed-*syn*+*anti*)

Following the general procedure A, *N,O*-acetal **1e** (59 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), propionaldehyde (35 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) r were allowed to react at room temperature for 29h. Subsequent flash chromatography (6 hexanes/4 Et_2O, R_f=0.15) gave a green oil as inseparable mixture of **3ed**-*syn(I)* and **3ed-***anti(II)* (44 mg, 72%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.67 (d, 1H$_{(II)}$, *J* = 1.3 Hz), 9.55 (d, 1H$_{(I)}$, *J* = 2.7 Hz), 8.14 – 8.05 (m, 1H$_{(I+II)}$), 7.98 (d, 1H$_{(I+II)}$, *J* = 2.6 Hz), 7.74 (dd, 1H$_{(I+II)}$,*J* = 9.0, 7.0 Hz,), 6.65 (m, 1H$_{(I+II)}$), 6.28 (dd, 1H$_{(II)}$, *J* = 9.6, 6.0 Hz), 6.16 (dd, 1H$_{(I)}$, *J* = 9.7, 6.0 Hz), 5.47 – 5.36 (m, 1H$_{(I+II)}$), 4.38 – 4.23 (m, 2H$_{(I+II)}$), 2.65 – 2.46 (m, 1H$_{(I+II)}$), 1.34 (t, 3H$_{(II)}$, *J* = 7.1 Hz), 1.33 (t, 3H$_{(I)}$, *J* = 7.1 Hz) 1.09 (t, 3H$_{(II)}$, *J* = 6.3 Hz), 1.04 (d, 3H$_{(I)}$, *J* = 7.2 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.8$_{(I)}$, 201.4$_{(II)}$, (154.0, 153.7) $_{(I+II)}$, (144.0, 143.9) $_{(I+II)}$, (140.9, 140.8) $_{(I+II)}$, 129.7$_{(II)}$, 128.0$_{(I)}$, 127.5$_{(II)}$, 127.3$_{(I)}$, 125.8$_{(I)}$, 125.1$_{(II)}$, 124.8$_{(I)}$, 124.7$_{(II)}$, 123.3$_{(I)}$, 123.2$_{(II)}$, 121.8$_{(I+II)}$, (63.43, 63.39) $_{(I+II)}$, 53.4$_{(I)}$, 53.3$_{(II)}$, 52.3$_{(II)}$, 50.8$_{(I)}$, 14.4$_{(I+II)}$, 9.8$_{(I)}$, 9.7$_{(II)}$.

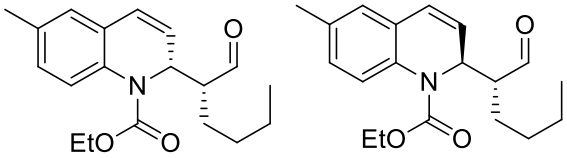


(*R*)-Methyl 6-methoxy-2-((*R*)-1-oxohexan-2-yl)quinoline-1(2H)-carboxylate and (*S*)-methyl 6-methoxy-2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate (3fa-*syn*+*anti*)

Following the general procedure A, *N,O*-acetal **1e** (45 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), hexanal (60 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL) were allowed to react at room temperature for 2d. Subsequent flash chromatography (7 hexanes/3 Et_2O, R_f=0.18) gave an oil as inseparable mixture of **3fa-***syn (I)* and **3fa-***anti(II)* (35 mg, 56%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, 1H$_{(II)}$, *J* = 2.8 Hz), 9.40 (d, 1H$_{(I)}$, *J* = 4.5 Hz), 7.3 (bs, 1H$_{(I+II)}$), 6.79 (dd, 1H$_{(I+II)}$, *J* = 8.7, 2.7 Hz,), 6.62 (d, 1H$_{(I+II)}$, *J* = 2.7 Hz), 6.57 – 6.46 (m, 1H$_{(I+II)}$) , 6.11 (dd, 1H$_{(I+II)}$, *J* = 9.4, 6.0 Hz), 5.29 (bs, 1H$_{(I+II)}$), 4.36 – 4.07 (m, 2H$_{(I+II)}$), 3.79 (s, 3H$_{(I+II)}$), 2.55 – 2.41 (m, 1H$_{(II)}$), 2.38 – 2.22 (m, 1H$_{(I)}$), 1.81 – 1.47 (m, 2H$_{(I+II)}$), 1.40 – 1.07 (m, 5H$_{(I+II)}$), 0.84 (t, *J* = 6.8 Hz, 3H$_{(I+II)}$).

^{13}C NMR (62.5 MHz, CDCl3) δ 202.9, 156.7, 142.0, 128.3, 127.8, 127.3, 126.8, 126.5, 120.0, 113.7, 111.1, 62.5, 56.5, 55.9, 55.5, 52.3, 29.9, 29.5, 25.4, 25.4, 22.8, 14.6, 14.5, 13.9.



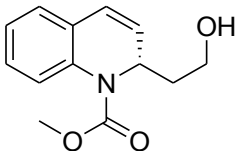
(*R*)-Ethyl 6-methyl-2-((*R*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate and (*R*)-ethyl 6-methyl-2-((*S*)-1-oxohexan-2-yl)quinoline-1(2*H*)-carboxylate (3ga-*syn*+*anti)*

Following the general procedure B, *N,O*-acetal **1g** (52 mg, 0.20 mmol), **L4b** (25 mg, 0.04 mmol), hexanal (60 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at room temperature for 17h. Subsequent flash chromatography (8 hexanes/2 Et_2O, R_f=0.20) afforded an oil (55 mg, 87%) as mixture of **3ga-*syn****(I)* and **3ga-*anti*** *(II*).

^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, 1H$_{(II)}$, *J* = 2.9 Hz), 9.42 (d, 1H$_{(I)}$, *J* = 4.6 Hz), 7.43 – 7.27 (m, 1H$_{(I+II)}$), 7.04 (dd, 1H$_{(I+II)}$, *J* = 8.3, 1.5 Hz), 6.90 (d, 1H$_{(I+II)}$, *J* = 1.5 Hz), 6.59 – 6.47 (m, 1H$_{(I+II)}$), 6.06 (dd, 1H$_{(I+II)}$, *J* = 9.5, 6.0 Hz), 5.29 (dd, 1H$_{(I+II)}$, *J* = 7.8, 6.0 Hz), 4.37 – 4.12 (m, 2H$_{(I+II)}$), 2.30 (s, 3H$_{(I+II)}$, *J* = 9.1 Hz), 1.80 – 1.68 (m, 1H$_{(I+II)}$), 1.60 – 1.46 (m, 1H$_{(I+II)}$), 1.36 – 1.11 (m, 9H$_{(I+II)}$), 0.84 (t, 3H$_{(I+II)}$, *J* = 6.9 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 202.8, 154.6, 134.5, 128.8, 127.1, 126.9, 126.8, 126.5, 125.0, 62.5, 56.7, 56.0, 52.2, 29.8, 29.5, 25.4, 22.8, 20.9, 14.5, 13.9.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 98:2) flow rate 1.0 ml/min; 220 nm; **3ga**-*syn* t_R (minor) = 10.3 min, t_R (major)= 11.0 min; 99%ee; **3ga**-*anti* t_R (minor) = 9.4 min, t_R (major)= 9.9 min; 99% ee.



(*S*)-Methyl 2-(2-hydroxyethyl)quinoline-1(2*H*)-carboxylate (5ab-*syn*)

Following the general procedure B, *N,O*-acetal **1a** (47 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), acetaldehyde (26 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at 0 °C for 3h. Subsequent flash chromatography (6 hexanes/4 AcOEt, R_f=0.21) gave a yellowish oil (35 mg, 75%).

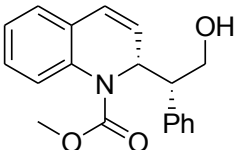
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 (d, 1H, *J* = 6.5 Hz,), 7.24–7.16 (m, 1H), 7.09 (d, 2H, *J* = 4.1 Hz), 6.48 (d, 1H, *J* = 9.6 Hz), 6.05 (dd, 1H, *J* = 9.6, 5.9 Hz,), 5.20–5.09 (m, 1H), 3.83 (s, 3H), 3.66 –3.51 (m, 2H), 3.32 (s, 1H), 1.80–1.63 (m, 1H), 1.58–1.41 (m, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.4, 133.4, 130.0, 127.6, 127.2, 126.5, 124.9, 124.8, 124.6, 58.1, 53.6, 50.0, 34.8.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{13}H_{15}NO_3Na$ 256.0950, found 256.0954.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 92:8) flow rate 0.5 ml/min; 220 nm; t_R (major) = 27.8 min, t_R (minor)= 32.5 min; 15.8% ee.

$[\alpha]^{20}_D$ +73.0 (*c* 0.66, $CHCl_3$).



(*R*)-Methyl 2-((*R*)-2-hydroxy-1-phenylethyl)quinoline-1(2*H*)-carboxylate (5ac-*syn*)

Following the general procedure B, *N,O*-acetal **1a** (47 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), phenylacetaldehyde (90% purity, 80 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at 0 °C for 1.5h. Subsequent flash chromatography (7 hexanes/3 AcOEt) gave an oil (59 mg, 95%) as a mixture of all regio- and diastereomers. The separation of **5ac-***syn* from the mixture of the isomers was accomplished by means of a preparative TLC (7 hexanes/3 AcOEt, 4 runs, R_f=0.52) to afford a white semisolid (36 mg, 58%**)**.

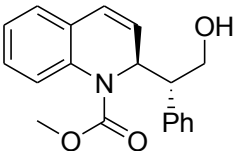
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 – 7.09 (m, 9H), 6.41 (d, 1H, *J* = 9.6 Hz), 5.65 (dd, 1H, *J* = 9.6, 5.9 Hz), 5.38 (dd, 1H, *J* = 11.9, 5.9 Hz), 3.99 (d, 1H, *J* = 9.2 Hz), 3.87 (s, 3H), 3.65 (t, 1H, *J* = 10.1 Hz), 2.70 (d, 1H, *J* = 10.8 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.4, 139.3, 129.5, 129.2, 129.0, 128.6, 128.1, 127.7, 127.3, 126.6, 125.1, 124.9, 124.7, 63.6, 53.7, 53.4, 49.9.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{19}NO_3Na$ 332.1263, found 332.1258

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; t_R (major) = 26.7 min, t_R (minor)= 42.8 min; 95.8% ee.

$[\alpha]^{20}_D$ +359.7 (*c* 0.99, $CHCl_3$)



(*S*)-Methyl 2-((*R*)-2-hydroxy-1-phenylethyl)quinoline-1(2*H*)-carboxylate (5ac-*anti*)

From the above preparative TLC (R_f=0.47) was collected the title compound as a white semisolid (14 mg, 25%).

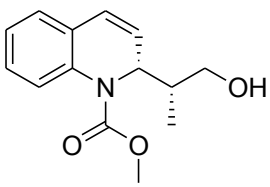
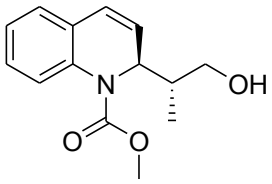
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 6.80 (m, 9H), 6.48 (d, 1H, *J* = 9.7 Hz), 6.13 (dd, 1H, *J* = 9.6, 5.9 Hz), 5.39 (bs, 1H), 4.01 – 3.77 (m, 2H), 3.65 (s, 3H), 2.88 (dd, 1H, *J* = 14.1, 6.8 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.3, 138.0, 135.0, 134.8, 129.0, 128.2, 127.9, 127.5, 127.2, 126.2, 125.3, 124.5, 62.7, 53.8, 53.2, 52.3.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{19}NO_3Na$ 332.1263, found 332.1260

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; t_R (minor) = 30.3 min, t_R (major)= 46.4 min; 89.6% ee.

$[\alpha]^{20}_D$ -261.1 (*c* 0.46, $CHCl_3$)

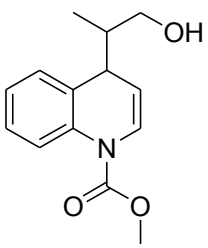
(*R*)-Methyl 2-((*R*)-1-hydroxypropan-2-yl)quinoline-1(2H)-carboxylate and (*R*)-methyl 2-((*S*)-1-hydroxypropan-2-yl)quinoline-1(2*H*)-carboxylate (*Syn*-5ad and *Anti*-5ad)

Following the general procedure B, *N,O*-acetal **1a** (47 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), propionaldehyde (35 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at 0 °C for 6h. The reaction crude was subjected to flash chromatography (7 hexanes/3 Et_2O, R_f=0.18) to give a colourless oil (46 mg, 93%) as a mixture of all isomers. Subsequent preparative TLC (2 hexanes/1 AcOEt/ 2 diisopropyl ether, 5 runs, R_f=0.41) allowed the separation of **5ad**-*syn*(*I*) and **5ad**-*anti*(*II*) as inseparable mixture (40 mg, 81%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (d, 1H$_{(I+II)}$, *J* = 7.0 Hz), 7.24 – 7.02 (m, 3H$_{(I+II)}$), 6.56 (d, 1 H$_{(II)}$, *J* = 10.0 Hz), 6.52 (d, 1H$_{(I)}$, *J* = 9.7 Hz), 6.16 (dd, 1H$_{(I)}$, *J* = 9.6, 6.0 Hz), 5.98 (dd, 1H$_{(II)}$, *J* = 9.7, 5.8 Hz), 5.19 (bs, 1H$_{(II)}$), 4.82 (dd, 1H$_{(I)}$, *J* = 10.6, 6.0 Hz), 3.82 (s, 3H$_{(I)}$), 3.81 (s, 3H$_{(II)}$), 3.70 (d, 1H$_{(I)}$, *J* = 11.9 Hz), 3.51-3.41(m, 2 H$_{(II)}$), 3.33 (t, 1H$_{(I)}$, *J* = 9.7 Hz), 3.08 (bs, 1H), 1.90 – 1.78 (m, 1H$_{(II)}$), 1.67 – 1.53 (m, 1H$_{(I)}$), 1.04 (d, 3H$_{(I)}$, *J* = 6.9 Hz), 0.55 (d, 3H$_{(II)}$, *J* = 6.5 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ (156.4, 135.6, 133.9) $_{(I+II)}$, 129.2$_{(I)}$, 128.9$_{(II)}$, (127.6, 127.6, 126.4, 126.3, 125.77) $_{(I+II)}$, 125.1$_{(I+II)}$, (124.7, 124.8, 124.6, 124.5) $_{(I+II)}$, 63.9$_{(I+II)}$, 54.1$_{(I)}$, 53.7$_{(II)}$, 53.6$_{(I+II)}$, 41.3$_{(II)}$, 38.3$_{(I)}$, 13.2$_{(I)}$, 10.8$_{(II)}$.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; **5ad**-*syn* t_R (major) = 16.9 min, t_R (minor)= 20.1 min, 98.4% ee; **5ad**-*anti* t_R (minor) = 22.6 min, *t*R (major)= 23.5 min, 89% ee.

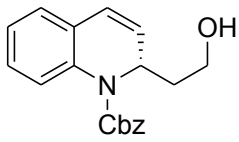


Methyl 4-(1-hydroxypropan-2-yl)quinoline-1(4*H*)-carboxylate (*Syn*-6ad and *Anti*-6ad)

From the above preparative TLC (R_f=0.50) was recovered a colourless oil as inseparable mixture of **4ad**-*syn* and **4ad**-*anti* (3 mg, 6%). Major diastereomer (I), minor diastereomer (II).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 – 7.87 (m, 1H$_{(I+II)}$), 7.24 – 6.99 (m, 4H$_{(I+II)}$), 5.38 (dd, 1H$_{(II)}$, *J* = 7.5, 6.2 Hz), 5.29 (dd, 1H$_{(I)}$, *J* = 7.7, 6.0 Hz), 3.87 (s, 3H$_{(I+II)}$), 3.68 – 3.44 (m, 3H$_{(I+II)}$), 2.01 – 1.80 (m, 1H$_{(I+II)}$), 0.86-0.75 (m, 3H$_{(I+II)}$).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 153.3, 137.1, 130.7, 129.4, 128.7, 127.6, 127.3, 126.6, 126.5, 125.1, 124.9, 121.7, 121.6, 112.7, 110.8, 65.7, 65.2, 53.6, 53.4, 43.5, 42.5, 40.2, 39.7, 13.4, 12.2.



(*S*)-Benzyl 2-(2-hydroxyethyl)quinoline-1(2*H*)-carboxylate (5cb)

Following the general procedure B, *N,O*-acetal **1c** (62 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), acetaldehyde (26 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) reacted at 0 °C for 17h. Subsequent flash chromatography (7 hexanes/3 AcOEt, R_f=0.13) gave a sticky white oil (48 mg, 80%).

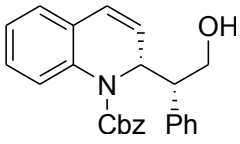
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 6H), 7.22 – 7.11 (m, 1H), 7.08 (d, *J* = 4.0 Hz, 2H), 6.48 (d, 1H, *J* = 9.6 Hz), 6.05 (dd, 1H, *J* = 9.6, 5.9 Hz), 5.43 – 5.27 (m, 1H), 5.26 – 5.10 (m, 2H), 3.68 – 3.41 (m, 2H), 1.82 – 1.60 (m, 1H), 1.50 (t, *J* = 12.5 Hz, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.1, 155.9, 135.8, 133.4, 129.9, 128.8, 128.5, 128.2, 127.5, 127.3, 126.5, 124.9, 124.8, 124.7, 68.4, 58.1, 50.0, 34.8.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{19}NO_3Na$ 332.1263, found 332.1260

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; **5cb** t_R (minor) = 29.9 min, t_R (major)= 41.4 min, 24.6 % ee.

$[\alpha]^{20}_D$ +90.1 (*c* 0.68, $CHCl_3$)



(*R*)-Benzyl 2-((*R*)-2-hydroxy-1-phenylethyl)quinoline-1(2*H*)-carboxylate (5cc-*syn*)

Following the general procedure B, *N,O*-acetal **1c** (62 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), phenylacetaldehyde (90%, 80 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at 0 °C for 1.5h. Subsequent preparative TLC (5 hexanes/5 Et_2O, 5 runs, R_f=0.55) gave a colourless oil (39 mg, 50%). We were unable to recover compound **5cc-*anti*** in an analytically pure state.

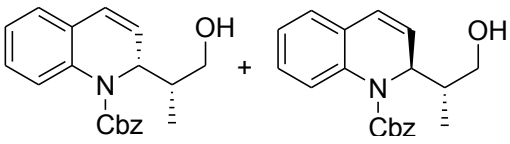
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52 – 7.04 (m, 14H), 6.42 (d, 1H, *J* = 9.6 Hz), 5.66 (dd, 1H, *J* = 9.6, 5.9 Hz), 5.49 – 5.33 (m, 2H), 5.24 (d, 1H, *J* = 12.3 Hz), 3.97 (dd, 1H, *J* = 11.7, 5.0 Hz), 3.78 – 3.55 (m, 1H), 3.30 (bs, 1H), 2.71 (d, 1H, *J* = 11.2 Hz).

^{13}C NMR (63 MHz, $CDCl_3$) δ 155.8, 139.3, 135.8, 133.4, 129.5, 129.2, 128.8, 128.6, 128.5, 128.2, 127.8, 127.6, 127.3, 126.5, 125.1, 125.0, 124.8, 68.6, 63.6, 53.5, 50.0.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{25}H_{23}NO_3Na$ 408.1576, found 408.1571.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 88:22) flow rate 1.0 ml/min; 254 nm; t_R (major) = 19.7 min, t_R (minor)= 24.6 min; 95.6% ee.

$[\alpha]^{20}_D$ +374.4 (*c* 0.73, $CHCl_3$)



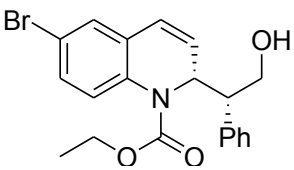
(*R*)-Benzyl 2-((*R*)-1-hydroxypropan-2-yl)quinoline-1(2H)-carboxylate and (*S*)-benzyl 2-((*R*)-1-hydroxypropan-2-yl)quinoline-1(2*H*)-carboxylate (5cd –syn + *anti*)

In a 10 mL round-bottom flask, a mixture of **3cd**-*syn* and **3cd**-*anti* (55 mg, 0.17 mmol) was dissolved in MeOH (1.13 mL) and sodium borohydride (13 mg, 0.34 mmol) was added at 0 °C. The resulting mixture was allowed to react for 30 minutes when water was added (2.0 mL). The aqueous phase was extracted with ethyl ether (4x5 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent afforded a colourless oil as a mixture of **5cd**-*syn*(*I*) and **5cd**-*anti*(*II*) (52 mg, 94%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 6.99 (m, 18H$_{(I+II)}$), 6.60 6.49 (m, 1H$_{(I+II)}$, *J* = 8.2 Hz), 6.15 (dd, 1H$_{(I)}$, *J* = 9.5, 5.9 Hz), 5.98 (dd, 1H$_{(II)}$, *J* = 9.6, 5.8 Hz), 5.43 – 5.11 (m$_{(I+II)}$, 5H), 4.84 (dd, 1H$_{(I)}$, *J* = 10.5, 6.0 Hz), 3.69 (d, 1H$_{(I)}$, *J* = 11.2 Hz), 3.46 (d, 2H$_{(II)}$, *J* = 6.7 Hz), 3.33 (d, 1H$_{(I)}$, *J* = 11.2 Hz), 1.93 – 1.77 (m, 1H$_{(II)}$), 1.75 – 1.55 (m, 1H$_{(I)}$), 1.03 (d, 3H$_{(I)}$, *J* = 6.8 Hz), 0.56 (bs, 3H$_{(II)}$)

^{13}C NMR (63 MHz, $CDCl_3$) δ 154.5, 135.9, 135.8, 135.5, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 126.4, 126.3, 125.8, 124.8, 124.7, 124.6, 68.4, 63.9, 54.1, 53.7, 41.3, 38.3, 13.2.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 95:5) flow rate 1.0 ml/min; 220 nm; ***Syn*-5cd** t_R (major) = 23.5 min, t_R (minor) = 30.2 min; 59.2% ee; ***Anti*-5cd** t_R (major) = 34.1 min, t_R (minor)= 43.4 min; 62.0% ee.



(*R*)-Ethyl 6-bromo-2-((R)-2-hydroxy-1-phenylethyl)quinoline-1(2*H*)-carboxylate (5dc-syn)

Following the general procedure B, *N,O*-acetal **1d** (65 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), phenylacetaldehyde (90% purity, 80 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) was allowed to react at 0 °C for 1h. Subsequent preparative TLC (5 hexanes/5 Et_2O, R_f=0.51) provided a white solid **(**31 mg, 36%). M.p.=137-139 °C

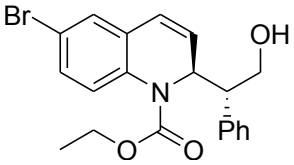
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.20 (m, 8H), 6.34 (d, 1H, *J* = 9.6 Hz), 5.70 (dd, 1H *J* = 9.6, 5.9 Hz), 5.37 (dd, 1H, *J* = 11.0, 5.9 Hz), 4.46 – 4.20 (m, 2H), 3.94 (dd, 1H, *J* = 11.5, 5.0 Hz), 3.73 – 3.56 (m, 1H), 3.20 (bs, 1H), 2.68 (d, 1H, *J* = 11.2 Hz), 1.34 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.8, 139.0, 131.0, 130.4, 129.4, 129.1, 128.7, 127.4, 126.5, 123.7, 117.8, 63.5, 63.2, 53.3, 50.1, 14.5.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{20}BrNO_3Na$ 424.0524, found 424.0529.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 88:22) flow rate 1.0 ml/min; 220 nm; t_R (major) = 11.7 min, t_R (minor)= 19.3 min; 97.7% ee.

$[\alpha]^{20}_D$ +420.8 (*c* 0.61, MeOH)



(*S*)-Ethyl 6-bromo-2-((*R*)-2-hydroxy-1-phenylethyl)quinoline-1(2H)-carboxylate (5dc-*anti*)

From the above preparative TLC (R_f=0.45) was collected **5dc-***anti* as a white amorphous solid **(**7 mg, 8%).

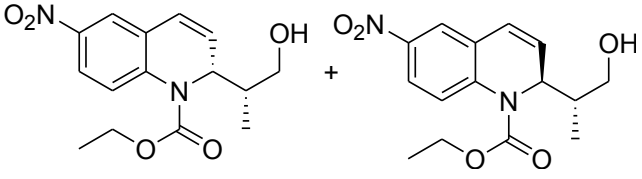
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 – 6.97 (m, 8H), 6.42 (d, 1H, *J* = 9.3 Hz), 6.19 (dd, 1H, *J* = 9.3, 5.9 Hz), 5.39 (bs, 1H), 4.22 – 3.98 (m, 2H), 3.98-3.80 (m, 2H), 2.86 (dd, 1H, *J* = 14.1, 6.7 Hz), 1.20 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.7, 137.7, 134.1, 130.2, 129.6, 129.4, 129.0, 128.7, 128.0, 127.3, 126.9, 126.2, 125.1, 117.2, 62.6, 53.6, 52.3, 14.4.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{20}BrNO_3Na$ 424.0524, found 424.0530.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 88:22) flow rate 1.0 ml/min; 220 nm; t_R (minor) = 12.1 min, t_R (major)= 23.9 min; 94.4% ee.

$[\alpha]^{20}_D$ -125.7 (*c* 0.77, MeOH)



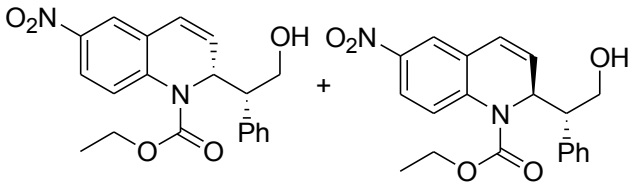
***R*)-Ethyl 2-((*R*)-1-hydroxypropan-2-yl)-6-nitroquinoline-1(2*H*)-carboxylate and (*S*)-ethyl 2-((*R*)-1-hydroxypropan-2-yl)-6-nitroquinoline-1(2H)-carboxylate (5ed-*syn* +*anti*)**

Following the general procedure B, *N,O*-acetal **1e** (59 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), propionaldehyde (35 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) reacted at 0 °C for 30h. Subsequent flash chromatography (6 hexanes/4 Et_2O, R_f= 0.20) gave a green oil (42 mg, 70%) as an inseparable mixture of **5ed**-*syn*(*I*) and **5ed-***anti*(*II*).

1H NMR (250 MHz, CDCl3) δ 8.07 (t, $1H_{(II)}$, J = 2.9 Hz), 8.04 (t, $1H_{(I)}$, J = 2.9 Hz), 7.99 (d, $1H_{(II)}$, J = 2.6 Hz), 7.95 (d, $1H_{(I)}$, J = 2.6 Hz), 7.59 (d, $1H_{(II)}$, J = 2.1 Hz), 7.56 (d, $1H_{(I)}$, J = 2.1 Hz), 6.69 – 6.55 (m, $1H_{(I+II)}$), 6.29 (dd, $1H_{(I)}$, J = 9.7, 6.0 Hz), 6.14 (dd, $1H_{(II)}$, J = 9.7, 5.9 Hz), 5.27 (*app.* t, $1H_{(II)}$, J = 4.8 Hz), 4.94 (dd, $1H_{(I)}$, J = 10.1, 6.1 Hz,), 4.44 – 4.21 (m, $2H_{(I+II)}$), 3.64 (dd, $1H_{(I)}$, J = 11.9, 3.2 Hz), 3.51 – 3.32 (m, $2H_{(II)}$ and $1H_{(I)}$), 2.65 (bs, 1H), 1.94 – 1.77 (m, $1H_{(II)}$), 1.64 (m, $1H_{(I)}$), 1.34 (t, J = 7.1 Hz, $3H_{(I+II)}$), 1.01 (d, $3H_{(I)}$, J = 6.9 Hz), 0.58 (d, $3H_{(II)}$, J = 7.0 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ $155.6_{(II)}$, $155.1_{(I)}$, $143.9_{(I+II)}$, $141.7_{(II)}$, $140.3_{(I)}$, $131.2_{(I+II)}$, $128.3_{(II)}$, $128.0_{(I)}$, $124.8_{(II)}$, $124.7_{(I)}$, $124.5_{(II)}$, $124.1_{(I)}$, $122.7_{(I+II)}$, $121.6_{(I)}$, $121.5_{(II)}$, $(63.7, 63.6)_{(I+II)}$, $54.4_{(I)}$, $54.2_{(II)}$, $41.7_{(II)}$, $39.3_{(I)}$, $14.4_{(I+II)}$, $12.9_{(I)}$, $11.0_{(II)}$.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 88:22) flow rate 1.0 ml/min; 220 nm; ***Syn*-5ed** t_R (major) = 17.4 min, t_R (minor)= 19.2 min, 91.2 %ee; ***Anti*-5ed** t_R (minor) = 22.7 min, t_R (major)= 44.8 min, 83.8 %ee.



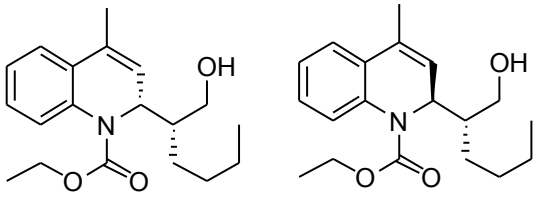
(*R*)-Ethyl 2-((*R*)-2-hydroxy-1-phenylethyl)-6-nitroquinoline-1(2*H*)-carboxylate and (*S*)-ethyl 2-((*R*)-2-hydroxy-1-phenylethyl)-6-nitroquinoline-1(2*H*)-carboxylate (5ec-*syn* +*anti*)

Following the general procedure A, *N,O*-acetal **1e** (59 mg, 0.20 mmol), **L3b** (25 mg, 0.04 mmol), phenylacetaldehyde (90%, 80 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at 0 °C for 3h. Subsequent flash chromatography (7 hexanes/3 AcOEt, R_f=0.13) gave a green oil as mixture of **5ec-***syn* and **5ec-***anti* (57 mg, 78% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (dd, $1H_{(I)}$, J = 9.0, 2.6 Hz), 8.02 – 7.94 (m, $2H_{(I+II)}$), 7.78 (bs, $1H_{(II)}$), 7.65 (d, $1H_{(I)}$, J = 9.2 Hz), 7.46 (d, $1H_{(II)}$, J = 9.1 Hz), 7.37 – 7.20 (m, $6H_{(I+II)}$), 7.19 – 6.96 (m, $4H_{(I+II)}$), 6.54 (d, $1H_{(II)}$, J = 10.0 Hz), 6.49 (d, $1H_{(I)}$, J = 9.6 Hz) 6.27 (dd, $1H_{(II)}$, J = 9.6, 6.0 Hz), 5.82 (dd, $1H_{(I)}$, J = 9.6, 6.0 Hz), 5.55 – 5.39 (m, $2H_{(I+II)}$), 4.50 – 4.29 (m, $2H_{(I+II)}$), 4.27 – 4.06 (m, $2H_{(I+II)}$), 4.04 – 3.86 (m, $3H_{(I+II)}$), 3.79 – 3.63 (m, $1H_{(I)}$), 2.87 (q, J = 6.7 Hz, $1H_{(II)}$), 2.79 – 2.65 (m, $1H_{(I)}$), 2.57 (bs, 1H), 2.37 (bs, 1H), 1.38 (t, J = 7.1 Hz, $3H_{(II)}$), 1.25 (t, J = 7.1 Hz, $3H_{(I)}$).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.9, 144.0, 143.5, 141.1, 139.8, 138.7, 138.5, 138.1, 137.1, 131.4, 130.5, 129.6, 129.4, 129.0, 128.7, 128.6, 127.9, 127.6, 127.5, 127.3, 126.6, 125.3, 125.1, 124.9, 123.8, 122.7, 122.4, 121.6, 121.3, 64.9, 63.6, 63.3, 63.2, 62.0, 54.2, 53.9, 52.6, 52.5, 51.0, 41.5, 14.4, 14.3.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 88:22) flow rate 1.0 ml/min; 220 nm; ***Syn*-5ec** t_R (minor) = 20.1 min, t_R (major)= 25.9 min, 96.8 %ee.



(*R*)-Ethyl 2-((*R*)-1-hydroxyhexan-2-yl)-4-methylquinoline-1(2*H*)-carboxylate and (R)-ethyl 2-((*S*)-1-hydroxyhexan-2-yl)-4-methylquinoline-1(2*H*)-carboxylate (5ha-*syn*+*anti)*

Following the general procedure B, *N,O*-acetal **1h** (52 mg, 0.20 mmol), **L4b** (25 mg, 0.04 mmol), hexanal (60 mg, 0.60 mmol), anhydrous *p*-toluensulfonic acid (7 mg, 0.04 mmol), toluene (0.80 mL), MeOH (0.40 mL) and sodium borohydride (45 mg, 1.20 mmol) were allowed to react at room temperature for 16h. Subsequent flash chromatography (8 hexanes/2 Et_2O, R_f=0.22) afforded an oil (56 mg, 88%) as mixture of **5ha-*syn****(I)* and **5ha-*anti*** *(II*).

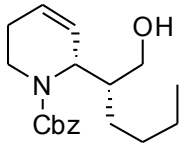
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 – 7.05 (m, $4H_{(I+II)}$), 5.99 (d, $1H_{(I)}$, J = 6.2 Hz), 5.81 (d, $1H_{(II)}$, J = 5.9 Hz), 5.13 (bs, $1H_{(II)}$), 4.74 (dd, $1H_{(I)}$, J = 10.5, 6.2 Hz), 4.45 – 4.12 (m, $2H_{(I+II)}$), 3.60 (d, $1H_{(I+II)}$, J = 11.2 Hz), 3.47 (bs, $1H_{(I+II)}$), 3.30 (bs, 1H), 2.10 (s, $3H_{(II)}$), 2.09 (s, $3H_{(I)}$), 1.66 – 1.52 (m, $1H_{(I+II)}$), 1.44 – 0.97 (m, $9H_{(I+II)}$), 0.85 (t, $3H_{(I)}$ J = 7.1 Hz), 0.73 (d, $3H_{(II)}$, J = 6.3 Hz).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 135.5, 133.9, 130.9, 130.2, 129.6, 129.4, 127.3, 127.3, 125.8, 124.9, 124.6, 124.6, 124.5, 123.5, 123.1, 62.8, 62.7, 61.9, 59.9, 53.2, 53.0, 45.9, 43.3, 29.8, 29.6, 26.1, 23.1, 22.8, 18.7, 18.5, 14.5, 14.1, 13.9.

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 92:8) flow rate 1.0 ml/min; 220 nm; **5ha**-*syn* t_R (minor) = 5.0 min, t_R (major)= 6.84 min; 99%ee; **5ha**-*anti* t_R (minor) = 10.3 min, t_R (major)= 11.8 min; 91% ee.

General Procedure for the enantioselective alkylation of tetrahydropyridines with aldehydes

An oven-dried 10 mL pyrex vial was charged with **7** (1.0 eq) in the specified solvent (0.5 M) followed by the appropriate catalyst (20 mol%) and aldehyde (3.0 eq). The resulting solution was cooled to the specified temperature and additioned with the specified Lewis acid (20 mol%). The mixture was allowed to react until no **7** was detected by TLC. The solution was then cooled at 0 °C, diluted with methanol (0.20 mL per 0.20 mmol of **7**) and additioned with sodium borohydride (2.0 eq). Upon disappearance of the corresponding aldehyde, the reaction mixture was quenched with water (4 mL per 0.20 mmol of **7**) and the resulting aqueous layer was extracted with Et_2O four times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford a residue which was purified by flash chromatography or/and preparative TLC.



(*R*)-Benzyl 2-((*R*)-1-hydroxyhexan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (*syn*-8a)

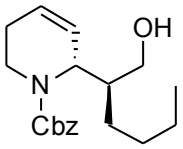
Following the general procedure, **7** (47 mg, 0.20 mmol), **L1***HCl (10.2 mg, 0.04 mmol), freshly distilled hexanal (74 μL, 0.60 mmol), $In(OTf)_3$ (22.5 mg, 0.04 mmol), THF (0.40 mL), MeOH (0.2 mL) and sodium borohydride (15 mg, 0.4 mmol) were allowed to react 18 hours at 0 °C. Subsequent preparative TLC (8 hexanes/ 2 AcOEt, 3 runs R_f= 0.49) afforded the title compound as colourless sticky oil (9 mg, 19%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 – 7.30 (m, 5H), 6.03 – 5.76 (m, 2H), 5.22 (d, 1H, *J* = 12.2 Hz), 5.14 (d, 1H, *J* = 12.2 Hz), 4.35 (d, 1H, *J* = 8.8 Hz), 4.12 (dd, 1H, *J* = 13.3, 5.6 Hz), 3.53 (bs, 3H), 3.02 – 2.76 (m, 1H), 2.39 – 2.16 (m, 1H), 2.10 – 1.89 (m, 1H), 1.72 – 1.22 (m, 7H), 0.90 (t, *J* = 6.6 Hz, 3H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.7, 136.6, 128.7, 128.3, 128.0, 127.7, 125.8, 67.7, 60.1, 53.1, 44.4, 37.9, 29.9, 27.0, 25.2, 23.2, 14.2.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{27}NO_3Na$ 340.1889, found 340.1888

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 92:8) flow rate 1.0 ml/min; 220 nm; t_R (minor) = 9.8 min, t_R (major)= 11.5 min, 99% ee.



***(R)*-Benzyl 2-(*(R)*-1-hydroxyhexan-2-yl)-5,6-dihydropyridine-1(*2H)*-carboxylate (*anti*-8a)**

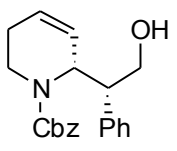
From the above preparative TLC (8 hexane/ 2 AcOEt, 3 runs, R_f=0.42) was collected the title compound as colourless oil (8 mg, 16%).

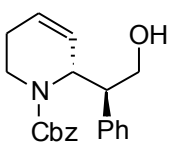
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.02 – 5.90 (m, 1H), 5.64 – 5.51 (m, 1H), 5.24 – 5.07 (m, 2H), 4.74 (bs, 1H), 4.28 – 4.11 (m, 1H), 3.66 (dd, 1H, *J* = 12.0, 4.3 Hz), 3.37 – 3.19 (m, 1H), 3.01 – 2.80 (m, 1H), 2.29 – 2.07 (m, 1H), 2.03 – 1.87 (m, 1H), 1.69 – 1.07 (m, 7H), 0.86 (t, 3H, *J* = 6.3 Hz).

^{13}C NMR (62.5 MHz, CD_3CN) δ 157.1, 138.3, 129.5, 128.9, 128.7, 126.9, 67.7, 62.1, 53.9, 46.5, 39.6, 30.9, 30.5, 30.4, 28.2, 25.4, 23.7, 14.3.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{27}NO_3Na$ 340.1889, found 340.1889

HPLC analysis: Daicel Chiralcel AD-H column (hexane–*i*-PrOH, 92:8) flow rate 1.0 ml/min; 220 nm; t_R (minor) = 11.6 min, t_R (major)= 12.6 min, 97% ee.



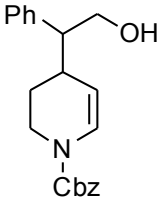


***(R)*-Benzyl 2-(*(R)*-2-hydroxy-1-phenylethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate and *(R)*-benzyl 2-(*(S)*-2-hydroxy-1-phenylethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (*syn*-8b and *anti*-8b)**

Following the general procedure, **7** (47 mg, 0.20 mmol), **L2** (9.9 mg, 0.04 mmol), phenyl acetaldehyde (90% purity, 80 mg, 0.60 mmol), $Er(OTf)_3$ (24.6 mg, 0.04 mmol), toluene (0.40 mL), MeOH (0.2 mL) and sodium borohydride (15 mg, 0.4 mmol) were allowed to react 1 hour at 0 °C. Subsequent flash chromatography (7 hexane/ 3 Et_2O, R_f=0.20) afforded a mixture of ***syn*-8b** and ***anti*-8b** as an oil (53 mg, 78%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 – 7.09 (m, 10H), 5.86 – 5.65 (m, 1H), 5.37 – 5.15 (m, 3H), 4.97 – 4.73 (m, 1H), 4.19 (dd, 1H, *J* = 13.5, 5.6 Hz), 3.98 – 3.51 (m, 3H), 3.06 – 2.84 (m, 1H), 2.77 (d, 1H, *J* = 11.0 Hz), 2.35 – 2.11 (m, 1H), 2.02 – 1.88 (m, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.6, 140.4, 136.5, 129.1, 128.9, 128.6, 128.6, 128.2, 127.9, 127.6, 127.3, 127.1, 126.9, 126.4, 126.3, 125.5, 67.7, 67.6, 64.3, 63.6, 53.9, 53.0, 52.6, 51.4, 39.26, 37.7, 37.4, 30.4, 29.7, 25.0, 24.4.

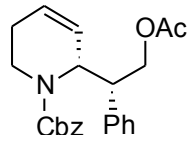


Benzyl 4-(2-hydroxy-1-phenylethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (9)

The slower eluting fraction of the above flash chromatography (R_f=0.16) afforded the title compound as an oil (1 mg, 2%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.14 (m, 10H), 6.96 (d, 1H, *J* = 8.9 Hz, minor rotamer), 6.86 (d, 1H, *J* = 8.9 Hz,major rotamer), 5.17 (s, 2H), 5.11 (dd, 1H, *J* = 8.6, 3.8 Hz, minor rotamer), 4.99 (dd, 1H, *J* = 8.6, 3.5 Hz, major rotamer), 4.07 – 3.79 (m, 2H), 3.66 – 3.45 (m, 2H), 2.74 – 2.61 (m, 1H), 2.59 – 2.42 (m, 1H), 1.67 – 1.49 (m, 1H), 1.47 – 1.34 (m, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ (153.5, 153.1, rotamers), 140.9, 136.3, 129.0, 128.7, 128.6, 128.4, 128.2, 127.9, 127.3, (125.8, 125.4, rotamers), (108.3, 107.9, rotamers), (67.75, 67.6, rotamers), 65.2, 53.6, 40.4, 33.6, 25.6.



***(R)*-Benzyl 2-(*(R)*-2-acetoxy-1-phenylethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (8b-Ac-*syn*)**

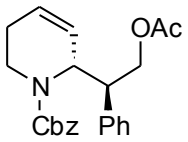
Following the general procedure, **7** (47 mg, 0.20 mmol), **L2** (9.9 mg, 0.04 mmol), phenylacetaldehyde (90% purity, 80 mg, 0.60 mmol), $Er(OTf)_3$ (24.6 mg, 0.04 mmol), toluene (0.40 mL), MeOH (0.2 mL) and sodium borohydride (15 mg, 0.4 mmol) were allowed to react 1 hour at 0 °C. After the standard work-up, the resulting reaction crude was dissolved in pyridine (0.4 mL) followed by acetic anhydride (0.20 mL). The reaction was allowed to react overnight. Removal of solvent gave an oil which was purified by flash chromatography (85 hexane/ 15 Et_2O, R_f=0.16) to provide the title compound as colourless oil (52 mg, 69%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 – 7.03 (m, 10H), 5.89 – 5.71 (m, 1H), 5.40 (d, 1H, *J* = 10.4 Hz), 5.30 – 5.09 (m, 2H), 4.88 (d, 1H, *J* = 8.9 Hz, rotamer), 4.75 (d, 1H, *J* = 9.0 Hz, rotamer), 4.51 – 3.98 (m, 3H), 3.38 – 3.17 (m, 1H), 2.80 – 2.48 (m, 1H), 2.29 – 2.05 (m, 1H), 2.01 – 1.76 (m, 4H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.1, (155.7, 155.5, rotamers), (138.9, 138.5, rotamers), (137.0, 136.7, rotamers), 128.8, 128.7, 128.3, 128.1, 128.0, 127.5, 127.4, 127.0, 126.4, 126.4, 125.7, (67.6, 67.3, rotamers), (66.0, 65.8, rotamers), 54.3, (48.9, 48.7, rotamers), (37.8, 37.3, rotamers), (25.0, 24.5, rotamers), (21.0, 20.9, rotamers).

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{25}NO_4Na$ 402.1681, found 402.1682.

HPLC analysis: Phenomenex® Lux 5u-Cellulose-1 column (hexane–*i*-PrOH, 99:1) flow rate 1.0 ml/min; 254 nm; t_R (minor) = 17.2 min, t_R (major)= 18.4 min, 93% ee.



***(R)*-Benzyl 2-(*(S)*-2-acetoxy-1-phenylethyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (8b-Ac-*anti*)**

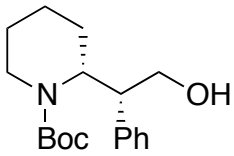
The slower eluting fraction of the above flash chromatography (R_f=0.14) afforded the title compound as an oil (6 mg, 8%).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 – 6.94 (m, 10H), 5.89 (bs, 1H), 5.79 – 5.60 (m, 1H), 5.17 – 5.00 (m, 1H+minor rotamer), 4.88 (d, *J* = 11.4 Hz, 1H), 4.68 (bs, 1H major rotamer with respect to 5.17-5.00), 4.54 – 4.33 (m, 2H), 4.22 – 4.09 (m, 1H, minor rotamer), 4.07 – 3.89 (m, 1H, major rotamer), 3.30 (bs, 1H), 2.68 – 2.52 (m, 1H), 2.20 – 1.82 (m, 4H).

^{13}C NMR (63 MHz, $CDCl_3$) δ 171.2, 155.6, 138.6, (136.9, 136.6, rotamers), 129.9, 129.5, 128.6, 128.4, 127.8, 127.6, 127.1, 126.4, 125.6,(67.6, 67.1, rotamers), (64.8, 64.5, rotamers), (54.7, 54.4, rotamers), 49.1, (38.4, 38.0, rotamers), 24.5, 21.0.

HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{25}NO_4Na$ 402,1681, found 402.1684.

HPLC analysis: Phenomenex® Lux 5u-Cellulose-1 column (hexane–*i*-PrOH, 99:1) flow rate 1.0 ml/min; 254 nm t_R (major) = 22.9 min, t_R (minor)= 28.0 min, 70% ee.



***(*1*R)*-1-[(2*R*)-N-*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenyl-2-hydroxyethane (10).**[9]

To a solution of **8b-Ac**-*syn* (95 mg, 0.25 mmol, 93% ee) in methanol (2.2 mL) was added 10% Pd/C (5 mg). The reaction mixture was flushed three times with hydrogen (1 atm) and allowed to react 8 hours under hydrogen atmosphere. The suspension was filtered over a short pad of Celite, washed several times with dichloromethane/AcOEt and concentrated to give 65 mg of crude (*R*)-2-phenyl-2-[(*R*)-piperidin-2-yl)ethanol acetate which directly dissolved in THF (2.0 mL), treated with Boc_2O (98 mg, 0.45 mmol) and NEt_3 (38 μL, 0.27 mmol) and allowed to stir overnight. After concentration in vacuo, the residue was diluted in methanol (4.5 mL) followed by NaOH/MeOH (2N) solution (0.17 mL). The reaction mixture was stirred at rt for 1h and then poured into saturated

aqueous NH_4OH (5 mL). Extraction with CH_2Cl_2 and evaporation of the organic solvent afforded a residue that was subjected to chromatographic purification on SiO_2 (AcOEt : hexanes= 20/80) to give the title compound (48 mg, 64% yield). Spectroscopic and analytical data were in agreement with those previously reported.[9] Optical rotatory power for this compound was $[\alpha]_D^{20}$= +11.2 (c= 1.5, CH_2Cl_2) with respect to $[a]_D^{20}$= +12.4 (c= 2.20, CH_2Cl_2).[9]

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