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DOI:

[10.1021/acs.joc.0c02998](https://doi.org/10.1021/acs.joc.0c02998)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Alamillo-ferrer, C., Nielsen, C. D., Salzano, A., Companyó, X., Di Sanza, R., Spivey, A. C., Rzepa, H. S., & Burés, J. (2021). Understanding the Diastereopreference of Intermediates in Aminocatalysis: Application to the Chiral Resolution of Lactols. *The Journal of organic chemistry*. <https://doi.org/10.1021/acs.joc.0c02998>

Published in:

The Journal of organic chemistry

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Understanding the diastereopreference of intermediates in aminocatalysis: application to the chiral resolution of lactols

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Supporting Information Placeholder

ABSTRACT: Downstream intermediates are crucial for the reactivity and selectivity of aminocatalytic reactions. We present an analysis of the stereopreference in aminocatalytic downstream intermediates, which reveals an inconspicuous mechanism of chiral recognition between the catalyst and the rest of the molecule. We delineate a stereoelectronic model to rationalize the mode of chiral transmission. We also exploit it for the resolution of chiral lactols relevant in organic synthesis as well as in the flavor and fragrance industry.

Mechanistic studies of asymmetric aminocatalytic reactions via enamine activation have shown the relevance of downstream catalytic intermediates in the overall reactivity and selectivity of these transformations.¹ Most of the downstream intermediates that have been identified are formed in addition reactions, where the attack of the enamine or dienamine to the electrophile is followed by the capture of the transient iminium ion by the developed nucleophile (Figure 1).^{1,2} As a result, these intermediates contain a cycle with a stereogenic carbon (in red in Figure 1) bound to the aminocatalyst through a single bond (blue in Figure 1). The configuration of this carbon center is crucial to control the other stereocenters contained in the cycle and, ultimately, the enantio and diastereoselectivity of the final products of aminocatalytic reactions. However, there is currently no explanation as to how the chiral aminocatalyst controls the configuration of this stereocenter through a single bond. *Herein, we describe and rationalize the mode of chiral transmission from aminocatalysts to the rest of downstream intermediates and exploit it for the resolution of valuable chiral lactols.*

Figure 1. The stereocenter in a chiral aminocatalyst (green) controls the configuration of the indicated stereogenic carbon (red) center via a single bond.

Most intermediates formed in aminocatalytic additions are single diastereoisomers even when equilibration with other diastereoisomers is possible.² This high predominance of one of the possible diastereoisomers implies that the chiral aminocatalyst controls the configuration of the stereogenic centers within the neighboring cycle. The mechanism whereby the stereochemical information is transmitted between both cycles is not immediately apparent, as they are linked by a single bond with presumed free rotation. However, our analysis of similar bicyclic crystal structures³ deposited in the Cambridge Structural Database (CSD)⁴ revealed three common structural features responsible for the predominance of particular diastereoisomers. The first one is that the nitrogen of the aminocatalyst is pyramidalized and adopts the configuration that minimizes the steric clash of the substituent/s in the aminocatalyst and the new ring (Figure 2a). All the analyzed structures show an angle larger than 180° between the C1'-N bond and the face of the N-ring that contains the steric unit (Figure 2a).⁵ This phenomenon is not surprising as it was observed even

in structures of related enamines.⁶ The second structural feature is that the nucleophile and the lone pair of the nitrogen are antiperiplanar, allowing the negative hyperconjugation of the lone pair orbital with the $\sigma^*C1'-Nu$. All the dihedral angles between the estimated position of the lone pair, the N, the C1' and the nucleophile are higher than 150° (Figure 2b).⁵ The third structural feature is the configuration of C1', which in all analyzed structures is such that the newly formed cycle is located on the less sterically hindered side of the aminocatalyst, while maintaining the negative hyperconjugation between the lone pair orbital of the nitrogen and the $\sigma^*C1'-Nu$. All the dihedral angles between the nucleophile, the C1', the nitrogen and the hydrogen attached to C1' are at $120 \pm 10^\circ$ when measured in the direction of the nitrogen substituent containing the steric unit (Figure 2c).⁵ In short, the stereogenic carbons in the nitrogen-containing ring determine the configuration of the nitrogen and, in turn, the configuration of C1' through a series of stereoelectronic effects.

The significance of the exquisite stereopreference of the downstream intermediates has been overlooked in the literature because the configuration of C1' is lost in all final products of aminocatalytic reactions. However, in addition to being fundamental for enabling high enantioselectivity in aminocatalytic addition reactions, the high stereopreference presents opportunities to develop new applications for aminocatalysts. In particular, we envisioned the possibility of resolving chiral lactols by selective formation of hemiaminal ethers. Enantiomerically pure lactols are useful compounds for stereoselective synthesis⁷ and enantioenriched lactones are important substances for the fragrance and flavor industry.⁸ Racemic lactones are cheap, but their resolution is challenging even at analytical scale.⁹ As a consequence, enantiomerically pure lactols have to be prepared from expensive, and in some cases commercially unavailable, enantiomerically pure starting materials.^{7a} Therefore, the resolution of lactols is a desirable process.

To efficiently resolve a racemic lactol with an enantiomerically pure cyclic amine, the diastereomeric hemiaminal ethers formed from each enantiomeric lactol should be significantly different in energy. DFT calculations (Figure 3, B3LYP + D3BJ dispersion term/Def2-TZVPP/SCRF = chloroform) estimated that the hemiaminal ether **3ab** formed with (*S*)- α,α -diphenylprolinol *tert*-butyldimethylsilyl ether [(*S*)-**2a**] and (*R*)- δ -hexalactol [(*R*)-**1b**] would be 2.5 kcal/mol lower in free energy than the diastereoisomer formed with the (*S*)- δ -hexalactol [(*S*)-**1b**].⁵ The greater stability of the hemiaminal ether formed with (*S*)-**2a** and (*R*)-**1b** is due to the lactol methyl substituent and the nitrogen-containing ring both adopting equatorial positions¹⁰ and the configuration of the hemiaminal carbon center adopting the preferred configuration (Figure 3) according to the stereoelectronic model adumbrated above. By contrast, the hemiaminal ether formed between (*S*)-**2a** and (*S*)-**1b** has to either locate one of the two substituents in an axial position or adopt an unfavorable configuration at the hemiaminal carbon; both possibilities entail large free energy penalties. We estimate the energetic penalty for having unfavorable configuration at the hemiaminal carbon center to be 4.5 kcal/mol by reference to the calculated energies of the diastereoisomers formed between the amine (*S*)-**2a**

and the unsubstituted δ -valerolactol **1a**.

a) The configuration of the N atom is controlled by the amine substituent

b) There is hyperconjugation of the n(N) with the $\sigma^*(C1'-Nu)$

c) The hemiaminal carbon (C1') has the stereochemistry that locates the newly formed ring on the less sterically hindered side of the amine ring

Figure 2. All the bicyclic crystal structures deposited in the Cambridge Structural Database (CSD) that are similar to the downstream intermediates formed in aminocatalytic additions have the same structural features.

Figure 3. DFT calculations¹¹ estimate that the (*R*)- δ -hexalactol [(*R*)-**1b**] forms the most stable hemiaminal ether, with a population of 97.6%, of the possible hemiaminal ethers formed by condensation of ($\pm$)-**1b** and (*S*)-**2a**.

By NMR spectroscopy, we observed only one diastereoisomer when mixing the amine (*S*)-**2a** with the unsubstituted δ -valerolactol (**1a**) in CDCl_3 (Figure 4), which confirms the exquisite stereocontrol of the amine over the hemiaminal carbon. To confirm that this astonishing diastereopreference is due to thermodynamic factors, we proved the reversibility of the hemiaminal ether formation by displacing the amine (*S*)-**2a** of the hemiaminal ether with its TMS congener amine (*S*)-**2b**.⁵

Figure 4. The amine controls the configuration of the hemiaminal carbon so exquisitely that only one, the (*S,R,R*)-**3aa**, of the possible diastereoisomers is observed.

We evaluated several amines for the resolution of racemic δ -hexalactol [($\pm$)-**1b**], the most challenging lactol to resolve due to the small size of the methyl group. The selectivity factor, defined as the ratio of equilibrium constants, was calculated using the conversion of ($\pm$)- δ -hexalactol [($\pm$)-**1b**] and the ratio of diastereoisomers in equilibrium for the reaction shown in Figure 5. The acyclic amine (*S*)-**2c** had a very poor selectivity factor ($K_{R,S} = 2.3$), probably due to the lack of control of the configuration at the nitrogen. Cyclic amines (*S*)-**2d**-**2f**, also had very poor selectivity factors (between 1.4 and 2.5) probably due to the insufficient steric hindrance generated by the substituent α to the nitrogen. The amine (*S*)-**2g**, with a tetrasubstituted carbon as the α substituent to the nitrogen, had a better although still insufficient selectivity factor ($K_{R,S} = 3.6$) to be practical. The pyrrolidines with large substituents [(*S*)-**2a**, (*S*)-**2b**, (*S*)-**2h**, and (*S*)-**2i**] had better selectivity factors, especially the amine (*S*)-**2a**, which had a selectivity factor higher than 150. This very high selectivity factor makes possible the efficient resolution of racemic lactols.

We carried out the resolution of lactols under two protocols to show the versatility of the method depending on the aim of the resolution.⁵ The first protocol (Figure 6a) prioritizes the enantiopurity of the final product over the recovery yield, which is

required, for example, when lactols are used in stereoselective synthesis. We obtained very high enantiopure δ -hexalactol [(*R*)-**1b**], δ -octalactol [(*R*)-**1c**], δ -nonalactol [(*R*)-**1d**], δ -decalactol [(*R*)-**1e**], and δ -

Figure 5. Useful selectivity factors ($K_{R,S} = K_R / K_S$) are only observed for amine that are cyclic and have a large substituent in α to the nitrogen [(*S*)-**2a**, (*S*)-**2b**, (*S*)-**2g**, (*S*)-**2h** and (*S*)-**2i**].

undecalactol [(*R*)-**1f**] by separating the corresponding racemic lactols obtained from the reduction of cheap available natural lactones. The second protocol (Figure 6b) prioritizes the quantity of lactol separated in one single batch over its enantiopurity. This protocol is interesting for lactols that are preferred as scalemic mixtures over the enantiomerically pure products due to, for example, their olfactory characteristics.^{8a} In single batch multigram separations, we isolated 1.47 g of (*R*)-**1c** with 82% ee and 6.02 g of (*S*)-**1c** with 26% ee, as well as 1.19 g of (*R*)-**1e** with 94% ee and 7.14 g of (*S*)-**1e** with 20% ee. We were able to control the yield and enantioselectivities by modifying the amount of amine and the extent of the equilibrium of lactol formation. The recovered amounts of lactols were smaller than predicted by the high selectivity factors because of the partial dimerization or oligomerization of the lactols during the purification process. This is a typical problem when working with lactols and it is not a specific problem of this methodology or a sign of a poor selectivity factor. The above-mentioned examples demonstrate the versatility on yields and enantioselectivities that can be achieved depending on the objective of the resolution.

In conclusion, the large difference in stability of intermediates involved in aminocatalytic addition reactions is due to prominent stereoelectronic effects. These stereoelectronic effects result in a chiral recognition mode that can be exploited to efficiently resolve chiral lactols. We have resolved different lactols, with high levels of enantiopurity for use in synthesis and in multigram quantities for use in the fragrance and flavor sector.

a) Chiral resolution of δ -lactols to obtain high ee

b) Resolution of lactols to obtain scalemic mixtures at multigram scale

Figure 6. Resolution of racemic lactols performed with amine (S)-2a yield: a) a highly enantioenriched lactol for synthesis; b) grams of scalemic lactols for perfumery.

EXPERIMENTAL SECTION

General Consideration. All NMR spectra were recorded on a Bruker AVII 500 MHz spectrometer or a Bruker AVIII HD 400 MHz spectrometer with BBO prodigy probe. ¹H-NMR chemical shifts (δ) are quoted in ppm relative to residual solvent peaks (CDCl₃: 7.26 ppm). ¹³C-NMR chemical shifts (δ) are quoted in ppm relative to residual solvent peaks (CDCl₃: 77.16 ppm). Lactols were synthesized by DIBAL-H reduction of the corresponding lactones and were purified by column chromatography (General Procedure 1, Page S6). Chiral amines (S)- α , α -diphenyl-2-pyrrolidinemethanol *tert*-butyldimethylsilyl ether (S)-2a, (S)- α , α -diphenylpyrrolidinemethanol trimethylsilyl ether ((S)-2b), (S)-1-phenylethylamine ((S)-2c), (S)-2-pyrrolidinemethanol ((S)-2d), *N*-[(2S)-2-pyrrolidinylmethyl]-trifluoromethanesulfonamide ((S)-2e), L-proline *tert*-butyl ester ((S)-2f), (S)-prolinemethanol *tert*-butyldiphenyl ether ((S)-2g), (S)-prolinol methyl ether ((S)-2h), (S)- α , α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol ((S)-2i), (S)- α , α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidine-methanol trimethylsilyl ether ((S)-2j), and (S)- α , α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol *tert*-butyldimethylsilyl ether ((S)-2k) were used as purchased from commercial sources. All

other reagents and solvents were used as purchased from Merck, Fluorochem and Alfa Aesar. Flash column chromatography was performed using 230-400 mesh silica, with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were performed on precoated glass-backed silica gel plates (Supelco TLC Silica gel 60 F₂₅₄). Visualization of the developed chromatogram was performed by UV absorbance (254 nm), aqueous potassium permanganate solution or anisaldehyde stain. Reported compounds matched literature data. Enantiomeric ratios were measured by chiral HPLC carried out on an Agilent 1260 Infinity II LC equipped with a diode array detector. Mass Spectra were recorded in an Exactive Plus EMR (Extended Mass Range) Orbitrap using HESI method in positive mode. Optical rotations were measured with a Autopol I Automatic polarimeter from Rudolph Research Analytical. The oximes, (R)-5-hydroxyoctanal oxime 4c and (R)-5-hydroxydecanal oxime 4e, and the benzoylated products, (R)-octane-1,5-diyl dibenzoate 5c and (R)-decane-1,5-diyl dibenzoate 5e, are also reported as scalemic mixtures. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments.

General Procedure 1: DIBAL-H reduction of lactones (1a-1f).¹² To a cooled (−78 °C) solution of lactone (1.0 equiv) in anhydrous CH₂Cl₂ (0.5 M) was added dropwise DIBAL-H (1.0 M in toluene, 1.1 equiv) over a period of 10 min under nitrogen. After the addition, the colourless reaction mixture was stirred at −78 °C for 40 min. The reaction was quenched by slowly adding a saturated solution of potassium sodium tartrate tetrahydrate (0.3 M) at −78 °C before the mixture was brought to room temperature and stirred until separation of layers was observed. The aqueous phase was extracted with CH₂Cl₂ (x3) and the organic layers were combined, washed with brine (x2), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The racemic lactols (1a-1f) were isolated after purification by flash column chromatography (2:1 Et₂O:hexane).

General Procedure 2: Amine recovery by oxime formation (4b-4f). To a solution of the hemiaminal ether (3b-3f) (1.0 equiv) in CHCl₃ (0.5 M) was added NH₂OH·HCl (10.0 equiv) in one portion. The resulting mixture was stirred at room temperature for 1 h. Upon reaction completion, the solids were removed by filtration and the filtrate was concentrated under reduced pressure. The desired oximes (4b-4f) were isolated by flash column chromatography (9:1:0.05 hexane:EtOAc:TEA followed by 100% EtOAc).

General Procedure 3: Hydrolysis of hydroxyoxime to obtain enantioenriched lactols (1b-1f). To a solution of the hydroxyoxime (4b-4f) (1.0 equiv) in CHCl₃ (0.5 M) was added a 0.5 M solution of HCl and the resulting mixture was stirred at room temperature for 18 h. Upon reaction completion, the reaction was quenched with a saturated solution of NaHCO₃. The aqueous phase was extracted with CHCl₃ (x3) and the organic layers were combined, washed with brine (x2), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The desired lactol (1b-1f) was isolated after purification by flash column chromatography (2:1 Et₂O:hexane).

General Procedure 4: Lactol derivatization for enantioselectivity analysis by chiral HPLC (5b-5f). To a solution of lactol (1b-1f) (1.0 equiv) in MeOH (0.5 M) was added NaBH₄ (5.0 equiv) in one portion. After stirring for 30 min at room temperature, the reaction was quenched with a saturated solution of

NH₄Cl. The aqueous phase was extracted with EtOAc (x3) and the organic layers were combined, washed with brine (x2), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude diol was used in the next step without further purification.

The crude diol was redissolved in CH₂Cl₂ (0.5 M) followed by the addition of TEA (2.5 equiv) and a catalytic amount of DMAP. The resulting mixture was cooled at 0 °C before the dropwise addition of BzCl (2.5 equiv). After the addition, the mixture was stirred at room temperature for 3 h. Upon reaction completion, the reaction was quenched with a saturated solution of NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ (x3) and the organic layers were combined, washed with NaHCO₃ (x3), H₂O (x1), brine (x1), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The benzoylated products (**5b-5f**) were isolated after purification by preparative TLC (100% CH₂Cl₂).

(±)-Valerolactol 1a.¹³ Reaction of δ -valerolactone (2.00 g, 19.61 mmol), DIBAL-H (1.0 M in toluene, 21.6 mL, 21.6 mmol) in CH₂Cl₂ (50.0 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (1.81 g, 17.74 mmol, 90%). ¹H NMR (400 MHz, CDCl₃) δ 4.89 – 4.86 (m, 1H), 4.00 (ddd, J = 11.1, 4.7, 2.9 Hz, 1H), 3.83 (d, J = 5.0 Hz, 1H), 3.55 – 3.49 (m, 1H), 1.88 – 1.75 (m, 2H), 1.57 – 1.44 (m, 4H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 94.6, 64.0, 32.0, 25.3, 20.4. LRMS (ESI, +ve) m/z : [M+Na]⁺ 124.9.

(±)- δ -Hexalactol 1b.¹² Reaction of δ -hexalactone (4.60 g, 38.98 mmol), DIBAL-H (1.0 M in toluene, 43.0 mL, 42.88 mmol) in CH₂Cl₂ (100 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (4.30 g, 37.03 mmol, 95%) in a 62:38 mixture of diastereoisomers. ¹H NMR (400 MHz, CDCl₃) δ 5.30 (s, 0.38H, *trans*), 4.71 (ddd, J = 9.2, 6.4, 2.1 Hz, 0.62H, *cis*), 4.14 – 4.06 (m, 0.38H, *trans*), 3.62 – 3.54 (m, 0.62H, *cis*), 3.40 (d, J = 6.3 Hz, 0.62H, OH *cis*), 2.83 (s, 0.38H, OH *trans*), 1.94 – 1.46 (m, 5H, *trans+cis*), 1.33 – 1.25 (m, 1H, *trans+cis*), 1.22 (d, J = 6.2 Hz, 2H, *trans*) 1.13 (d, J = 6.3 Hz, 1H, *cis*). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 96.5, 92.1, 72.6, 65.1, 33.2, 32.7, 32.3, 29.7, 22.3, 22.0, 21.8, 17.6. LRMS (GC-MS) m/z : [M]⁺ 116.1.

(±)- δ -Octalactol 1c.¹⁴ Reaction of δ -octalactone (13.03 g, 91.60 mmol), DIBAL-H (1.0 M in toluene, 100 mL, 101 mmol) in CH₂Cl₂ (230 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (11.23 g, 78.00 mmol, 85%) in a 62:38 mixture of diastereoisomers. ¹H NMR (400 MHz, CDCl₃) δ 5.30 – 5.29 (m, 0.38H, *trans*), 4.69 (ddd, J = 9.1, 6.4, 2.1 Hz, 0.62H, *cis*), 3.96 – 3.91 (m, 0.38H, *trans*), 3.51 (d, J = 6.4 Hz, 0.62H, *cis*), 3.44 – 3.39 (m, 0.62H, *cis*), 2.90 (s, 0.38H, *trans*), 1.88 – 1.09 (m, 10H, *trans+cis*), 0.90 (t, J = 6.7 Hz, 3H, *trans+cis*). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 96.6, 92.0, 76.4, 68.6, 38.4, 38.2, 33.0, 31.3, 30.5, 30.0, 22.3, 18.8, 18.7, 17.6, 14.3, 14.2. LRMS (GC-MS) m/z : [M]⁺ 144.1.

(±)- δ -Nonalactol 1d.¹⁵ Reaction of δ -nonalactone (4.40 g, 21.81 mmol), DIBAL-H (1.0 M in toluene, 24.0 mL, 24.0 mmol) in CH₂Cl₂ (43.0 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (3.10 g, 19.59 mmol, 90%) in a 56:44 mixture of diastereoisomers. ¹H NMR (500 MHz, CDCl₃) δ 5.30 (s, 0.44H, *trans*), 4.69 (ddd, J = 9.1, 6.4, 2.1 Hz, 0.56H, *cis*), 3.94 – 3.89 (m, 0.44H, *trans*), 3.40 (dddd, J = 12.3, 7.4, 5.1, 2.0 Hz, 0.56H, *cis*), 3.12 (bs, 0.56H, *cis*), 2.57 (bs, 0.44H, *trans*), 1.87 – 1.11 (s, 12H, *trans+cis*), 0.89 (t, J = 6.9 Hz, 3H, *trans+cis*). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 96.6, 92.1,

76.6, 68.9, 36.0, 35.9, 33.1, 31.3, 30.6, 30.0, 27.8, 27.8, 22.9, 22.9, 22.3, 17.6, 14.2, 14.2. LRMS (ESI, +ve) m/z : [M+Na]⁺ 181.1.

(±)- δ -Decalactol 1e.¹⁶ Reaction of δ -decalactone (13.00 g, 76.47 mmol), DIBAL-H (1.0 M in toluene, 84.0 mL, 83.9 mmol) in CH₂Cl₂ (190 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (10.80 g, 62.79 mmol, 82%) in a 63:37 mixture of diastereoisomers. ¹H NMR (400 MHz, CDCl₃) δ 5.27 (m, 0.37H, *trans*), 4.67 (ddd, J = 8.9, 6.4, 2.0 Hz, 0.63H, *cis*), 3.92 (d, J = 6.4 Hz, 0.63H, *cis*), 3.96 – 3.89 (m, 0.37H, *trans*), 3.41 – 3.35 (m, 0.63H, *cis*), 3.28 (s, 0.37H, *trans*), 1.87 – 1.11 (m, 14H, *trans+cis*), 0.87 (t, J = 6.8 Hz, 3H, *trans+cis*). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 96.6, 91.9, 76.7, 68.9, 36.2, 36.0, 33.0, 32.03, 31.96, 31.2, 30.5, 30.0, 25.3, 25.2, 22.73, 22.71, 22.3, 17.5, 14.1 (missing 1 carbon). LRMS (GC-MS) m/z : [M]⁺ 172.1.

(±)- δ -Undecalactol 1f.¹⁷ Reaction of δ -undecalactone (1.80 g, 9.77 mmol), DIBAL-H (1.0 M in toluene, 12.0 mL, 11.7 mmol) in CH₂Cl₂ (20.0 mL) according to the *General Procedure 1* gave the title compound as a colourless oil (1.50 g, 8.10 mmol, 84%) in a 63:37 mixture of diastereoisomers. ¹H NMR (500 MHz, CDCl₃) δ 5.29 (m, 0.37H, *trans*), 4.69 (ddd, J = 9.5, 6.4, 2.1 Hz, 0.63H, *cis*), 3.94 – 3.89 (m, 0.37H, *trans*), 3.40 (ddd, J = 11.3, 7.3, 5.1, 2.0 Hz, 0.63H, *cis*), 3.31 (d, J = 6.4 Hz, 0.63H, *cis*), 2.74 – 2.73 (m, 0.37H, *trans*), 1.86 – 1.81 (m, 1H, *trans+cis*), 1.67 – 1.10 (m, 15H, *trans+cis*), 0.87 (t, J = 6.8 Hz, 3H, *trans+cis*). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 96.6, 92.0, 76.7, 68.9, 36.3, 36.2, 33.0, 32.0, 31.9, 31.3, 30.5, 30.0, 29.5, 29.5, 25.6, 25.5, 22.7, 22.3, 17.6, 14.2 (missing 2 carbon). LRMS (ESI, +ve) m/z : [M+Na]⁺ 209.1.

Protocol to obtain high enantiopure lactols.

Step 1. Formation and partial hydrolysis of hemiaminal ethers (**3b-3f**).

(2S)-2-(((tert-Butyldimethylsilyl)oxy(diphenylmethyl))-1-((2R,6R)-6-methyltetrahydro-2H-pyran-2-yl)pyrrolidine 3ab. To a solution of racemic δ -hexalactol ($\pm$)-**1b** (2.0522 g, 17.69 mmol, 0.5 M) in CHCl₃ (35.4 mL) was added amine (*S*)-**2a** (2.5969 g, 7.08 mmol, 0.2 M) followed by AcOH (0.1 mL, 1.77 mmol, 0.05 M). The mixture was concentrated under reduced pressure with a 28% conversion of lactol **1b**. The crude yellow oil was quenched with TEA (7.4 mL, 53.07 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1b** (1.0928 g, 9.42 mmol, 53% recovery, 50% ee, [α]_D¹⁸ = -8.8 (c 0.66, CH₂Cl₂)), free amine (*S*)-**2a** (0.3846 g, 1.04 mmol) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ab** with amine (*S*)-**2a** in a ratio of 86:14 (total of 2.5278 g, 2.1739 g (*R,R,R,S*)-**3ab** + 0.3539 g of amine (*S*)-**2a**). **Partial Hydrolysis:** To a mixture of hemiaminal ether (*R,R,R,S*)-**3ab** and amine (*S*)-**2a** (in a ratio of 86:14, total of 2.5278 g, 2.1739 g (*R,R,R,S*)-**3ab** + 0.3539 g of amine (*S*)-**2a**) in CDCl₃ (6.0 mL) was added 3.0 mL of AcOH (0.05 M). A ¹H NMR of the organic layer was immediately checked and showed a formation of 6% of the δ -hexalactol (*S*)-**1b**. The reaction mixture was rapidly quenched with TEA (2.0 mL) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give a mixture of hemiaminal ether (*R,R,R,S*)-**3ab** and amine (*S*)-**2a** in a ratio of 72:28 (total of 2.3424 g, 1.6887 g of (*R,R,R,S*)-**3ab** + 0.6537 g of amine (*S*)-**2a**).

¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.53 (m, 2H), 7.50 – 7.47 (m, 2H), 7.29 – 7.24 (m, 6H), 4.53 (dd, J = 9.2, 3.5 Hz, 1H), 4.22 (bd,

$J = 9.3$ Hz, 1H), 3.39 (dq, $J = 12.3, 6.1, 1.7$ Hz, 1H), 2.87 (td, $J = 8.8, 7.1$ Hz, 1H), 2.29 – 2.24 (m, 1H), 1.96 – 1.86 (m, 1H), 1.84 – 1.75 (m, 1H), 1.73 – 1.69 (m, 1H), 1.51 – 1.26 (m, 5H), 1.23 (d, $J = 6.2$ Hz, 3H), 1.09 – 0.99 (m, 1H), 0.92 (s, 9H), 0.44 – 0.32 (m, 1H), -0.42 (s, 3H), -0.46 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.4, 143.5, 130.3, 130.0, 127.2, 127.0, 126.7, 126.6, 90.5, 84.2, 72.4, 65.5, 46.6, 33.5, 30.8, 29.0, 26.5, 24.2, 24.1, 22.4, 19.2, -2.7, -3.2. HRMS (+p APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{29}\text{H}_{44}\text{O}_2\text{NSi}$ 466.3136; Found: 466.3137.

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-propyltetrahydro-2*H*-pyran-2-yl)pyrrolidine **3ac**. To a solution of racemic δ -octalactol ($\pm$)-**1c** (200.5 mg, 1.39 mmol, 0.5 M) in CHCl_3 (2.8 mL) was added amine (*S*)-**2a** (204.2 mg, 0.56 mmol, 0.2 M) followed by AcOH (8 μL , 0.14 μmol , 0.05 M). The mixture was concentrated under reduced pressure with a 28% conversion of lactol **1c**. The crude yellow oil was quenched with TEA (0.6 mL, 4.17 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1c** (128.2 mg, 0.89 mmol, 64% recovery, 23% ee) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ac** with amine (*S*)-**2a** in a ratio of 86:14 (total of 264.8 mg, 227.7 mg (*R,R,R,S*)-**3ac** + 37.1 mg of amine (*S*)-**2a**). *Partial Hydrolysis*: To a mixture of hemiaminal ether (*R,R,R,S*)-**3ac** and amine (*S*)-**2a** (in a ratio of 86:14, total of 264.8 mg, 227.7 mg (*R,R,R,S*)-**3ac** + 37.1 mg of amine (*S*)-**2a**) in CDCl_3 (1.0 mL) was added 0.5 mL of AcOH (0.05 M). A ^1H NMR of the organic layer was immediately checked and showed a formation of 31% of the δ -octalactol (*S*)-**1c**. The reaction mixture was rapidly quenched with TEA (1.0 mL) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give a mixture of hemiaminal ether (*R,R,R,S*)-**3ac** and amine (*S*)-**2a** in a ratio of 62:38 (total of 238.0 mg, 147.6 mg of (*R,R,R,S*)-**3ac** + 90.5 mg of amine (*S*)-**2a**).

^1H NMR (500 MHz, CDCl_3) δ 7.57 – 7.55 (m, 2H), 7.49 – 7.47 (m, 2H), 7.30 – 7.24 (m, 6H), 4.58 (dd, $J = 9.0, 3.5$ Hz, 1H), 4.24 (bd, $J = 10.4$ Hz, 1H), 3.30 (dddd, $J = 10.6, 6.5, 4.3, 1.9$ Hz, 1H), 2.90 – 2.86 (m, 1H), 2.28 – 2.25 (m, 1H), 1.93 – 1.81 (m, 2H), 1.74 – 1.72 (m, 1H), 1.67 – 1.23 (m, 10H), 1.09 – 1.04 (m, 1H), 1.02 (t, $J = 7.2$ Hz, 3H), 0.93 (s, 9H), 0.39 – 0.30 (m, 1H), -0.34 (s, 3H), -0.48 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 144.6, 143.6, 130.3, 130.0, 127.2, 127.1, 126.7, 126.6, 90.5, 84.1, 76.0, 65.3, 46.9, 38.9, 31.9, 31.0, 29.0, 26.5, 24.2, 19.3, 19.1, 14.4, -2.7, -3.3. HRMS (+p APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{31}\text{H}_{48}\text{O}_2\text{NSi}$ 494.3449; Found: 494.3443.

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-butyltetrahydro-2*H*-pyran-2-yl)pyrrolidine **3ad**. To a solution of racemic δ -nonalactol ($\pm$)-**1d** (217.1 mg, 1.39 mmol, 0.5 M) in CHCl_3 (2.8 mL) was added amine (*S*)-**2a** (204.2 mg, 0.56 mmol, 0.2 M) followed by AcOH (8 μL , 0.14 μmol , 0.05 M). The mixture was concentrated under reduced pressure with a 27% conversion of lactol **1d**. The crude yellow oil was quenched with TEA (0.6 mL, 4.17 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1d** (143.1 mg, 0.92 mmol, 66% recovery, 39% ee) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ad** with amine (*S*)-**2a** in a ratio of 86:14 (total of 263.9 mg, 234.9 mg (*R,R,R,S*)-**3ad** + 36.9 mg of amine (*S*)-**2a**). *Partial Hydrolysis*: To a mixture of hemiaminal ether (*R,R,R,S*)-**3ad** and amine (*S*)-**2a** (in a ratio of 86:14, total of 263.9 mg, 234.9 mg (*R,R,R,S*)-**3ad** + 36.9 mg of amine (*S*)-**2a**) in CDCl_3 (1.0 mL) was

added 0.5 mL of AcOH (0.05 M). A ^1H NMR of the organic layer was immediately checked and showed a formation of 43% of the δ -nonalactol (*S*)-**1d**. The reaction mixture was rapidly quenched with TEA (1.0 mL) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give a mixture of hemiaminal ether (*R,R,R,S*)-**3ad** and amine (*S*)-**2a** in a ratio of 66:34 (total of 247.8 mg, 163.5 mg of (*R,R,R,S*)-**3ad** + 84.3 mg of amine (*S*)-**2a**).

^1H NMR (500 MHz, CDCl_3) δ 7.56 – 7.53 (m, 2H), 7.47 – 7.44 (m, 2H), 7.28 – 7.23 (m, 6H), 4.58 (dd, $J = 8.9, 3.6$ Hz, 1H), 4.21 (bd, $J = 9.9$ Hz, 1H), 3.29 – 3.23 (m, 1H), 2.86 (td, $J = 8.8, 7.0$ Hz, 1H), 2.28 – 2.24 (m, 1H), 1.90 – 1.80 (m, 2H), 1.74 – 1.69 (m, 1H), 1.64 – 1.54 (m, 5H), 1.50 – 1.20 (m, 13H), 0.97 (t, $J = 7.5$ Hz, 3H), 0.91 (s, 9H), 0.36 – 0.26 (m, 1H), -0.34 (s, 3H), -0.51 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ 144.6, 143.6, 130.3, 130.0, 127.1, 126.5, 90.4, 84.0, 76.3, 65.1, 47.0, 36.3, 31.9, 31.0, 28.9, 28.4, 26.5, 24.2, 24.1, 23.0, 19.1, 14.4, -2.7, -3.3. HRMS (+p APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{50}\text{O}_2\text{NSi}$ 508.3605; Found: 508.3611.

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-pentyltetrahydro-2*H*-pyran-2-yl)pyrrolidine **3ae**. To a solution of racemic δ -decalactol ($\pm$)-**1e** (239.1 mg, 1.39 mmol, 0.5 M) in CHCl_3 (2.8 mL) was added amine (*S*)-**2a** (204.2 mg, 0.56 mmol, 0.2 M) followed by AcOH (8 μL , 0.14 μmol , 0.05 M). The mixture was concentrated under reduced pressure with a 25% conversion of lactol **1e**. The crude yellow oil was quenched with TEA (0.6 mL, 4.17 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1e** (163.6 mg, 0.95 mmol, 68% recovery, 33.2% ee) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ae** with amine (*S*)-**2a** in a ratio of 82:18 (total of 275.6 mg, 226.0 mg (*R,R,R,S*)-**3ae** + 49.6 mg of amine (*S*)-**2a**). *Partial Hydrolysis*: To a mixture of hemiaminal ether (*R,R,R,S*)-**3ae** and amine (*S*)-**2a** (in a ratio of 82:18, total of 275.6 mg, 226.0 mg (*R,R,R,S*)-**3ae** + 49.6 mg of amine (*S*)-**2a**) in CDCl_3 (1.0 mL) was added 0.5 mL of AcOH (0.05 M). A ^1H NMR of the organic layer was immediately checked and showed a formation of 33% of the δ -decalactol (*S*)-**1e**. The reaction mixture was rapidly quenched with TEA (1.0 mL) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give a mixture of hemiaminal ether (*R,R,R,S*)-**3ae** and amine (*S*)-**2a** in a ratio of 60:40 (total of 239.0 mg, 143.4 mg of (*R,R,R,S*)-**3ae** + 95.6 mg of amine (*S*)-**2a**).

^1H NMR (400 MHz, CDCl_3) δ 7.57 – 7.55 (m, 2H), 7.49 – 7.47 (m, 2H), 7.30 – 7.24 (m, 6H), 4.59 (dd, $J = 8.8, 3.7$ Hz, 1H), 4.23 (bd, $J = 9.4$ Hz, 1H), 3.30 – 3.25 (m, 1H), 2.91 – 2.84 (m, 1H), 2.29 – 2.25 (m, 1H), 1.94 – 1.81 (m, 2H), 1.74 – 1.71 (m, 1H), 1.63 – 1.23 (m, 15H), 1.10 – 1.01 (m, 1H), 0.96 (t, $J = 6.7$ Hz, 3H), 0.92 (s, 9H), 0.39 – 0.27 (m, 1H), -0.34 (s, 3H), -0.49 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 144.6, 143.6, 130.3, 130.0, 127.3, 127.1, 126.7, 126.6, 90.5, 84.1, 76.2, 65.3, 46.9, 36.6, 32.1, 32.0, 31.0, 29.0, 26.51, 26.49, 25.8, 24.2, 23.0, 19.1, 14.3, -2.7, -3.3. HRMS (+p APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{33}\text{H}_{52}\text{O}_2\text{NSi}$ 522.3762; Found: 522.3764.

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-hexyltetrahydro-2*H*-pyran-2-yl)pyrrolidine **3af**. To a solution of racemic δ -undecalactol ($\pm$)-**1f** (258.9 mg, 1.39 mmol, 0.5 M) in CHCl_3 (2.8 mL) was added amine (*S*)-**2a** (204.2 mg, 0.56 mmol, 0.2 M) followed by AcOH (8 μL , 0.14 μmol , 0.05

M). The mixture was concentrated under reduced pressure with a 30% conversion of lactol **1f**. The crude yellow oil was quenched with TEA (0.6 mL, 4.17 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (S)-**1f** (174.5 mg, 0.92 mmol, 66% recovery, 28% ee) and a mixture of hemiaminal ether (R,R,R,S)-**3af** with amine (S)-**2a** in a ratio of 91:9 (total of 279.7 mg, 254.5 mg (R,R,R,S)-**3af** + 25.2 mg of amine (S)-**2a**). *Partial Hydrolysis:* To a mixture of hemiaminal ether (R,R,R,S)-**3af** and amine (S)-**2a** (in a ratio of 91:9, total of 279.7 mg, 254.5 mg (R,R,R,S)-**3af** + 25.2 mg of amine (S)-**2a**) in CDCl₃ (1.0 mL) was added 0.5 mL of AcOH (0.05 M). A ¹H NMR of the organic layer was immediately checked and showed a formation of 33% of the δ-undecalactol (S)-**1f**. The reaction mixture was rapidly quenched with TEA (1.0 mL) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give a mixture of hemiaminal ether (R,R,R,S)-**3af** and amine (S)-**2a** in a ratio of 95:5 (total of 145.4 mg, 138.1 mg of (R,R,R,S)-**3af** + 7.3 mg of amine (S)-**2a**) and free amine (S)-**2a** (94.9 mg, 0.26 mmol).

¹H NMR (500 MHz, CDCl₃) δ 7.56 – 7.52 (m, 2H), 7.48 – 7.44 (m, 2H), 7.29 – 7.23 (m, 6H), 4.57 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.21 (bd, *J* = 9.5 Hz, 1H), 3.28 – 3.23 (m, 1H), 2.89 – 2.83 (m, 1H), 2.28 – 2.23 (m, 1H), 1.93 – 1.79 (m, 2H), 1.74 – 1.70 (m, 1H), 1.62 – 1.17 (m, 18H), 1.08 – 0.99 (m, 1H), 0.91 (s, 9H), 0.36 – 0.26 (m, 1H), -0.36 (s, 3H), -0.50 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 144.6, 143.6, 130.3, 130.0, 127.3, 127.1, 126.7, 126.5, 90.5, 84.0, 76.2, 65.2, 46.9, 36.6, 32.3, 32.0, 31.0, 29.6, 28.9, 26.5, 26.1, 24.2, 24.2, 22.9, 19.1, 14.3, -2.7. HRMS (+p APCI) *m/z*: [M+H]⁺ Calcd for C₃₄H₅₄O₂NSi 536.3913; Found: 536.3900.

Step 2. Recovery of amine (S)-**2a** by oxime formation (4b-4f) and oxime hydrolysis to obtain enantioenriched lactol (R)-(1b-1f).

(R)-5-Hydroxyhexanal oxime **4b**. Reaction of hemiaminal ether (R,R,R,S)-**3ab** (1.6887 g, 3.86 mmol), NH₂OH·HCl (2.6634 g, 38.60 mmol) in CHCl₃ (5.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (R)-**4b** as a colourless oil (0.4723 g, 3.60 mmol, 93%) and amine (S)-**2a** was recovered as a white solid (1.9700 g, 5.36 mmol, 99%). Total recovered amine (S)-**2a** (1.9700 g + 0.3846 g = 2.3186 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (br, 1H), 7.92 (br, 1H), 7.43 (t, *J* = 5.8 Hz, 1H), 6.72 (t, *J* = 5.3 Hz, 1H), 3.87 – 3.78 (m, 2H), 2.43 – 2.38 (m, 2H), 2.26 – 2.21 (m, 2H), 1.68 – 1.46 (m, 8H), 1.21 (d, *J* = 4.0 Hz, 3H), 1.19 (d, *J* = 4.2 Hz, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 152.8, 152.1, 67.9, 67.8, 38.8, 38.6, 29.5, 24.9, 23.7, 23.7, 22.6, 22.4. HRMS (+p APCI) calculated for C₆H₁₄O₂N [M+H]⁺: 132.1019, found: 132.1018. The purified oxime (R)-**4b** (0.4723 g, 3.60 mmol) was then dissolved in 1:1 mixture of 0.5 M HCl:CHCl₃ (12.8 mL) according to the *General Procedure 3* to give enantioenriched lactol (R)-**1b** (0.3829 g, 3.30 mmol, 92%, > 99% ee, [α]_D¹⁸ = +22.5 (c 0.42, CH₂Cl₂)).

(R)-5-Hydroxyoctanal oxime **4c**. Reaction of hemiaminal ether (R,R,R,S)-**3ac** (147.6 mg, 0.30 mmol), NH₂OH·HCl (207.0 mg, 3.0 mmol) in CHCl₃ (1.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (R)-**4c** as a colourless oil (40.7 mg, 0.25 mmol, 83%) and amine (S)-**2a** was recovered as a white solid (201.5 mg, 0.55 mmol, 98%). ¹H NMR (400 MHz, CDCl₃) δ 9.79 (br, 1H), 9.42 (br, 1H), 7.40 (t, *J* = 6.0 Hz, 1H), 6.69 (t, *J* = 5.5 Hz, 1H), 3.67 – 3.56 (m, 2H), 2.43 – 2.31 (m, 2H), 2.22 – 2.17 (m, 2H), 1.69 – 1.29 (m, 16H), 0.89 (d, *J* = 5.9 Hz, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.5, 151.9, 71.3, 71.2, 39.7, 39.6, 36.9, 36.6, 29.5, 25.0, 22.5, 22.2, 18.9, 14.2

(missing 2 carbons). HRMS (+p APCI) *m/z*: [M+H]⁺ Calcd for C₈H₁₈O₂N 160.1332; Found: 160.1332. The purified oxime (R)-**4c** (40.7 mg, 0.25 mmol) was then dissolved in 1:1 mixture of 0.5 M HCl:CHCl₃ (1.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (R)-**1c** (30.1 mg, 0.21 mmol, 84%, > 99% ee).

(R)-5-Hydroxynonanal oxime **4d**. Reaction of hemiaminal ether (R,R,R,S)-**3ad** (163.5 mg, 0.32 mmol), NH₂OH·HCl (220.8 mg, 3.2 mmol) in CHCl₃ (1.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (R)-**4d** as a colourless oil (56.1 mg, 0.32 mmol, 99%) and amine (S)-**2a** was recovered as a white solid (200.3 mg, 0.54 mmol, 98%). ¹H NMR (500 MHz, CDCl₃) δ 9.36 (br, 1H), 9.01 (br, 1H), 7.41 (t, *J* = 5.9 Hz, 1H), 6.70 (t, *J* = 5.5 Hz, 1H), 3.63 – 3.57 (m, 2H), 2.45 – 2.33 (m, 3H), 2.23 – 2.19 (m, 2H), 1.70 – 1.25 (m, 21H), 0.90 – 0.87 (m, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 152.6, 152.0, 71.6, 71.6, 37.3, 37.2, 36.9, 36.7, 29.6, 27.91, 27.92, 25.0, 22.8, 22.6, 22.3, 14.2 (missing 2 carbons). HRMS (+p APCI) *m/z*: [M+H]⁺ Calcd for C₉H₂₀O₂N 174.1489; Found: 174.1486. The purified oxime (R)-**4d** (56.1 mg, 0.32 mmol) was then dissolved in 1:1 mixture of 0.5 M HCl:CHCl₃ (1.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (R)-**1d** (48.1 mg, 0.31 mmol, 97%, 97% ee).

(R)-5-Hydroxydecanal oxime **4e**. Reaction of hemiaminal ether (R,R,R,S)-**3ae** (143.4 mg, 0.27 mmol), NH₂OH·HCl (186.3 mg, 2.7 mmol) in CHCl₃ (1.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (R)-**4e** as a colourless oil (50.1 mg, 0.26 mmol, 96%) and amine (S)-**2a** was recovered as a white solid (193.9 mg, 0.53 mmol, 95%). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (bs, 1H), 8.13 (bs, 1H), 7.43 (t, *J* = 5.9 Hz, 1H), 6.72 (t, *J* = 5.5 Hz, 1H), 3.65 – 3.57 (m, 2H), 2.47 – 2.33 (m, 2H), 2.25 – 2.20 (m, 2H), 1.72 – 1.28 (m, 24H), 0.89 (d, *J* = 6.6 Hz, 6H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 152.8, 152.1, 71.72, 71.69, 37.7, 37.6, 37.0, 36.8, 32.0, 29.6, 25.4, 25.0, 22.8, 22.6, 22.4, 14.2 (missing 4 carbons). HRMS (+p APCI) *m/z*: [M+H]⁺ Calcd for C₁₀H₂₂O₂N 188.1645; Found: 188.1645. The purified oxime (R)-**4e** (50.1 mg, 0.26 mmol) was then dissolved in 1:1 mixture of 0.5 M HCl:CHCl₃ (1.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (R)-**1e** (40.8 mg, 0.24 mmol, 92%, 99% ee).

(R)-5-Hydroxyundecanal oxime **4f**. Reaction of hemiaminal ether (R,R,R,S)-**3af** (138.1 mg, 0.26 mmol), NH₂OH·HCl (179.4 mg, 2.6 mmol) in CHCl₃ (1.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (R)-**4f** as a colourless oil (48.9 mg, 0.24 mmol, 92%) and amine (S)-**2a** was recovered as a white solid (104.1 mg, 0.28 mmol, 98%). Total recovered amine (S)-**2a** (94.9 mg + 104.1 mg = 199.0 mg, 97%). ¹H NMR (500 MHz, CDCl₃) δ 8.93 (br, 1H), 8.60 (br, 1H), 7.42 (t, *J* = 5.9 Hz, 1H), 6.71 (t, *J* = 5.5 Hz, 1H), 3.65 – 3.57 (m, 2H), 2.42 – 2.36 (m, 2H), 2.24 – 2.19 (m, 2H), 1.72 – 1.23 (m, 30H), 0.90 – 0.86 (m, 6H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ 152.7, 152.0, 71.70, 71.65, 37.7, 37.6, 37.0, 36.7, 32.0, 29.6, 29.5, 25.7, 25.0, 22.7, 22.6, 22.3, 14.2 (missing 5 carbons). HRMS (+p ESI) *m/z*: [M+H]⁺ Calcd for C₁₁H₂₃O₂NNa 224.1621; Found: 224.1612. The purified oxime (R)-**4f** (48.9 mg, 0.24 mmol) was then dissolved in 1:1 mixture of 0.5 M HCl:CHCl₃ (1.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (R)-**1f** (39.1 mg, 0.21 mmol, 88%, 99.4% ee).

Protocol to obtain scalemic mixtures.

Step 1. Formation of hemiaminal ethers (3c, 3e).

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-propyltetrahydro-2*H*-pyran-2-yl)pyrrolidine)-1-ol (**3ac**). To a solution of racemic δ -octalactol ($\pm$)-**1c** (9.7741 g, 67.89 mmol, 1.0 M) in CHCl_3 (68.0 mL) was added amine (*S*)-**2a** (4.9685 g, 13.54 mmol, 0.2 M) followed by AcOH (0.2 mL, 3.40 mmol, 0.05 M). The mixture was concentrated under reduced pressure with a 20% conversion of lactol **1c**. The crude yellow oil was quenched with TEA (28.4 mL, 203.67 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1c** (6.0247 g, 41.84 mmol, 62% recovery, 26% ee, $[\alpha]_D^{19} = -9.4$, c 0.51, CH_2Cl_2) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ac** with amine (*S*)-**2a** in a ratio of 94:6 (total of 6.3802 g, 5.9974 g (*R,R,R,S*)-**3ac** + 0.3828 g of amine (*S*)-**2a**).

(2*S*)-2-(((*tert*-Butyldimethylsilyl)oxy(diphenylmethyl)-1-((2*R*,6*R*)-6-pentyltetrahydro-2*H*-pyran-2-yl)pyrrolidine)-1-ol (**3ae**). To a solution of racemic δ -decalactol ($\pm$)-**1e** (10.8000 g, 62.69 mmol, 1.0 M) in CHCl_3 (63.0 mL) was added amine (*S*)-**2a** (4.6000 g, 12.57 mmol, 0.2 M) followed by AcOH (0.2 mL, 3.40 mmol, 0.05 M). The mixture was concentrated under reduced pressure with a 20% conversion of lactol **1e**. The crude yellow oil was quenched with TEA (26.2 mL, 188.07 mmol) and the products were separated after purification by flash column chromatography (9:1:0.5 hexane:EtOAc:TEA followed by 100% EtOAc) to give enantioenriched lactol (*S*)-**1e** (7.1420 g, 41.46 mmol, 66% recovery, 20% ee, $[\alpha]_D^{20} = -5.1$, c 0.64, CH_2Cl_2) and a mixture of hemiaminal ether (*R,R,R,S*)-**3ae** with amine (*S*)-**2a** in a ratio of 75:25 (total of 5.8620 g, 4.3965 g (*R,R,R,S*)-**3ae** + 1.4655 g of amine (*S*)-**2a**).

Step 2. Recovery of amine (*S*)-**2a** by oxime formation (**4c**, **4e**) and oxime hydrolysis to obtain enantioenriched lactol (*R*)-(**4c**, **4e**).

(*R*)-5-Hydroxyoctanal oxime **4c**. Reaction of hemiaminal ether (*R,R,R,S*)-**3ac** (5.9974 g, 12.17 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (8.6307 g, 124.2 mmol) in CHCl_3 (12.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (*R*)-**4c** as a colourless oil (1.8668 g, 11.74 mmol, 95%) and amine (*S*)-**2a** was recovered as a white solid (4.8144 g, 13.11 mmol, 97%).

The purified oxime (*R*)-**4c** (1.8668 g, 11.74 mmol) was then dissolved in 1:1 mixture of 0.5 M $\text{HCl}:\text{CHCl}_3$ (24.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (*R*)-**1c** (1.4708 g, 10.21 mmol, 87%, 82% ee, $[\alpha]_D^{19} = +14.3$, c 0.52, CH_2Cl_2)).

(*R*)-5-Hydroxydecanal oxime **4e**. Reaction of hemiaminal ether (*R,R,R,S*)-**3ae** (4.3965 g, 8.43 mmol), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (5.8167 g, 84.30 mmol) in CHCl_3 (8.0 mL) according to the *General Procedure 2* gave a 1:1 diastereomeric mixture *E/Z* oxime (*R*)-**4e** as a colourless oil (1.4920 g, 7.97 mmol, 95%) and amine (*S*)-**2a** was recovered as a white solid (4.5291 g, 12.4 mmol, 98%). The purified oxime (*R*)-**4e** (1.4920 g, 7.97 mmol) was then dissolved in 1:1 mixture of 0.5 M $\text{HCl}:\text{CHCl}_3$ (16.0 mL) according to the *General Procedure 3* to give enantioenriched lactol (*R*)-**1e** (1.1926 g, 6.93 mmol, 87%, 94% ee, $[\alpha]_D^{20} = +34.6$, c 0.51, CH_2Cl_2)).

Derivatization of lactols (**1b-1f**) to measure the enantiomeric excess by chiral HPLC.

(*R*)-Hexane-1,5-diyl dibenzoate **5b**.¹⁸ Reaction of δ -hexalactol (*R*)-**1b** (25.7 mg, 0.22 mmol), NaBH_4 (42.9 mg, 83.9 mmol) in

MeOH (0.6 mL) according to the *General Procedure 4* gave the crude diol as a colourless oil without further purification. The crude diol was redissolved in CH_2Cl_2 (0.6 mL) followed by the addition of TEA (68.0 μL , 0.66 mmol), DMAP and BzCl (57.0 μL , 0.66 mmol) according to the *General Procedure 4*. The dibenzoylated product (*R*)-**5b** was isolated after purification by preparative TLC ($R_f = 0.70$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 8.04 – 8.00 (m, 4H), 7.56 – 7.52 (m, 2H), 7.44 – 7.39 (m, 4H), 5.24 – 5.16 (m, 1H), 4.33 (t, $J = 6.5$ Hz, 2H), 1.89 – 1.59 (m, 6H), 1.36 (d, $J = 6.3$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 166.3, 133.0, 132.9, 130.9, 130.5, 129.66, 129.65, 128.47, 128.45, 71.5, 64.8, 35.8, 28.7, 22.2, 20.3. HPLC Chiralpak OD-H, hexane/IPA = 98:2, 1 mL/min, 220 nm. $t = 10.3$ min (*S*) and 14.8 min (*R*). LRMS (GC-MS) m/z 325.9 $[\text{M}]^+$.

(*R*)-Octane-1,5-diyl dibenzoate **5c**. Reaction of δ -octalactol (*R*)-**1c** (200 mg, 1.39 mmol), NaBH_4 (271 mg, 6.94 mmol) in MeOH (3.5 mL) according to the *General Procedure 4* gave the crude diol as a colourless oil without further purification. The crude diol was redissolved in CH_2Cl_2 (3.5 mL) followed by the addition of TEA (484 μL , 3.45 mmol), DMAP and BzCl (404 μL , 3.45 mmol) according to the *General Procedure 4*. The dibenzoylated product (*R*)-**5c** was isolated after purification by preparative TLC ($R_f = 0.82$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 7.2$ Hz, 2H), 8.00 (d, $J = 7.2$ Hz, 2H), 7.57 – 7.52 (m, 2H), 7.44 – 7.38 (m, 4H), 5.22 – 5.16 (m, 1H), 4.31 (t, $J = 6.5$ Hz, 2H), 1.87 – 1.59 (m, 7H), 1.54 – 1.35 (m, 3H), 0.93 (d, $J = 7.4$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 166.5, 132.94, 132.90, 130.8, 130.5, 129.68, 129.66, 128.47, 128.45, 74.6, 64.9, 36.6, 34.0, 28.7, 22.1, 18.8, 14.2. HPLC Chiralpak OD-H, hexane/IPA = 98:2, 1 mL/min, 220 nm. $t = 8.3$ min (*S*) and 10.6 min (*R*). HRMS (+p APCI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4$ 355.1904; Found: 355.1905.

(*R*)-Nonane-1,5-diyl dibenzoate **5d**. Reaction of δ -nonalactol (*R*)-**1d** (48.1 mg, 0.31 mmol), NaBH_4 (57.4 mg, 1.55 mmol) in MeOH (0.6 mL) according to the *General Procedure 4* gave the crude diol as a colourless oil without further purification. The crude diol was redissolved in CH_2Cl_2 (0.6 mL) followed by the addition of TEA (108 μL , 0.75 mmol), DMAP and BzCl (87.0 μL , 0.75 mmol) according to the *General Procedure 4*. The dibenzoylated product (*R*)-**5d** was isolated after purification by preparative TLC ($R_f = 0.70$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 8.05 – 7.99 (m, 4H), 7.57 – 7.52 (m, 2H), 7.44 – 7.38 (m, 4H), 5.20 – 5.15 (m, 1H), 4.31 (t, $J = 6.5$ Hz, 2H), 1.86 – 1.65 (m, 6H), 1.39 – 1.28 (m, 6H), 1.26 (d, $J = 7.1$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 166.5, 132.9, 132.9, 130.8, 130.5, 129.7, 129.7, 128.5, 128.4, 74.8, 64.9, 34.1, 34.0, 28.7, 27.7, 22.8, 22.1, 14.1. HPLC Chiralpak OD-H, hexane/IPA = 98:2, 1 mL/min, 220 nm. $t = 8.6$ min (*S*) and 11.3 min (*R*). HRMS (+p ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_4\text{Na}$ 391.1853; Found: 391.1867.

(*R*)-Decane-1,5-diyl dibenzoate **5e**. Reaction of δ -decalactol (*R*)-**1e** (100 mg, 0.58 mmol), NaBH_4 (113 mg, 2.91 mmol) in MeOH (1.5 mL) according to the *General Procedure 4* gave the crude diol as a colourless oil without further purification. The crude diol was redissolved in CH_2Cl_2 (1.5 mL) followed by the addition of TEA (202 μL , 1.45 mmol), DMAP and BzCl (168 μL , 1.45 mmol) according to the *General Procedure 4*. The dibenzoylated product (*R*)-**5e** was isolated after purification by preparative TLC ($R_f = 0.91$, CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 8.04 (d, $J = 7.6$ Hz, 2H), 8.00 (d, $J = 7.6$ Hz, 2H), 7.57 – 7.52 (m, 2H), 7.44 – 7.38 (m, 4H), 5.20 – 5.14 (m, 1H), 4.31 (t, $J = 6.5$ Hz, 2H), 1.86 – 1.65 (m, 6H), 1.43 – 1.25 (m, 8H), 0.86 (d, $J = 6.7$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3) δ 166.8, 166.5, 133.0, 132.9, 130.9, 130.5, 129.7, 129.7, 128.48, 128.45, 74.8, 64.9, 34.4, 34.0,

31.9, 28.7, 25.2, 22.7, 22.1, 14.2. HPLC Chiralpak OD-H, hexane/IPA = 98:2, 1 mL/min, 220 nm. *t* = 7.5 min (*S*) and 9.5 min (*R*). HRMS (+p ESI) *m/z*: [M+H]⁺ Calcd for C₂₄H₃₁O₄ 383.2217; Found: 383.2201.

(*R*)-Undecane-1,5-diyl dibenzoate **5f**. Reaction of δ -undecalactol (*R*)-**1f** (39.1 mg, 0.21 mmol), NaBH₄ (38.9 mg, 1.05 mmol) in MeOH (0.4 mL) according to the *General Procedure 4* gave the crude diol as a colourless oil without further purification. The crude diol was redissolved in CH₂Cl₂ (0.4 mL) followed by the addition of TEA (73 μ L, 0.53 mmol), DMAP and BzCl (61 μ L, 0.53 mmol) according to the *General Procedure 4*. The dibenzoylated product (*R*)-**5f** was isolated after purification by preparative TLC (*R*_f = 0.70, CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.99 (m, 4H), 7.57 – 7.52 (m, 2H), 7.45 – 7.38 (m, 4H), 5.20 – 5.14 (m, 1H), 4.31 (t, *J* = 6.5 Hz, 2H), 1.87 – 1.61 (m, 8H), 1.39 – 1.26 (m, 8H), 0.86 (d, *J* = 6.7 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 166.6, 166.3, 132.8, 132.8, 130.8, 130.4, 129.6, 129.5, 128.3, 128.3, 74.7, 64.7, 34.3, 33.8, 31.7, 29.2, 28.6, 25.3, 22.6, 21.9, 14.1. HPLC Chiralpak OD-H, hexane/IPA = 98:2, 1 mL/min, 220 nm. *t* = 8.6 min (*S*) and 11.0 min (*R*). HRMS (+p ESI) *m/z*: [M+Na]⁺ Calcd for C₂₅H₃₂O₄Na 419.2193; Found: 419.2179.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

CCDC structures, complete experimental procedures, characterization data, NMR spectra and HPLC data (PDF)

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Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

The research leading to these results has received funding from EPSRC (EP/S005315/1) and the European Union FP7/2007-2013 under Grant Agreement No. PCIG 13-GA-2013-618589 (J.B.) and PIEF-GA-2013- 627895 (X.C.).

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