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# Applications of the amino-Cope rearrangement: synthesis of tetrahydropyran, δ-lactone and piperidine targets

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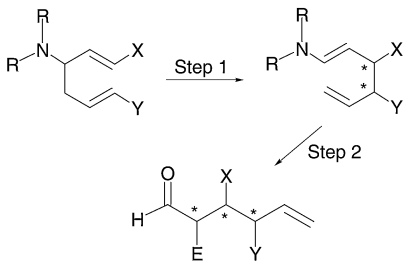
We report a novel approach to some chiral tetrahydropyran and δ-lactone targets that utilizes the asymmetric amino-Cope rearrangement as a key synthetic step. Products of amino-Cope rearrangement chemistry have also been applied to access piperidine targets, further demonstrating the potential of the methodology.

## Introduction

Asymmetric synthetic routes to tetrahydropyran and lactone sub-units are of considerable interest since these heterocyclic components are found in many biologically active molecules and natural products. In this paper we wish to demonstrate the synthetic utility of the asymmetric anionic amino-Cope rearrangement, and highlight its potential for future application in natural product synthesis. The novel route described in this paper delivers functionalized disubstituted tetrahydropyrans and lactones in high enantiomeric excess from readily available precursors. The key step in our synthetic protocol is the introduction of asymmetry by our recently developed asymmetric anionic amino-Cope methodology. To further demonstrate the potential of this chemistry we have achieved the synthesis of a simple piperidine target from a product of an amino-Cope rearrangement.

## Discussion

There is growing interest in asymmetric variants of sigmatropic rearrangements,[1] and we are continuing to develop the amino-Cope rearrangement as a new synthetic protocol. Scheme 1 summarizes our ultimate goal: the one-pot asymmetric synthesis of acyclic targets containing (up to) three contiguous chiral centres *via* amino-Cope rearrangement (step 1) and subsequent (tandem) enamine derivatization and hydrolysis (step 2).




**Scheme 1** Synthetic potential of the amino-Cope rearrangement.

Our group has demonstrated the key steps of this protocol, including a successful tandem amino-Cope rearrangement/enamine derivatization reaction.[2] More recently we have established that an anionic variant of the amino-Cope rearrangement is possible, and that asymmetric induction can be achieved at a chiral centre created during the rearrangement of a diastereoisomerically pure substrate.[3]

Although the precise mechanism of the amino-Cope rearrangement remains a matter for debate,[4] we have demonstrated that the asymmetric amino-Cope rearrangement can have significant advantages over the analogous oxy-Cope rearrangement in terms of asymmetric induction.[5] For example the axial/equatorial preference of an oxy-anion substituent in the proposed chair-like transition state of the oxy-Cope rearrangement can be low, leading to a rearrangement product with a correspondingly low e.e.[6]

The preparation of the 3-amino-1,5-diene substrate required for the asymmetric amino-Cope rearrangement has been detailed elsewhere.[5] Substrate **1** was readily isolated in diastereoisomerically pure form by recrystallization, and the relative stereochemistry has now been confirmed by single crystal X-ray analysis (Fig. 1).

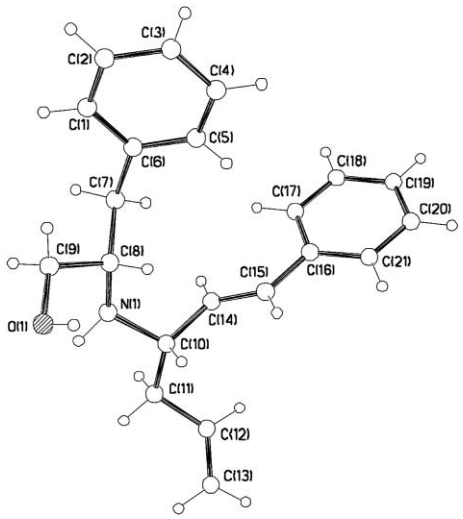



**Fig. 1** Crystal structure of amino-diene **1**.

Amino-Cope rearrangement of **1** was carried out by treating the substrate with 2.5 equivalents of *n*-BuLi at −78 °C in THF, the reaction mixture was subsequently allowed to reach room temperature, and then heated under reflux for 2 h before an aqueous quench (Scheme 2). The target aldehyde **3** was not observed in the crude product mixture by $^1$H NMR spectroscopy, but rather as the oxazolidine **2** resulting, presumably, from ring-closure of the intermediate enamine on work-up. Liberation

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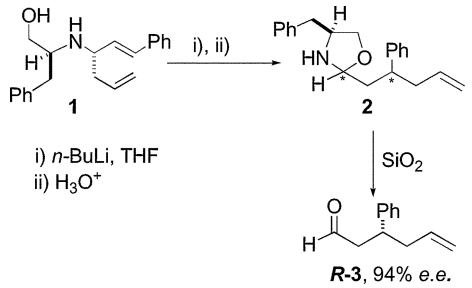



**Scheme 2** Asymmetric amino-Cope rearrangement.

and purification of aldehyde **3** was effected simply by column chromatography of the crude oxazolidine on silica gel.

The enantiomeric excess and absolute configuration of aldehyde **3** was determined by conversion to the corresponding diastereoisomeric oxazolidine derived from 1*R*, 2*S*-(−)-ephedrine, as described by Agami.[7] The absolute stereochemistry induced on rearrangement of the 3-amino-1,5-diene substrates used in all of our studies to date has been rationalized by invoking a chair-like transition state model, **4**, having the amine component occupying a pseudo-equatorial orientation (Fig. 2), although a model such as this is surely an over-simplification. Indeed, as mentioned above, there is currently some debate over the mechanism of the rearrangement, with certain 4-substituted 3-amino-1,5-dienes having been shown[4] to rearrange by a stepwise mechanism. Nevertheless, model **4** provides a useful "rule of thumb" in our studies.

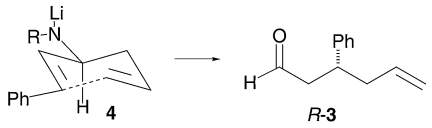



**Fig. 2** Predictive model for amino-Cope rearrangement.

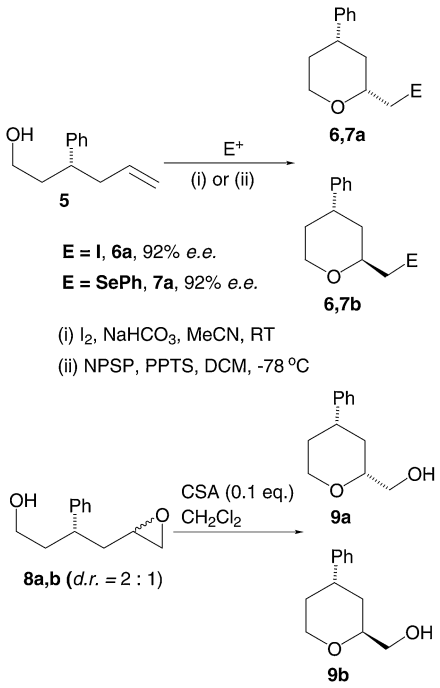
One useful method for the formation of oxygen heterocycles involves the electrophile-induced cyclization of an unsaturated alcohol precursor.[8] We were able to access the corresponding alcohol **5** from aldehyde **3** in 99% yield by sodium borohydride reduction. Analysis of **5** by chiral HPLC[9] showed essentially the same level of e.e. for the alcohol product (92%) as was observed for the aldehyde precursor by NMR determination.

With **5** in hand we performed an iodine-induced cyclization at room temperature ($I_2$, $NaHCO_3$, MeCN) and achieved an almost quantitative conversion to the target iodo-THP **6** (Scheme 3). $^1$H NMR analysis of the crude reaction mixture revealed that the cyclization had proceeded with a diastereoselectivity of 4 : 1 in favour of the *cis*-diastereoisomer **6a**.[10]

The major diastereoisomer **6a** was isolated by column chromatography in 60% yield and further analysis by chiral HPLC[11] showed this compound to have an e.e. of 92%, confirming no loss of stereochemical integrity during cyclization.

After our success with iodine as the electrophile we chose to investigate a variant of this cyclization methodology. The phenylselenyl group is a useful handle that can allow further molecular elaboration, and by applying a suitable selenium electrophile, *N*-(phenylseleno)phthalimide (NPSP, 1.7 eq.), in the presence of pyridinium *p*-toluenesulfonate (PPTS, 0.3 eq.) in dichloromethane at −78 °C we were able to achieve cyclization to the corresponding tetrahydropyran products. In this case, however, a 1 : 1 diastereoisomeric ratio was observed by $^1$H NMR analysis of the crude reaction mixture. We were able to separate each component by column chromatography to yield 39% of **7a** and 36% of **7b**.

A significant reduction in the level of product diastereoselectivity is observed on moving from the $I^+$ to the $PhSe^+$ electrophile; this has been noted previously by Greeves for similar substrates and is referred to in more detail below.[8c]







**Scheme 3** Electrophile-mediated cyclizations to access tetrahydropyran targets.

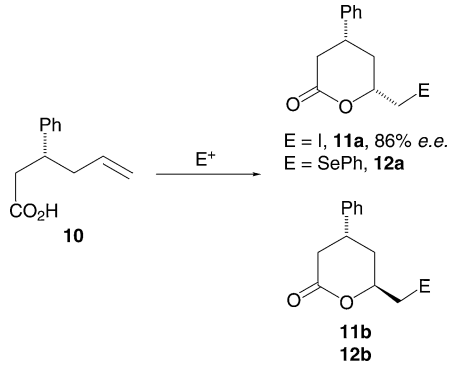
Analysis of the separated diastereoisomers by chiral HPLC[11] showed that THP **7a** had an e.e. of 92%, again in good agreement with the e.e. of the starting alcohol **5**. The chromatogram of THP **7b** was not fully resolved, although the HPLC trace clearly showed that the compound was highly enantiomerically enriched.

One final class of tetrahydropyran was prepared through epoxidation of the double bond followed by treatment with catalytic CSA. The intermediate epoxides (a 2 : 1 mixture of diastereoisomers **8a** and **8b**) were not separated, but directly treated with CSA in dichloromethane at 0 °C to yield the target THP **9** as a 2 : 1 mixture of diastereoisomers. We were able to separate the diastereoisomers to yield 28% of the major diastereoisomer **9a** and 12% of **9b**, and confirm the relative stereochemistries by comparison with the $^1$H NMR spectra of the iodotetrahydropyrans.[10] In this case we were unable to confirm the e.e. of either diastereoisomer by NMR or HPLC techniques.

Based on the success of the approach described above, we then investigated a similar electrophile-induced cyclization route to access the target δ-lactones, as described by others.[12] We were able to access the corresponding carboxylic acid derivative **10** from aldehyde **3** in 70% yield by sodium chlorite oxidation. We then performed an iodine-induced cyclization at low temperature ($I_2$, $NaHCO_3$, THF, −78 °C) and isolated the target iodolactone **11** in 70% overall yield (Scheme 4). $^1$H NMR analysis of the crude reaction mixture revealed that the cyclization reaction gave an excellent level of diastereoselectivity of 13 : 1, which was confirmed by single crystal X-ray analysis of the isolated major isomer to be in favour of the *cis*-diastereoisomer, **11a** (Fig. 3).

The major diastereoisomer **11a**, isolated by column chromatography, was shown to have an e.e. of 86% by chiral HPLC[13] confirming minimal loss of stereochemical integrity during derivatization and subsequent cyclization of the aldehyde.

Performing this cyclization under a range of alternative reaction conditions gave variation in both the *cis* : *trans* isomer ratio and the product yield, although all other conditions investigated gave inferior diastereoisomeric ratios to the low temperature cyclization described above (−78 °C, kinetic conditions). For example, raising the reaction temperature in THF to room temperature gave a 6 : 1 ratio in favour of the *cis*-diastereoisomer, **11a**, with a slightly improved overall yield of 75%. Alternatively,




**Scheme 4** Electrophile-mediated cyclizations to access lactone targets.

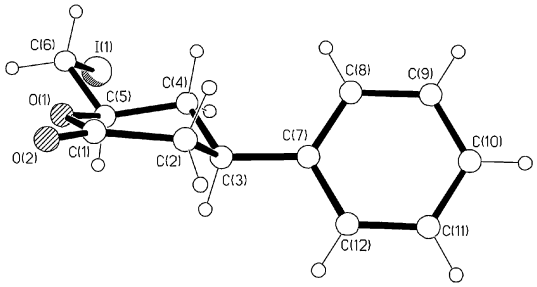



**Fig. 3** Crystal structure of **11a**

use of acetonitrile as solvent at 0 °C gave a 6 : 1 ratio (*cis* : *trans*) in 70% overall yield, and at room temperature gave 4 : 1 (*cis* : *trans*) in 73% overall yield.

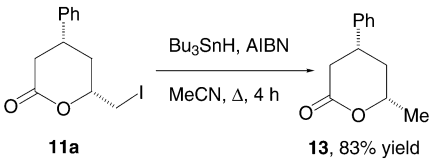
Selective formation of *cis*-3,5-disubstituted lactones *via* iodolactonization has been noted by others,[14] and is consistent with a chair-like transition state with attack onto a pseudo-equatorial iodonium species during cyclization, as is also suggested by our own X-ray crystal structure of **11a** (Fig. 3).

By applying a selenium electrophile, phenylselenium chloride (1.1 eq.), in the presence of pyridine (1.1 eq.) in dichloromethane at −78 °C we were able to achieve cyclization of **10** to deliver the corresponding δ-lactone product **12** in 71% overall yield (Scheme 4). In this case a 3 : 1 diastereoisomeric ratio, again in favour of the *cis*-isomer **12a**, was observed by $^1$H NMR analysis of the crude reaction mixture.[15] We were unable to separate the diastereoisomeric components of this mixture by column chromatography, and so were unable to determine the e.e. of the major isomer. Based on the iodolactonization result described above for the carboxylic acid, and also our results detailing the synthesis of the enantiomerically enriched tetrahydropyrans using a selenium-induced cyclization route, we would not expect to observe any significant loss of e.e. during this current derivatization procedure.

In the case of the seleno-lactonization procedure, variation of the reaction conditions (kinetic *vs*. thermodynamic) had little effect on the diastereoselectivity of the cyclization. For example, use of dichloromethane solvent at room temperature gave a 2 : 1 ratio (*cis* : *trans*; **12a** : **12b**) in 58% yield. Use of THF solvent at −78 °C gave 2 : 1 (*cis* : *trans*) in 67% yield, and at room temperature only a 1.5 : 1 ratio in 55% yield.

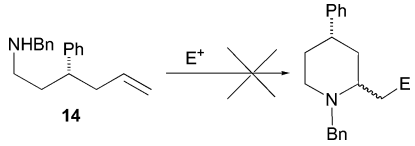
Again a significant reduction in the level of product diastereoselectivity is observed on moving from the $I^+$ to the $PhSe^+$ electrophile. We believe that this may result from a reduced preference by the $PhSe^+$ electrophile to adopt the equatorial orientation during cyclization *via* a chair-like transition state that is clearly favoured by $I^+$. Indeed, the work of Greeves shows that $PhSe^+$ favours an axial orientation during cyclization of δ,ε-unsaturated hexenols to yield the corresponding tetrahydropyran products.[8c]

We were able to further manipulate lactone **11a** by removing the iodo-substituent using a radical induced method (Scheme 5) to generate the methyl-substituted derivative, **13**.




**Scheme 5** Dehalogenation of lactone **11a**.

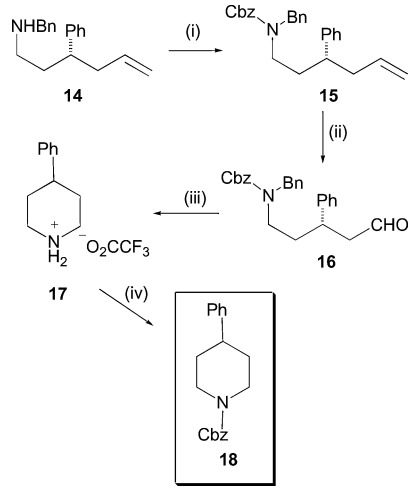
Having achieved the asymmetric synthesis of tetrahydropyran and lactone products we turned our attention to piperidine targets, and so were required to achieve a successful cyclization of an aminated derivative of aldehyde **3**. The starting point for this study was the model secondary amine derivative **14**, prepared in 73% yield by reductive amination of **3** with benzylamine. Despite repeated attempts to access the corresponding piperidine targets through application of known electrophile-induced cyclization methodologies (Scheme 6), we were unable to induce formation of the target heterocycle.




**Scheme 6** Attempted electrophile-induced cyclizations to access piperidines: $E^+$ = (i) $I_2$;[16] (ii) $Hg(OCOCF_3)_2$;[17] (iii) $PdCl_2$;[18] (iv) PhSeCl and PhSeBr.[19]

Although the precise reason for the failure to observe cyclization of **14** is not known, it should be noted that in most cases the substrates reported in literature were more heavily substituted than **14**, and consequently the resulting conformational effects may perhaps lead to a more favourable arrangement of the carbon backbone to allow for cyclization with other substrate types.

Finally we decided to employ the oxidative cleavage-cyclization route, described by Xue[20] and highlighted in Scheme 7, in order to access the corresponding 4-phenylpiperidine derivative **18**.




**Scheme 7** Successful synthesis of a piperidine target. *Reagents and conditions*: (i) *N*-(benzyloxycarbonyloxy)succinimide, NMM, DCM, RT, 18 h (79%); (ii) $O_3$, $PPh_3$, DCM, RT, 18 h, (85%); (iii) $H_2$ (50 psi), Pd/C, TFA, MeOH, RT, 18 h; (iv) *N*-(benzyloxycarbonyloxy)succinimide, NMM, DCM, RT, 18 h (29%).

As noted in Scheme 7, protection of the secondary amine as its Cbz-analogue, **15**, was followed by ozonolysis to yield the amino-aldehyde, **16**. One-pot reductive removal of both benzyl and Cbz-protecting groups induced *in situ* cyclization of the primary amine product to generate the 4-phenyl piperidine derivative **17** that was initially isolated as its TFA salt but then used as crude

to access the Cbz-protected piperidine target **18**, that was easier to handle. Although this method generates an achiral piperidine in this case (due to the centre of symmetry in **18**), the importance of having, eventually, discovered a suitable method to access the important piperidine nucleus from simple products of amino-Cope rearrangement should not be overlooked.

In summary, we have demonstrated the preparation of various substituted tetrahydropyran, lactone and piperidine targets, with high enantiomeric excess in the asymmetric series, representing the first synthetic applications of the asymmetric amino-Cope rearrangement.

## Experimental

Where necessary, solvents were dried, distilled and stored over 4 Å molecular sieves prior to use. Reagent chemicals were purchased from Lancaster Synthesis Ltd. and Aldrich Chemical Co. Ltd, and were purified where necessary before use.

Flash-column chromatography was carried out using Merck silica gel (70–230 Mesh ASTM). Analytical thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under UV light (at 254 nm) or by staining with either potassium permanganate solution or iodine. Yields quoted are for isolated, purified products.

IR spectra were recorded in the range 4000–600 $cm^{-1}$, using a Perkin Elmer Paragon 100 FT-IR spectrometer as Nujol mulls or as liquid films. $^1H$ and $^{13}C$ NMR spectra were recorded using either a Bruker Avance 400 MHz Spectrometer or a Bruker AC 250 MHz Spectrometer. NMR samples were made up in deuterated solvents with all values quoted in ppm relative to TMS as reference. Coupling constants ($J$ values) are reported in hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the proton NMR spectra. Mass spectra were recorded using a Fisons VG Quattro II SQ instrument and accurate-mass mass spectra were recorded using a Kratos MS80 instrument. Melting points were determined on a Gallenkamp Melting Point apparatus. Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Optical rotations were performed using an Optical Activity AA-10 Automatic Polarimeter and are reported in units of $10^{-1}$ deg $cm^2$ $g^{-1}$ at 20 °C.

### (3*R*)-3-Phenylhex-5-enol, 5 [21]

Aldehyde **3** (0.20 g, 1.2 mmol) was dissolved in methanol (20 $cm^3$) and cooled to 0 °C in an ice-bath. Sodium borohydride (0.13 g, 3.5 mmol) was added neat in two portions and the mixture stirred for 2 h whilst warming slowly to room temperature. The solvent was removed under reduced pressure and the gelatinous residue was dissolved in dichloromethane (30 $cm^3$), to which flash silica (0.50 g) was added and the solvent removed again. Flash column chromatography on silica, eluting with hexane–diethyl ether (4 : 1) gave alcohol **5** (0.20 g, 99%) as a colourless oil: $\nu_{max}$ (film)/$cm^{-1}$ 3334, 3076, 3027, 2928, 1640, 1602, 1494, 1452, 1440, 1047, 1028, 994, 913, 761 and 701; $\delta_H$ (400 MHz; $CDCl_3$) 1.25 (1 H, br s, O*H*), 1.80 (1 H, m, C*H*HCH$_2$OH), 1.99 (1 H, m, CH*H*CH$_2$OH), 2.38 (2 H, t, C$H_2$CH=CH$_2$), 2.80 (1 H, m, C*H*Ph), 3.46 (1 H, m, C*H*HOH), 3.54 (1 H, m, CH*H*OH), 4.96 (2 H, m, CH=C$H_2$), 5.67 (1 H, m, C*H*=CH$_2$), 7.19 (3 H, m, Ar-*H*) and 7.30 (2 H, m, Ar-*H*); $\delta_C$ (100 MHz; $CDCl_3$) 39.0 ($CH_2$), 41.7 ($CH_2$), 42.7 (CH), 61.3 ($CH_2$), 116.6 ($CH_2$), 126.7 (CH), 128.0 (2 × CH), 128.8 (2 × CH), 137.1 (CH) and 144.9 (q); $m/z$ (EI) 176 ($M^+$, 3%), 158 (9), 135 (43), 131 (8), 117 (9), 105 (100), 91 (52) and 77 (6). Found $M^+$ 176.12008; $C_{12}H_{16}O$ requires 176.12011.

HPLC analysis (ChiralCel OD, hexanes–propan-2-ol [95 : 5], 0.6 mL $min^{-1}$) gave an e.e. of 92% which is in good agreement with the e.e. of the starting aldehyde measured by $^1H$ NMR.

### (2*R*, 4*S*) and (2*S*, 4*S*)-2-(Iodomethyl)-4-phenyltetrahydro-2*H*-pyran, 6a and 6b

A solution of alcohol **5** (0.08 g, 0.57 mmol) in acetonitrile (15 $cm^3$) was stirred with 4 Å MS and sodium hydrogencarbonate (0.15 g, 1.8 mmol) at room temperature. Iodine (0.44 g, 1.7 mmol) was added in one portion and the mixture stirred for 24 h before quenching with saturated aqueous sodium thiosulfate solution (2 $cm^3$). The acetonitrile was removed under reduced pressure and the residue was partitioned between ethyl acetate and water (40 $cm^3$, 1 : 1). The organic layer was removed and the aqueous portion extracted with a further 20 $cm^3$ of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil which was shown to be a mixture of diastereoisomers (4 : 1) by $^1H$ NMR spectroscopy. Flash column chromatography on silica gel, eluting with light petroleum (bp range 40–60 °C)–ethyl acetate (10 : 1) gave the major diastereoisomer **6a** (0.08 g, 60%) as a colourless oil (the minor diastereoisomer **6b** was isolated using preparative TLC to provide a $^1H$ NMR reference thus enabling d.e. measurement).

**6a**: $\nu_{max}$ (film)/$cm^{-1}$ 3060, 3026, 2934, 2828, 1602, 1494, 1452, 1378, 1254, 1193, 1125, 1084, 1029, 1012, 756 and 699; $\delta_H$ (400 MHz; $CDCl_3$) 1.39 (1 H, dt, $J$ 12.3 and 11.1, C(3)$H_{ax}$H), 1.77 (2 H, m, C(5)$H_2$), 2.04 (1 H, m, C(3)H$H_{eq}$), 2.82 (1 H, tt, $J$ 11.6 and 4.4, C$H_{ax}$Ph), 3.22 (1 H, dd, $J$ 10.4 and 6.4, C*H*HI), 3.25 (1 H, dd, $J$ 10.4 and 5.2, CH*H*I), 3.46 (1 H, m, C(2)$H_{ax}$), 3.63 (1 H, m, C$H_{ax}$HO), 4.19 (1 H, ddd, $J$ 11.6, 4.4 and 1.8, CH$H_{eq}$O) and 7.21–7.34 (5 H, m, Ar-*H*); $\delta_C$ (100 MHz; $CDCl_3$) 9.9 ($CH_2$), 33.4 ($CH_2$), 39.6 ($CH_2$), 41.8 (CH), 68.9 ($CH_2$), 77.4 (CH), 126.9 (CH), 127.1 (2 × CH), 129.1 (2 × CH) and 145.4 (q); $m/z$ (EI) 302 ($M^+$, 32%), 175 (33), 161 (100), 131 (28), 117 (23), 104 (25), 91 (43), 77 (12) and 43 (15). Found $M^+$ 302.01672; $C_{12}H_{15}IO$ requires 302.01676.

HPLC analysis (ChiralCel OD-H, hexanes–propan-2-ol [99.5 : 0.5], 0.25 mL $min^{-1}$) gave an e.e. of 92% that is in good agreement with the e.e. of the starting alcohol.

**6b**: $\delta_H$ (400 MHz; $CDCl_3$)1.91 (4 H, m, C(3)$H_2$ and C(5)$H_2$), 3.08 (1 H, m, C$H_{ax}$Ph), 3.41 (2 H, m, C$H_2$I), 3.80 (2 H, t, C$H_2$O), 3.95 (1 H, m, C(2)$H_{eq}$) and 7.22–7.37 (5 H, m, Ar-*H*).

### (2*R*,4*S*) and (2*S*,4*S*)-4-Phenyl-2-[(phenylseleno)methyl]-tetrahydro-2*H*-pyran, 7a and 7b

A solution of alcohol **5** (0.068 g, 0.39 mmol) in dry dichloromethane (20 $cm^3$) was cooled to −78 °C. Pyridinium *p*-toluenesulfonate (0.032 g, 0.12 mmol) was added and the mixture was stirred for 10 min before addition of neat *N*-phenylselenylphthalimide (0.208 g, 0.68 mmol) in one portion. The reaction was stirred at −78 °C for 2 h then for a further 3 h at 0 °C. When the reaction was complete by TLC the solution was filtered through Celite and the solvent then removed under reduced pressure furnished a yellow oil which was shown to be a mixture of diastereoisomers (1 : 1) by $^1H$ NMR spectroscopy. Flash column chromatography on silica gel, eluting with light petroleum (bp range 40–60 °C)–ethyl acetate (7 : 1) gave **7a** (0.048 g, 39%) and **7b** (0.045 g, 36%) as light yellow oils.

**7a**: $\nu_{max}$ (film)/$cm^{-1}$ 3056, 3025, 2932, 2845, 1601, 1577, 1493, 1477, 1451, 1436, 1377, 1251, 1155, 1124, 1085, 1072, 1022, 1012, 756, 736, 691 and 669; $\delta_H$ (400 MHz; $CDCl_3$) 1.51 (1 H, m, C(3)$H_{ax}$H), 1.77 (2 H, m, C(5)$H_2$), 2.03 (1 H, m, C(3)H$H_{eq}$), 2.77 (1 H, m, C$H_{ax}$Ph), 2.98 (1 H, dd, $J$ 12.0 and 5.6, C*H*HSePh), 3.13 (1 H, dd, $J$ 12.0 and 6.8, CH*H*SePh), 3.60 (2 H, m, C(2)$H_{ax}$ and C$H_{ax}$HO), 4.15 (1 H, m, CH$H_{eq}$O) and 7.19–7.30 (8H, m, Ar-*H*), 7.51–7.53 (2 H, m, Ar-*H*); $\delta_C$ (100 MHz; $CDCl_3$) 33.3 ($CH_2$), 33.5 ($CH_2$), 39.2 ($CH_2$), 41.6 (CH), 68.5 ($CH_2$), 77.3 (CH), 126.4 (CH), 126.7 (CH), 126.8 (2 × CH), 128.6 (2 × CH), 129.1 (2 × CH), 130.6 (q), 132.5 (2 × CH) and 145.4 (q); $m/z$ (EI) 332 ($M^+$, 74%), 161 (99), 143 (23), 131 (31), 117 (38), 105 (46), 91 (100), 77 (32), 57 (19) and 43 (24). Found $M^+$ 332.06827; $C_{18}H_{20}OSe$ requires 332.06793.

HPLC analysis (ChiralCel OD-H, hexanes–propan-2-ol [99.5 : 0.5], 0.25 mL $min^{-1}$) clearly showed that the sample was greatly enantiomerically enriched when compared to an authentic racemic sample, although full baseline separation was not achieved.

**7b**: $[a]_D^{25}$ −20.0 ($c = 0.6$, $CHCl_3$); $\nu_{max}$ (film)/$cm^{-1}$ 3056, 3025, 2932, 2845, 1601, 1577, 1493, 1477, 1451, 1436, 1377, 1251, 1155, 1124, 1085, 1072, 1022, 1012, 756, 736, 691 and 669; $\delta_H$ (400 MHz; $CDCl_3$) 1.91 (3 H, m, C(3)$H_2$ and C(5)H$H_{ax}$), 2.09 (1 H, ddd, $J$ 13.6, 9.2 and 4.4, C(5)$H_{eq}$H), 3.01 (1 H, m, C$H_{ax}$Ph), 3.10 (1 H, dd, $J$ 12.0 and 7.2, C$H$HSePh), 3.35 (1 H, dd, $J$ 12.0 and 7.2, CH$H$SePh), 3.79 (2 H, m, C(2)$H_{eq}$ and C$H_{ax}$HO), 4.06 (1 H, tt, $J$ 7.2 and 4.8, CH$H_{eq}$O), 7.18–7.32 (8H, m, Ar-$H$), 7.51–7.55 (2 H, m, Ar-$H$); $\delta_C$ (100 MHz; $CDCl_3$) 30.5 ($CH_2$), 32.1 ($CH_2$), 35.2 (CH), 35.3 ($CH_2$), 62.2 ($CH_2$), 72.4 (CH), 126.2 (CH), 127.0 (CH), 127.1 (2 × CH), 128.5 (2 × CH), 129.1 (2 × CH), 130.1 (q), 132.9 (2 × CH), 144.6 (q); $m/z$ (EI) 332 ($M^+$, 40%), 161 (100), 143 (17), 131 (24), 117 (28), 105 (35), 91 (73), 77 (23), 57 (14) and 43 (18). Found $M^+$ 332.06811; $C_{18}H_{20}OSe$ requires 332.06793.

The e.e. determined by HPLC analysis was in good agreement with that of the starting alcohol (92%, ChiralCel OD-H, hexanes–propan-2-ol [99.5 : 0.5], 0.25 mL $min^{-1}$).

### (3*S*, 5*R*) and (3*S*, 5*S*)-4-Oxiranyl-3-phenylbutan-1-ol, 8a and 8b

Alcohol **5** (0.20 g, 1.1 mmol) was dissolved in dichloromethane (20 $cm^3$) and cooled to 0 °C in an ice-bath. Purified *m*-chloroperbenzoic acid (0.49 g, 2.8 mmol) was added portion-wise over 5 min to the stirred alcohol solution followed by sodium hydrogencarbonate (0.27 g, 3.2 mmol). After 18 h the crude reaction mixture was washed with saturated sodium sulfite solution (2 × 20 $cm^3$) to remove excess *m*CPBA and the organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation of solvent under reduced pressure furnished the crude epoxide. To prevent spontaneous cyclisation, flash column chromatography on silica gel, eluting with diethyl ether–hexane (2 : 1), had to be performed quickly and gave a mixture of inseparable epoxides **8a** and **8b** (0.16 g, 73%) as a light yellow oil with a diastereoisomeric ratio of 2 : 1.

Analysis of mixture: $\nu_{max}$ (film)/$cm^{-1}$ 3405, 3027, 2930, 1602, 1494, 1453, 1261, 1047, 847, 764 and 702; $\delta_H$ (400 MHz, $CDCl_3$) (* = minor isomer) 1.66–2.07 (4 H, m, C$H_2$CH(Ph)C$H_2$), 2.22 (1 H, br. s, O$H$), 2.29 (1 H, dd, $J$ 4.9 and 2.8, CH(O)C$H$H), 2.44* (1 H, dd, $J$ 4.9 and 2.8, CH(O)C$H$H), 2.58 (1 H, t, $J$ 4.9, CH(O)CH$H$), 2.60* (1 H, t, $J$ 4.9, CH(O)CH$H$), 2.73 (1 H, m, C$H$(O)$CH_2$), 2.80* (1 H, m, C$H$(O)$CH_2$), 2.99 (1 H, m, PhC$H$), 3.48 (2 H, m, C$H_2$OH) and 7.19–7.32 (5 H, m, Ar-$H$); $\delta_C$ (100 MHz, $CDCl_3$) (* = minor isomer) 39.1* ($CH_2$), 39.7 ($CH_2$), 39.9* ($CH_2$), 40.2* (CH), 40.4 ($CH_2$), 40.5 (CH), 47.7* ($CH_2$), 47.9 ($CH_2$), 51.2* (CH), 51.5 (CH), 60.9 ($CH_2$), 126.9 (CH), 127.9* (CH), 128.0 (2 × CH), 129.0 (2 × CH), 144.4* (q) and 144.5 (q); $m/z$ (EI) 192 ($M^+$, 5%), 161 (45), 156 (16), 143 (36), 129 (48), 117 (52), 105 (100), 91 (92), 77 (22) and 71 (16). Found $M^+$ 192.11486; $C_{12}H_{16}O_2$ requires $M^+$ 192.11503.

### [(2*R*,4*S*) and (2*S*,4*S*)-4-Phenyltetrahydro-2*H*-pyran-2-yl]-methanol, 9a and 9b

A solution of epoxides **8a** and **8b** (0.153 g, 0.80 mmol) in dichloromethane (20 $cm^3$) was stirred at room temperature with a catalytic amount of camphorsulfonic acid (0.019 g, 0.08 mmol) for 20 h. The organic layer was washed once with saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to give a colourless oil which was shown to be a mixture of diastereoisomers (2 : 1) by $^1$H NMR spectroscopy. Flash column chromatography on silica gel, eluting with diethyl ether–hexanes (2 : 1) gave tetrahydropyrans **9a** (0.043 g, 28%) and **9b** (0.018 g, 12%) as colourless oils.

**9a**: $\nu_{max}$ (film)/$cm^{-1}$ 3421, 3027, 2934, 2849, 1602, 1495, 1452, 1381, 1259, 1131, 1086, 1069, 1040, 996, 758 and 700; $\delta_H$ (400 MHz; $CDCl_3$) 1.53 (1 H, m, C(3)$H_{ax}$H), 1.84 (3 H, m, C(3)H$H_{eq}$ and C(5)$H_2$), 2.43 (1 H, br s, O$H$), 2.81 (1 H, m, C$H_{ax}$Ph), 3.62 (4 H, m, C$H_2$OH, C(2)$H_{ax}$ and C$H_{ax}$HO), 4.19 (1 H, ddd, $J$ 11.6, 6.0 and 3.6, CH$H_{eq}$O) and 7.19–7.36 (5 H, m, Ar-$H$); $\delta_C$ (100 MHz, $CDCl_3$) 33.9 ($CH_2$), 35.3 ($CH_2$), 41.6 (CH), 66.6 ($CH_2$), 68.4 ($CH_2$), 78.5 (CH), 126.8 (CH), 127.1 (2 × CH), 128.9 (2 × CH) and 140.6 (q); $m/z$ (EI) 192 ($M^+$, 10%), 161 (100), 143 (14), 131 (12), 117 (24), 105 (25), 91 (27) and 77 (8). Found $M^+$ 192.11503; $C_{12}H_{16}O_2$ requires 192.11503.

**9b**: $\delta_H$ (400 MHz; $CDCl_3$) 1.82 (1 H, m, C(3)$H_{ax}$H), 2.00 (3 H, m, C(3)H$H_{eq}$ and C(5)$H_2$), 2.43 (1 H, br s, O$H$), 3.08 (1 H, m, C$H_{ax}$Ph), 3.57 (1 H, m, C(2)$H_{eq}$), 3.84 (4 H, C$H_2$OH and C$H_{ax}$C$H_{eq}$O) and 7.19–7.36 (5 H, m, Ar-$H$); $\delta_C$ (63 MHz, $CDCl_3$) 32.0 ($CH_2$), 32.7 ($CH_2$), 35.5 (CH), 62.7 ($CH_2$), 63.6 ($CH_2$), 73.7 (CH), 126.5 (CH), 127.6 (2 × CH), 128.9 (2 × CH) and 140.5 (q).

### (3*R*)-3-Phenyl-hex-5-enoic acid, 10[22]

Aldehyde **3** (0.10 g, 0.57 mmol) was dissolved in aqueous buffer (pH 4.0, 20 $cm^3$) and cooled to 0 °C in an ice-bath. Sodium chlorite (80% w/w, 0.195 g, 1.72 mmol) was added neat in two portions followed by 2-methyl-2-butene (2.0 M, 0.86 $cm^3$, 1.72 mmol) and the mixture was stirred vigorously for 3 h. The aqueous solution was extracted with dichloromethane (3 × 30 $cm^3$), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to furnish an orange oil. Flash column chromatography on silica gel, eluting with hexanes-diethyl ether (4 : 1) gave carboxylic acid **10** (0.075 g, 70%) as a yellow oil: $[a]_D^{25} = -20.0$ ($c = 1.27$, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 3357, 3063, 3028, 2924, 2855, 1706, 653, 1640, 1602, 1553, 1494, 1453, 1276, 1161, 1031, 911, 735 and 700; $\delta_H$ (250 MHz; $CDCl_3$) 2.41 (2H, t, $J$ 7.0, C$H_2$), 2.62 (1H, dd, $J$ 15.5 and 7.4, CH$H$C(O)OH), 2.75 (1H, dd, $J$ 15.7 and 6.7, CH$H$C(O)OH), 3.22 (1H, m, C$H$Ph), 5.02 (2H, m, =C$H_2$), 5.65 (1H, m, C$H$=) and 7.19–7.33 (5H, m, Ar$H$); $\delta_C$ (100 MHz; $CDCl_3$) 39.6 ($CH_2$), 40.4 ($CH_2$), 40.8 (CH), 116.0 ($CH_2$), 126.9 (CH), 127.2 (2 × CH), 127.9 (2 × CH), 134.8 (CH), 142.9 (q), and 177.2 (q); $m/z$ (EI) 190 ($M^+$, 15%), 149 (30), 107 (100), 91 (23) and 79 (24); Found $M^+$ 190.09982; $C_{12}H_{14}O_2$ requires 190.09938.

### (4*R*, 6*R*)- and (4*R*, 6*S*)-6-Iodomethyl-4-phenyltetrahydro-2*H*-pyran-2-one, 11a and 11b[23]

A solution of carboxylic acid **10** (0.090 g, 0.48 mmol) in THF (20 $cm^3$) was stirred with 4Å molecular sieves and sodium hydrogencarbonate (0.394 g, 1.58 mmol) at room temperature. Iodine (0.134 g, 1.58 mmol) was added and the mixture stirred for 24 h before being quenched with saturated aqueous sodium thiosulfate solution (2 $cm^3$). Solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and brine (40 $cm^3$, 1 : 1). The organic layer was removed and the aqueous portion extracted with further 20 $cm^3$ of dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and solvent removed under reduced pressure to give orange oil which was shown to be a mixture of diastereoisomers (4 : 1) by $^1$H NMR. Flash column chromatography on silica gel, eluting with hexanes–diethyl ether (1 : 1) gave the major diastereoisomer **11a** (0.080 g, 53%) as a light yellow solid. The minor diastereoisomer **11b** (0.030 g, 20%) as a colourless oil which was obtained using preparative TLC.

**11a**: $\nu_{max}$ (film)/$cm^{-1}$ 1734, 1630, 1600, 1454, 1228, 1179, 1035 and 756; $\delta_H$ (400 MHz; $CDCl_3$) 1.86 (1H, ddd, $J$ 13.6, 12.4 and 11.6, C(5)$H_{ax}$), 2.43 (1H, ddd, $J$ 13.6, 5.2 and 3.2, C(5)$H_{eq}$), 2.57 (1H, dd, $J$ 18 and 12, C(3)$H_{ax}$), 2.92 (1H, ddd, $J$ 18, 5.6 and 2.0, C(3)$H_{eq}$), 3.21–3.25 (1H, m, C$H$Ph), 3.38 (1H, dd, $J$ 10.8 and 6.4, C$H$I), 3.44 (1H, dd, $J$ 10.4 and 4.4, C$H$I), 4.37–4.42 (1H, m, C(6)$H_{ax}$) and 7.20–7.39 (5H, m, Ar$H$); $\delta_C$ (100 MHz; $CDCl_3$)

8.1 ($CH_2$), 36.7 ($CH_2$), 37.4 (CH), 37.6 ($CH_2$), 78.8 (CH), 126.8 (2 × CH), 127.8 (CH), 129.5 (2 × CH), 142.5 (q) and 170.1 (q); *m/z* (EI) 316 ($M^+$, 20%), 189 (11), 175 (10), 131 (50), 129 (100), 104 (53), 91 (21), 77 (31) and 43 (13); Found $M^+$ 315.99623; $C_{12}H_{13}O_2I$ requires 315.99603.

HPLC analysis (ChiralCel OD-H, hexanes–propan-2-ol [99 : 1], 0.25 mL $min^{-1}$) gave an e.e. of 86%. Retention times: major enantiomer = 16.96 min, minor = 14.57 min.

**11b**: $\nu_{max}$ (film)/$cm^{-1}$ 1734, 1630, 1600, 1454, 1228, 1179, 1035 and 756; $\delta_H$ (400 MHz; $CDCl_3$) 2.25 (2H, t, *J* 4.0, C(5)$H_2$), 2.79–2.87 (2H, m, C(3)$H_2$), 3.31–3.43 (3H, m, C$H_2$I and C*H*Ph), 4.36 (1H, ddd, *J* 12.0, 8.0 and 4.0, C(6)$H_{eq}$) and 7.20–7.39 (5H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 6.9 ($CH_2$), 34.8 (CH), 35.4 ($CH_2$), 35.9 ($CH_2$), 76.2 (CH), 126.9 (2 × CH), 127.7 (CH), 129.5 (2 × CH), 142.6 (q) and 170.69 (q).

### (4*R*, 6*R*)- and (4*R*, 6*S*)-4-Phenyl-6-[(phenylseleno)methyl]-tetrahydro-2*H*-pyran-2-one, 12a and 12b

To a magnetically stirred solution of carboxylic acid **10** (0.23 g, 1.21 mmol) in dry dichloromethane (5 $cm^3$) under nitrogen, pyridine (0.105 g, 1.33 mmol) was added and the solution was stirred for 30 min at room temperature. The solution was then cooled to −78 °C and phenylselenium chloride (0.255 g, 1.33 mmol) was added. The reaction was stirred until completion, which was indicated by the decoloration of the red orange colour of phenylselenium chloride and confirmed by TLC. The solvent was removed under reduced pressure to give an orange solid, which was shown to be a mixture of diastereoisomers (3 : 1) by $^1H$ NMR spectroscopy. Purification by flash column chromatography eluting with petroleum ether–ethyl acetate (7 : 1) gave the inseparable isomeric lactones **12a** and **12b** (305 mg, 71%) as orange oils.

**12a**: $\nu_{max}$ (film)/$cm^{-1}$ 2923, 1732, 1578, 1495, 1477, 1381, 1227, 738 and 699; $\delta_H$ (400 MHz; $CDCl_3$) 1.86 (1H, ddd, *J* 13.6, 12.0 and 10.4, C(5)$H_{ax}$), 2.53 (1H, ddd, *J* 13.6, 5.2 and 3.2, C(5)$H_{eq}$), 2.62 (1H, dd, *J* 18 and 11.6, C(3)$H_{ax}$), 2.98 (1H, ddd, *J* 18.0, 6.0 and 2.0, C(3)$H_{eq}$), 3.16 (1H, dd, *J* 13.0 and 7.7, C$H_2$SePh), 3.21–3.26 (1H, m, C*H*Ph), 3.41 (1H, dd, *J* 12.87 and 4.67, C$H_2$SePh), 4.63–4.69 (1H, m, C(6)$H_{ax}$), 7.16–7.35 (8H, m, Ar*H*) and 7.53–7.54 (2H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 32.9 ($CH_2$), 36.1 ($CH_2$), 37.8 (CH), 37.9 ($CH_2$), 80.1 (CH), 126.8 (2 × CH), 129.4 (2 × CH), 129.4 (CH), 129.75 (CH), 129.76 (2 × CH), 133.4 (2 × CH), 142.9 (q) and 170.6 (2 × q); *m/z* (EI) 346 ($M^+$, 54%), 189 (13), 175 (23), 157 (28), 143 (39), 131 (94), 117 (24), 105 (92), 91 (100) and 77 (69); Found $M^+$ 346.04793; $C_{18}H_{18}O_2Se$ requires 346.04720.

**12b**: $\delta_H$ (400 MHz; $CDCl_3$) 2.25–2.36 (2H, m, C(3)$H_2$), 2.79 (1H, dd, *J* 17.1 and 8.70, C(5)*H*), 2.90 (1H, dd, *J* 17.1 and 6.4, C(5)*H*), 3.13 (1H, dd, *J* 12.9 and 3.5, C*H*SePh), 3.37 (1H, dd, *J* 12.9 and 4.7, C*H*SePh), 3.42 (1H, m, C*H*Ph), 4.61 (1H, m, C(6)$H_{eq}$), 7.16–7.35 (8H, m, Ar*H*) and 7.53–7.54 (2H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 32.1 ($CH_2$), 34.5 ($CH_2$), 34.8 (CH), 36.3 ($CH_2$), 77.1 (CH), 126.9 (2 × CH), 127.6 (CH), 127.7 (2 × CH), 127.9 (2 × CH), 128.1 (CH), 133.8 (2 × CH), 142.9 (q) and 171.3 (2 × q).

### (4*R*, 6*S*)-6-Methyl-4-phenyltetrahydro-2*H*-pyran-2-one, 13[24]

Tributyltin hydride (0.231 $cm^3$, 0.873 mmol) dissolved in toluene (2 $cm^3$) was added to a solution of **11a** (0.092 g, 0.29 mmol) dissolved in dry toluene (5 $cm^3$) under an inert atmosphere. The mixture was heated to reflux, AIBN (0.005 g) was added and the reaction was heated under reflux for a further 4 h. AIBN (0.005 g) was added every 45 min until completion of the reaction, confirmed by TLC. The solvent was removed under reduced pressure and the residue was partitioned between acetonitrile and hexane (20 $cm^3$, 1 : 1) to remove excess tributyltin hydride. The acetonitrile layer was further washed with hexane (20 $cm^3$) and solvent removed under reduced pressure furnishing a yellow oil. Flash column chromatography on silica gel, eluting with light petroleum (bp range 40–60 °C)–diethyl ether (10 : 1) gave the lactone **13** (0.046 g, 83%) as a colourless oil: $[\alpha]_D^{25}$ = −17.2 (*c* = 1.00, $CH_2Cl_2$); $\nu_{max}$ (film)/$cm^{-1}$ 2923, 2854, 1731, 1456, 1253, 1230, 757 and 700; $\delta_H$(400 MHz; $CDCl_3$) 1.45 (3H, d, *J* 8.0, C$H_3$), 1.69–1.76 (1H, m, C(5)$H_{ax}$), 2.15 (1H, m, C(5)$H_{eq}$), 2.53 (1H, dd, *J* 18.0 and 11.6, C(3)$H_{ax}$), 2.92 (1H, ddd, *J* 17.6, 6 and 2.0 Hz, C(3)$H_{eq}$), 3.15–3.23 (1H, m, C*H*Ph), 4.53–4.61 (1H, m, C*H*$CH_3$) and 7.19–7.35 (5H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 22.3 ($CH_3$), 37.7 ($CH_2$), 38.1 ($CH_2$), 38.4 ($CH_2$), 77.1 (CH), 126.8 (2 × CH), 127.6 (CH), 129.4 (2 × CH), 143.2 (q), and 170.2 (q); *m/z* (EI) 190 ($M^+$, 25%), 104 (100), 91 (15) and 78 (14); Found $M^+$ 190.09938; $C_{12}H_{14}O_2$ requires 190.09937.

### *N*-[(3*R*)-3-Phenylhex-5-enyl]-*N*-phenylmethylamine, 14

To a stirred solution of (*R*)-3-phenylhex-5-enal, **3**, (3.35 g, 19.24 mmol) in dichloromethane (30 $cm^3$) was added benzylamine (2.1 $cm^3$, 19.24 mmol) dropwise. The solution was stirred for 30 min and $MgSO_4$ was added. After 10 min, the mixture was filtered and solvent was removed under reduced pressure. The resultant light yellow oil was redissolved in dry MeOH (40 $cm^3$) and cooled to 0 °C. $NaBH_4$ (2.4 g, 63.5 mmol) in MeOH (10 $cm^3$) was added and the solution was allowed to warm to room temperature and stirred for 18 h. Solvent was removed under reduced pressure and the crude was purified by flash column chromatography (3 : 2 hexanes–EtOAc). The product was isolated as a yellow oil (3.69 g, 73%). $[\alpha]_D^{25}$ −8.7 (*c* = 1.7, $CHCl_3$) $\nu_{max}$ (film/$cm^{-1}$); 3027, 2922, 1640, 1602, 1494, 1453, 912, 734 and 700; $\delta_H$ (400 MHz; $CDCl_3$) 1.40 (1H, br, s, N*H*), 1.73–1.81 (1H, m, NHC$H_2$C*H*H), 1.87–1.94 (1H, m, NHC$H_2$CH*H*), 2.36 (2H, t, *J* 7.2, C$H_2$CH=C$H_2$), 2.44–2.53 (2H, m, NHC$H_2$C$H_2$), 2.66–2.74 (1H, m, PhC*H*), 3.63–3.72 (2H, m, PhC$H_2$), 4.90–4.98 (2H, m, CH=C$H_2$), 5.60–5.68 (1H, m, C*H*=C$H_2$), 7.14–7.29 (10H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 36.2 ($CH_2$), 41.5 ($CH_2$), 43.9 (CH), 47.5 ($CH_2$), 54.0 ($CH_2$), 116.1 ($CH_2$), 126.2 (CH), 126.9 (CH), 127.6 (2 × CH), 128.1 (2 × CH), 128.4 (4 × CH), 136.9 (CH), 140.4 (C), 144.8 (C); *m/z* (EI) 265 [$M^+$, 14%] 91 (100), 120 (51); Found $M^+$ 265.1832; $C_{19}H_{23}N$ requires 265.1831.

### Phenylmethyl-*N*-[(3*R*)-3-phenylhex-5-enyl]-*N*-phenylmethyl-carbamate, 15

To a solution of **14**, (1.6 g, 6.03 mmol) in DMF (20 $cm^3$) was added *N*-(benzyloxycarbonyloxy)succinimide (1.65 g, 6.63 mmol) and NMM (2.7 $cm^3$, 24.12 mmol). The reaction was stirred for 18 h and EtOAc (20 $cm^3$) was added. The solution was acidified with aqueous 1 M HCl, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (9 : 1 light petroleum (bp range 40–60 °C)–EtOAc) and the product was isolated as a yellow oil (1.90 g, 79%). $[\alpha]_D^{25}$ −1.4 (*c* = 1.5, $CHCl_3$); $\nu_{max}$ (film/$cm^{-1}$) 3027, 2924, 1700, 1494, 1472, 1452, 1421, 1228, 1214, 699; $\delta_H$ (400 MHz; $CDCl_3$) 1.75–2.00 (2H, m, NHC$H_2$C$H_2$), 2.25–2.32 (2H, m, C$H_2$CH=C$H_2$), 2.48–2.58 (1H, m, PhC*H*), 3.00–3.22 (2H, m, NC$H_2$C$H_2$) 4.29–4.49 (2H, m, PhC$H_2$), 4.89–4.95 (2H, m, CH=C$H_2$), 5.11–5.18 (2H, m, OC$H_2$), 5.51–5.63 (1H, m, C*H*=C$H_2$), 6.97–7.35 (15H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 33.4 ($CH_2$), 41.5 ($CH_2$), 43.4 (CH), 44.8 ($CH_2$), 50.6 ($CH_2$), 67.2 ($CH_2$), 116.2 ($CH_2$), 126.3 (2 × CH), 127.3 (CH), 127.5 (2 × CH), 127.9 (2 × CH), 128.4 (4 × CH), 128.5 (4 × CH), 136.5 (CH), 136.8 (2 × C), 137.8 (C), 144.1 (2 × C); MS (EI) *m/z* 399 [$M^+$, 5%] 91 (100), 92 (16), 120 (14), 210 (17), 308 (11); Found: $M^+$, 399.2195; $C_{27}H_{29}NO_2$ requires 399.2198.

### Phenylmethyl-*N*-[(3*S*)-5-oxophenylpentyl]-*N*-phenylmethyl-carbamate, 16

To a solution of **15**, (1.55 g, 3.87 mmol) in DCM (30 $cm^3$) at −78 °C was bubbled $O_2$ for 10 min followed by $O_3$. The solution turned blue after 5 min and bubbling was continued for

an additional 15 min. Triphenylphosphine (1.12 g, 4.26 mmol) was added, the solution was stirred for 18 h at room temperature and the reaction was quenched by addition of aqueous 1 M HCl. The resultant mixture was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (4 : 1 hexanes–EtOAc) and the product was isolated as a transparent oil (1.32 g, 85%). $[\alpha]_D^{25}$ −5.0 ($c$ = 1.3, $CHCl_3$); $\nu_{max}$ (film/cm$^{-1}$) 3028, 2932, 1721, 1698, 1494, 1471, 1452, 1422, 1231, 1215, 1120, 766, 736, 700; $\delta_H$ (400 MHz; $CDCl_3$) 1.78–1.89 (2H, m, $NCH_2CH_2$), 2.53–2.70 (2H, m, $CH_2CHO$), 3.00–3.16 (3H, m, PhC*H* & $NCH_2CH_2$), 4.31–4.47 (2H, m, $PhCH_2N$), 5.10–5.18 (2H, m, $OCH_2$), 6.99–7.63 (15H, m, Ar*H*), 9.56 (1H, d, $J$ 23.2, C*H*O); $\delta_C$ (100 MHz; $CDCl_3$) 34.1 ($CH_2$), 37.6 (CH), 45.5 ($CH_2$), 50.6 (2 × $CH_2$), 67.3 ($CH_2$), 126.9 (2 × CH), 127.4 (3 × CH), 128.0 (2 × CH), 128.6 (4 × CH), 128.8 (4 × CH), 136.7 (C), 137.7 (C), 142.7 (2 × C), 201.3 (CH). MS (EI) $m/z$ 401 [$M^+$, 6%] 49 (42), 84 (40), 91 (100), 92 (38), 120 (65), 164 (51), 266 (74); Found: $M^+$, 401.1997; $C_{26}H_{27}NO_3$ requires 401.1991.

### Phenylmethyl 4-phenylhexahydropyridine-1-carboxylate, 18

To a solution of **16**, (0.50 g, 1.25 mmol) in MeOH (100 cm$^3$) in a Parr bottle was added TFA (0.11 cm$^3$, 1.4 mmol) and 10% palladium on carbon (0.05 g). The mixture was stirred for 18 h under nitrogen at 50 psi. The catalyst was removed by filtration through Celite and the solution was concentrated under reduced pressure. The product was redissolved in DMF (15 cm$^3$) and *N*-(benzyloxycarbonyloxy)succinimide (0.50 g, 2.00 mmol) and NMM (0.88 cm$^3$, 8.00 mmol) were added to the solution. The reaction was stirred overnight and EtOAc (20 cm$^3$) was added. The mixture was acidified with aqueous 1 M HCl, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography (4 : 1 hexanes–EtOAc) and the product was isolated as a light yellow oil (0.108 g, 29%).$\nu_{max}$ (film/cm$^{-1}$) 2936, 2850, 1700, 1696, 1452, 1429, 1221, 698; $\delta_H$ (400 MHz; $CDCl_3$) 1.63–1.77 (2H, m, 2 × (CHC*H*H)), 1.83–1.90 (2H, m, 2 × (CHCH*H*)), 2.66 (1H, tt, $J$ 12.1, 3.5, C*H*Ph), 2.88–2.94 (2H, m, 2 × NC*H*H), 4.25–4.40 (2H, m, 2 × NCH*H*), 5.16 (2H, s, $OCH_2$), 7.18–7.38 (10H, m, Ar*H*); $\delta_C$ (100 MHz; $CDCl_3$) 33.1 (2 × $CH_2$), 42.6 (CH), 44.7 (2 × $CH_2$), 67.1 ($CH_2$), 126.4 (CH), 126.8 (2 × CH), 127.9 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 136.9 (C), 145.6 (C), 155.3 (C). MS (EI) $m/z$ 296 [$M^+$, 13%] 91(100); Found: $(M + H)^+$, 296.1657; $C_{19}H_{21}NO_2$ requires 296.1651.

### Crystallography

**Crystal data for 1.** $C_{21}H_{25}NO$, $M$ = 307.42, orthorhombic, $P2_12_12_1$, $a$ = 4.9818(5), $b$ = 9.4157(10), $c$ = 37.792(4) Å, $V$ = 1772.7(3) Å$^3$, $Z$ = 4, $wR2$ = 0.1036 for all 4177 independent reflections, $R1$ = 0.0432 for 3284 reflections with [$I > 2\sigma(I)$]. Absolute structure not determined (Flack parameter −0.2(15)). CCDC reference number 242655.

**Crystal data for 11a.** $C_{12}H_{13}IO_2$, $M$ = 316.12, orthorhombic, $P2_12_12_1$, $a$ = 6.6491(4), $b$ = 6.8227(4), $c$ = 25.8973(14) Å, $V$ = 1174.83(12) Å$^3$, $Z$ = 4, $wR$ = 0.0338 for all 2793 unique data, $R1$ = 0.0150 for 2708 data with $F^2 \geq 2\sigma(F^2)$. Absolute structure parameter = 0.001(16), thus reliably determined. CCDC reference number 206872.

See http://www.rsc.org/suppdata/ob/b4/b416179c/ for crystallographic data in .cif or other electronic format.

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10 In all cases, the major (*cis*) diastereoisomers display a large diaxial coupling of *ca.* 12 Hz between the C-2 proton at the chiral centre created on electrophile-induced cyclisation and the axial C-3 proton. For the minor (*trans*) diastereoisomers, the now equatorial C-2 proton displays a much weaker axial–equatorial coupling (*ca.* 4 Hz) to the same C-3 proton.
11 Chiral HPLC study carried out using a Chiralcel-OD column eluting with a 99.5% hexanes–0.5% propan-2-ol solvent mixture at 0.25 ml min$^{-1}$. A racemic sample of the target under study was prepared and investigated prior to the enantiomerically enriched product. Retention times: **6a**: major enantiomer = 46.9 min, minor = 42.5 min; **7a**: major enantiomer = 51.2 min, minor = 60.1 min.
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