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Development of a solid-phase 'asymmetric resin-capture–release' process: application of an ephedrine chiral resin in an approach to γ-butyrolactones†

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The potential of a solid-phase asymmetric resin-capture–release strategy for high-throughput synthesis has been evaluated. Fukuzawa's Sm(II)-mediated, asymmetric approach to γ-butyrolactones was selected to illustrate the feasibility of such a process. α,β-Unsaturated esters immobilised on an ephedrine chiral resin have been applied in an asymmetric approach to γ-butyrolactones. Lactone products are obtained in moderate isolated yields with selectivities up to 96% ee. In addition, we have shown that the ephedrine resin can be conveniently recovered and recycled although in some cases lower yields were obtained on reuse of the chiral resin. A short synthesis of a moderate DNA-binding microbial metabolite using asymmetric resin-capture–release is also described.

Introduction

Solid phase organic synthesis in which organic substrates are manipulated whilst linked to an insoluble polymer is an important tool for the synthetic chemist who wishes to prepare collections of compounds in an efficient manner.[1] The area of solid-phase synthesis continues to evolve and recently a shift towards the use of solid-supported reagents to effect the transformation of substrates in solution has been seen.[2] 'Resin-capture–release' is a new concept which may also play a role in the future of solid-phase synthesis.[3] Resin-capture–release is a hybrid technique that combines elements of traditional solid-phase synthesis and the use of supported reagents. In a conventional resin-capture–release process, a small molecule B is trapped as an activated polymer intermediate A–B, by a functionalised resin A. The addition of a second reaction partner C transforms the polymer-bound intermediate and releases a product B–C into solution whilst generating a modified polymer (Fig. 1a).[3]

We envisaged that the use of a functionalised *chiral* resin as an immobilised chiral auxiliary[4] would give rise to an 'asymmetric resin-capture–release' process (Fig. 1b). Attachment of a substrate B to a chiral resin followed by asymmetric addition of a second reaction partner C generates an activated, diastereoisomeric intermediate. This breaks down to release a non-racemic product B–C* into solution. Crucially, the chiral resin is regenerated directly and should be recyclable.

To explore the feasibility of such a process we choose to use Fukuzawa's Sm(II)-mediated, asymmetric route to γ-butyrolactones[5] in our proof of concept studies. In Fukuzawa's studies, α,β-unsaturated esters bearing an ephedrine chiral auxiliary are reacted with aldehydes and ketones in the presence of SmI_2 to give γ-butyrolactones.[5] Several features of the process make it ideal for illustrating the concept of asymmetric resin-capture–release: Firstly, the ephedrine auxiliary should be amenable for linkage to a solid-phase thus giving a functionalised chiral resin. Secondly, immobilised ephedrinyl α,β-unsaturated esters should be easily accessible by acylation of a chiral ephedrine resin. Finally, after asymmetric radical addition, an unstable diastereoisomeric polymer-bound intermediate will be formed which should collapse to release an enantiomerically enriched lactone product from the resin, while simultaneously regenerating the chiral ephedrine resin (Scheme 1).

Our interest in new linker systems for solid-phase synthesis[6] has led us to develop a pseudoephedrine resin for asymmetric solid phase synthesis.[7] Furthermore, we have demonstrated the potential of the chemistry for asymmetric library synthesis.[7b] In this contribution we describe in full our studies[8] on the use of an ephedrine resin in the development of an asymmetric resin-capture–release process, employing Fukuzawa's γ-butyrolactone synthesis[5] to illustrate the concept.

Results and discussion

We began by preparing the chiral ephedrine resin necessary to investigate an asymmetric resin-capture–release process based on Fukuzawa's asymmetric reductive-coupling methodology.[5] Inexpensive (1*R*,2*S*)-ephedrine was immobilised on commercially available bromo Wang resin selectively through nitrogen and in one step, by adaptation of a literature procedure.[9] The efficiency and chemoselectivity of the immobilisation step was clearly illustrated by the following solution phase model reaction. Benzyl bromide (1 eq.) was heated with (1*R*,2*S*)-ephedrine (2 eq.) at 85 °C in DMF. After 4 days, (1*R*,2*S*)-*N*-benzyl ephedrine was obtained in near quantitative yield with no trace of (1*R*,2*S*)-*O*-benzyl ephedrine[10] observed in the crude ^{1}H NMR of the reaction. The loading of the resultant ephedrine resin **1** was found to be approximately 1 mmol g^{-1}.[7,11] Straightforward esterification of the resin with acryloyl or crotonyl chloride then gave the desired resins **2** (ν_{max}(C=O) 1724 cm^{-1}) and **3** (ν_{max}(C=O) 1734 cm^{-1}), respectively (Scheme 2).

Using acetophenone and acrylate resin **2**, optimised conditions for the asymmetric-release step were developed. Typically, ketyl radical anion–olefin couplings of this type are carried out by adding a mixture of the carbonyl compound and the acrylate to a solution of SmI_2.[12] Using solution phase model studies, we found that changing the order of addition, *i.e.* adding SmI_2 to a mixture of the resin and the carbonyl compound, a prerequisite for a convenient solid-phase experimental procedure, did not significantly lower the enantioselectivities obtained. For example, adding acetophenone, alcohol and acrylate to SmI_2 at 0 °C, gave lactone **4** in 73% ee, while adding SmI_2 to acetophenone, alcohol and acrylate, gave **4** in 68% ee. The yields obtained using both orders of addition were also similar, 84% and 79% respectively.

Temperature was found to have a dramatic effect on the efficiency of the asymmetric catch–release process. At −78 °C, only a trace of lactone **4** was detected, while at −40 °C, a disappointing

† Electronic supplementary information (ESI) available: Additional experimental and characterisation data, ^{1}H and ^{13}C NMR for new compounds, ^{1}H NMR for literature compounds, general chiral GC conditions, chiral GC traces for lactone products and FTIR spectra of resins. See http://www.rsc.org/suppdata/ob/b4/b408836k/

DOI: 10.1039/b408836k

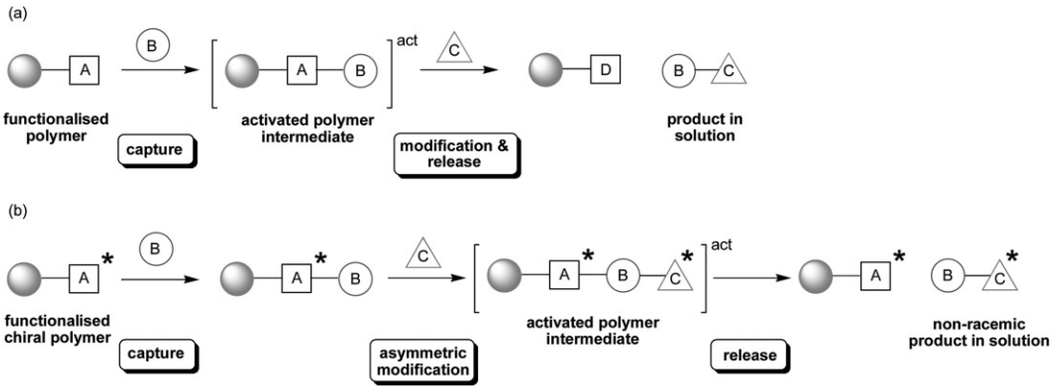
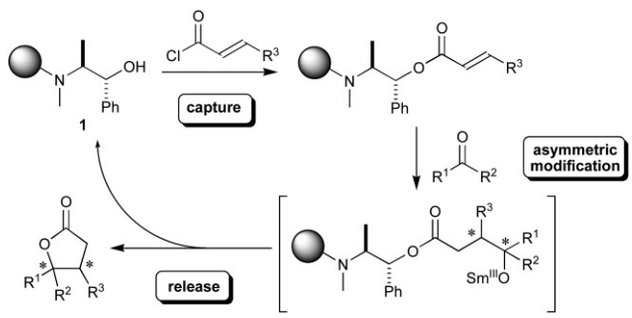
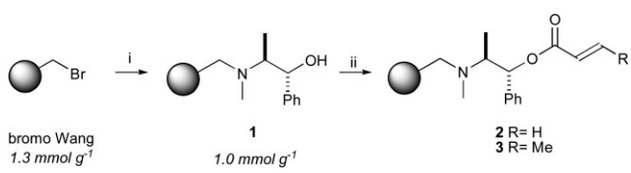


Fig. 1 (a) Conventional 'resin-capture–release'. (b) Asymmetric 'resin-capture–release'.



Scheme 1 'Asymmetric resin-capture–release': proof of concept studies using Fukuzawa's asymmetric approach to γ-butyrolactones.



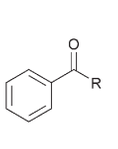
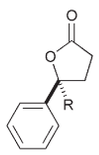
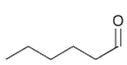
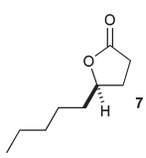
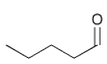
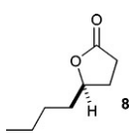
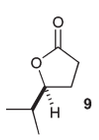
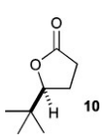
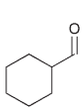
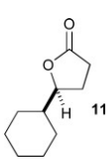
Scheme 2 *Reagents and conditions:* i, (1*R*,2*S*)-ephedrine, DMF, 85 °C; ii, acryloyl chloride or crotonyl chloride, NEt_3, Et_2O, rt.

23% yield of **4** was isolated. Carrying out the reaction at −15 °C using an excess of the acrylate resin **2**, however, gave a satisfactory isolated yield of lactone **4** (50%) in good enantiomeric excess (74% ee). Higher temperatures may be essential for efficient cyclative cleavage of the diastereoisomeric intermediate from the resin. Our adaptation of Fukuzawa's methodology to the solid-phase represents one of a limited number of examples of the addition of radicals to immobilised acceptors.[13]

Employing the optimised conditions, the asymmetric resin-capture–release process involving acrylate resin **2** and a range of ketones and aldehydes was investigated (Table 1). Phenyl alkyl ketones were found to give the corresponding lactones in moderate yield and enantiomeric excess (70–74% ee) (entries 1–3). In general, aldehydes were found to give higher enantioselectivities upon reaction with acrylate resin **2** (up to 81% ee) (entries 4–8), with more substituted aldehydes giving the highest enantioselectivities (entries 7 and 8). Significant ketyl-radical homo-coupling was not observed and few by-products were visible in the crude ^{1}H NMR spectra. In general, the *isolated* yields obtained using **2** compare favourably with the GC yields of Fukuzawa[5] although the use of an excess of **2** is important to give satisfactory conversion.

Treatment of the analogous crotonate resin **3** with aldehydes under optimised conditions gave the expected γ-butyrolactones in good yield and high enantiomeric excess. Enantioselectivities were considerably higher than those obtained using acrylate resin **2** at the same temperature (−15 °C). Again, more substituted aldehydes give the highest enantioselectivities (entries 1 and 2). In line with Fukuzawa's observations, only the *cis*-lactones were observed in the crude ^{1}H NMR spectra of the reactions with aldehydes.[14] In contrast, the reaction with 2-hexanone gave **17** as an inseparable 3 : 1 mixture of diastereoisomers (entry 6) (Table 2).

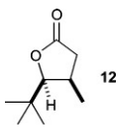
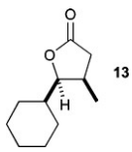
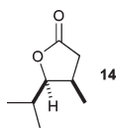
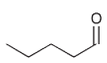
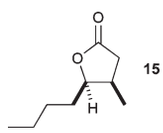
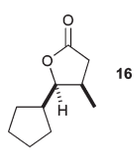
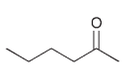
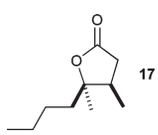
Table 1 'Asymmetric resin-capture–release' with acrylate resin **2**

Entry	Substrate	Product	Isolated yield
1–3			**4** R = Me, 50% (74% ee)[a] **5** R = Et, 73% (70% ee)[a] **6** R = Pr, 43% (74% ee)[a]
4			37% (71% ee)[a]
5			52% (66% ee)[a]
6			56% (70% ee)[b]
7			56% (81% ee)[a]
8			66% (76% ee)[a]

See Experimental Section for details. [a] Enantiomeric excess determined by chiral GC (see Electronic Supporting Information). [b] Enantiomeric excess determined by optical rotation.

Although our studies aim to illustrate the general feasibility of asymmetric resin-capture–release processes rather than to provide a solid-phase process superior to solution-phase methodology,[5] it is interesting to compare the two processes. Enantioselectivities obtained from reactions using acrylate resin **2** are lower than those reported in solution.[5] It is likely this difference originates from the different temperatures at which the two processes are carried out (−78 °C *versus* −15 °C). As previously stated, the yields obtained using **2** compare favourably with the GC yields of Fukuzawa[5] although the use of an excess of **2** is important to give satisfactory conversion. Enantioselectivities in reactions using crotonate resin **3** are comparable to those obtained in solution despite the difference in the reaction temperatures.

Table 2 'Asymmetric resin-capture–release' with crotonate resin **3**

Entry	Substrate	Product	Isolated yield
1		 **12**	56% (93% ee)[a]
2		 **13**	66% (96% ee)[b]
3		 **14**	55% (91% ee)[a]
4		 **15**	50% (91% ee)[a]
5		 **16**	43% (88% ee)[a]
6		 **17**	36% (89% ee)[a,c]

See Experimental Section for details. [a] Enantiomeric excess determined by chiral GC (see Electronic Supporting Information). [b] Enantiomeric excess determined by optical rotation. [c] A 3 : 1 mixture of *cis* (89% ee) and *trans* (76% ee) diastereoisomers was obtained. The *cis*-product was assumed to be the major diastereoisomer.

Despite the utility of Fukuzawa's asymmetric approach to γ-butryolactones,[5] no explanation has been advanced for the high selectivities observed. It is clear that chelation of the ephedrine auxiliary to samarium(III) is important as it has been reported that racemic products were obtained when HMPA was employed as an additive.[5] In addition, the original screen of auxiliaries, suggests that both the phenyl and the amino group play a key role.[5] To account for the observed enantio- and diastereoselectivity in the reaction, we therefore propose the transition structure shown in Fig. 2. Coordination of samarium(III) to both the auxiliary and to the incoming ketyl-radical anion gives rise to a well-ordered transition structure. Such chelation is only possible when the substrate adopts a s-*trans* conformation. In this conformation, the lower face of the substrate is blocked by the phenyl group of the ephedrine auxiliary so the radical addition occurs from the top face. The chelation not only orders the transition structure but also leads to Lewis acid activation of the substrate towards radical addition (Fig. 2).

The greater selectivities we have observed in additions to the crotonate resin **3** (average 92% ee) compared to those obtained using acrylate resin **2** (average 73% ee), at −15 °C, are more difficult to explain. Such a difference in selectivity may arise from the different reactivities of the two radical acceptors. Lewis acid activation of the less reactive crotonate acceptor is likely to be important, thus addition only occurs to the chelated substrate (Fig. 2) where the diastereofacial selectivity is strictly controlled by the auxiliary. The more reactive acrylate may undergo a non-selective background reaction through a non-chelated transition structure thus eroding the enantiomeric excess of the products.

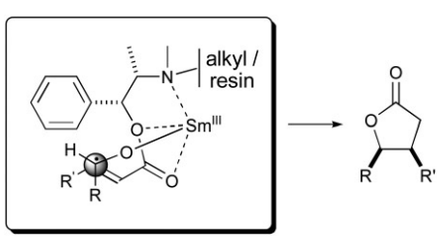


Fig. 2 Possible origin of selectivity in the reaction.

Our studies have shown that asymmetric resin-capture–release is a viable strategy for solid-phase synthesis. The efficacy of any such process clearly depends on the careful design/selection of the key reaction with regard to the asymmetry-controlling auxiliary, reagent compatibility with the polymer support, and the mechanism of product release. In our original outline of the process (Fig. 1), we highlighted that regeneration of the chiral resin after product release should allow recovery and reuse of the chiral resin. Again using Fukuzawa's methodology to illustrate this feature of the process, we have carried out preliminary studies into the feasibility of recycling the chiral ephedrine resin **1**. For example, employing crotonate resin **3** with pivalaldehyde gave lactone **12** in 54% yield and 92% ee. Recovery of the resin **1** and re-esterification with crotonyl chloride gave recycled **3**. Re-treatment with pivalaldehyde gave **12** in virtually identical yield and enantiomeric excess (56%, 92% ee). However, recovering and using the resin a third time gave **12** in substantially lower yield (27%) although the enantioselectivity of the reaction was still high (86% ee). (Scheme 3).

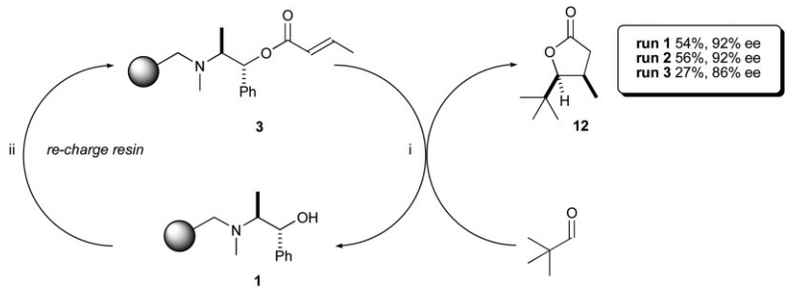
Attempts to recycle the acrylate resin **2** were less successful. For example, employing acrylate resin **2** with pivalaldehyde, gave lactone **10** in 50% yield and 79% ee. Recovery of the resin **1** and re-esterification with acryloyl chloride gave recycled **2**. Treatment of the recycled resin with pivalaldehyde gave **10** in substantially lower yield and enantiomeric excess (27%, 68% ee) (Scheme 4).

Although we have shown the feasibility of recycling the chiral ephedrine resin, some difficulties remain to be addressed. The drop in yield encountered using recovered resin may be due either to a build up of inorganic salts in the polymer support or less likely, could be caused by background reduction of the acrylate and crotonate resins by SmI_2.[15] Thus repeated re-charging and reuse of the resin would lead to the observed drop in the efficacy of the resin and the yield of the reaction. Studies are currently under way to develop a more efficient protocol for the recycling of the resin, which will allow multiple runs to be carried out, making different lactone products in each cycle.

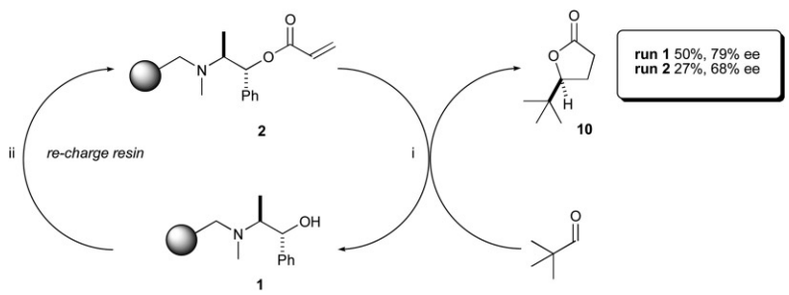
To illustrate the utility of asymmetric resin-capture–release for the synthesis of biologically active compounds, we have undertaken a short synthesis of γ-butyrolactone **21**, a moderate DNA-binding metabolite isolated from Streptomyces GT61115.[16] Diol **18** was prepared from δ-valerolactone according to a literature method.[17] Mono-protected diol **19** was prepared by bis-protection followed by cleavage of the primary TMS ether under basic conditions. Dess–Martin oxidation[18] of **19** then gave aldehyde **20** in excellent yield. On treatment with acrylate resin **2** and SmI_2 in the presence of *tert*-butanol, aldehyde **20** gave **21**, after loss of the TMS protection during work up, in 50% yield and 73% ee.[19] Our synthesis confirms the postulated absolute stereochemistry of **21** (Scheme 5).[16]

Conclusions

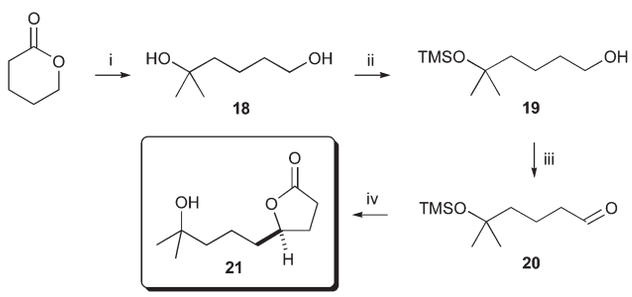
In summary, we have sought to evaluate 'asymmetric resin-capture–release' as a potential process for the asymmetric, solid-phase synthesis of small molecules. We have utilised an asymmetric approach to γ-butyrolactones in our proof of concept studies. In the resultant process, an ephedrine chiral resin is loaded and the immobilised substrate undergoes asymmetric transformation through capture of a reactive intermediate from solution. Cyclative cleavage gives γ-butyrolactones in moderate yield and good enantiomeric excess. We have proposed an explanation for the origin of enantioselectivity in the process and have shown that the ephedrine chiral resin can be recovered and reused although in some cases reduced yields and enantioselectivities were observed. Finally, we have applied



Scheme 3 *Reagents and conditions:* i, SmI_2 (0.1 M in THF), THF, −15 °C, *t*-BuOH; ii, crotonyl chloride, NEt_3, Et_2O, rt.



Scheme 4 *Reagents and conditions:* i, SmI_2 (0.1 M in THF), THF, −15 °C, *t*-BuOH; ii, acryloyl chloride, NEt_3, Et_2O, rt.



Scheme 5 *Reagents and conditions:* i, MeLi (1.5 M in Et_2O), THF, −78 °C to rt, 66%; ii, a) TMSCl, NEt_3, CH_2Cl_2, rt, b) K_2CO_3, MeOH, 0 °C, 96% for two steps; iii, Dess Martin periodinane, CH_2Cl_2, rt, 98%; iv, acrylate resin **2**, SmI_2 (0.1 M in THF), THF, −15 °C, *t*-BuOH, 50%.

the asymmetric resin-capture–release process in a short asymmetric synthesis of a moderate DNA-binding metabolite.

Our studies have shown that asymmetric resin-capture–release is a viable and potentially powerful strategy for solid-phase synthesis. We are currently developing other asymmetric resin-capture–release processes and investigating the application of this concept in high-throughput asymmetric synthesis.

Experimental

General considerations

See the Electronic Supporting Information.†

Preparation of (1*R*,2*S*)-*N*-Wang bound ephedrine 1

To a suspension of bromo Wang resin (4.23 g, 5.90 mmol, 1 equiv.) in DMF (42 mL) was added (1*R*,2*S*)-ephedrine (5.87 g, 35.5 mmol, 6 equiv.). The resulting suspension was heated at 85 °C and stirred gently for 4 days. After this time, the reaction suspension was filtered and the resin was washed with EtOH (3 × 50 mL), water (3 × 50 mL), THF–water; 1 : 1 (3 × 50 mL), THF (3 × 50 mL), and EtOH (3 × 50 mL). Resin **1** was then dried *in vacuo*: ν_{max} (Golden Gate)/cm^{-1} 2919m, 1606m, 1508s.

Preparation of (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate 2

To a suspension of (1*R*,2*S*)-*N*-Wang bound ephedrine **1** (2.15 g, 2.69 mmol, 1 equiv.) in Et_2O (21.5 mL) was added triethylamine (0.90 mL, 6.46 mmol, 2.4 equiv.) followed by acryloyl chloride (0.54 mL, 6.46 mmol, 2.4 equiv.). The resulting suspension was allowed to stir at room temperature for 24 h. After this time, the reaction suspension was filtered and the resin was washed with THF (3 × 25 mL), THF–water; 2 : 1 (3 × 25 mL), THF–water; 1 : 1 (3 × 25 mL), THF–water; 1 : 2 (3 × 25 mL), (MeOH, 25 mL then CH_2Cl_2, 25 mL) × 3, and MeOH (3 × 25 mL). The acrylate resin **2** was then dried *in vacuo*: ν_{max} (Golden Gate)/cm^{-1} 1724s (C=O).

Preparation of (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate 3

To a suspension of (1*R*,2*S*)-*N*-Wang bound ephedrine **1** (3.48 g, 4.07 mmol, 1 equiv.) in Et_2O (36.0 mL) was added triethylamine (1.36 mL, 9.78 mmol, 2.4 equiv.) followed by *trans*-crotonyl chloride (1.04 mL, 9.78 mmol, 2.4 equiv.). The resulting suspension was allowed to stir at room temperature for 24 h. After this time, the reaction suspension was filtered and the resin was washed with THF (3 × 50 mL), THF–water; 2 : 1 (3 × 50 mL), THF–water; 1 : 1 (3 × 50 mL), THF–water; 1 : 2 (3 × 50 mL), (MeOH, 50 mL then CH_2Cl_2, 50 mL) × 3, and MeOH (3 × 50 mL). The crotonate resin **3** was then dried *in vacuo*: ν_{max} (Golden Gate)/cm^{-1} 1734s (C=O).

General procedure A. Reaction of (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate/crotonate with ketones and aldehydes

A suspension of (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate/crotonate resin, **2** or **3**, (3.2 equiv.) in THF (5 mL) under argon was gently stirred for 15 min prior to the addition of an aldehyde (1 equiv.) or a ketone (1 equiv.) and *t*-BuOH (2 equiv.). The resultant suspension was then allowed to stir for another 1 hour at room temperature before being cooled to −15 °C. A pre-cooled SmI_2 solution (0.1 M in THF, 5.5 equiv.) was then added and the dark blue–black solution was allowed to stir at −15 °C until TLC analysis showed that the reaction was complete. The reaction was then allowed to warm to room temperature over 5–6 hours before filtration. The filtered resin was washed repeatedly with THF. The filtrate was then concentrated to about 30 mL and washed with aqueous saturated NaCl (4 mL). The aqueous layer was separated and washed with Et_2O (3 × 15 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated *in vacuo.* The crude product was purified by column chromatography on silica to afford the purified product as a pale yellow or colourless oil.

(*S*)-5-Methyl-5-phenyl dihydro-furan-2-one 4[5]

As for general procedure A. Reaction of acetophenone (18 μL, 0.16 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.50 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **4** (13.8 mg, 50%) as a pale yellow oil: $[\alpha]_D$ −31.3 (*c* 0.63 in MeOH); lit.,[5] (90% ee) $[\alpha]_D$ −34.1 (*c* 0.21 in

MeOH); ν_{max} (neat)/cm^{-1} 3028s, 1772s (C=O); δ_H (400 MHz, $CDCl_3$) 7.31–7.21 (5H, m, Ar*H* of Ph), 2.62–2.31 (4H, m, CH_2CH_2C=O), 1.66 (3H, s, CH_3C); δ_C (100 MHz, $CDCl_3$) 170.6 (*C*=O), 144.7 (Ar*C*), 128.9 (Ar*C*H), 128.0 (2 × Ar*C*H), 124.5 (2 × Ar*C*H), 87.4 (*C*–O), 36.6 (*C*H$_2$C=O), 29.8 (*C*H$_3$C), 29.3 (*C*H$_2$C); *m*/*z* (EI$^+$ mode) 176 (M$^+$, 15%), 161 (100), 121 (30), 105 (23), 82 (10), 77 (18) (Found M$^+$ 176.0837. $C_{11}H_{12}O_2$ requires 176.0837).

74% ee, determined by chiral GC (see supporting information†).

(*S*)-5-Ethyl-5-phenyl dihydro-furan-2-one 5[5]

As for general procedure A. Reaction of propiophenone (21 μL, 0.16 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.50 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **5** (22.1 mg, 73%) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 2963m, 1776s (C=O), 1448m, 1232m, 1196m; δ_H (400 MHz, $CDCl_3$) 7.39–7.21 (5H, m, Ar*H*), 2.65–2.39 (4H, m, 2 × CH_2), 2.00 (2H, q, *J* 7.4, CH_2CH$_3$), 0.82 (3H, t, *J* 7.4, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 177.0 (*C*=O), 143.1 (Ar*C*), 128.9 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 125.1 (Ar*C*H), 90.2 (*C*–O), 35.7 (*C*H$_2$CH$_3$), 35.0 (*C*H$_2$), 29.1 (*C*H$_2$C=O), 8.6 (*C*H$_3$C); *m*/*z* (EI$^+$ mode) 190 (M$^+$, 2.5%), 161 (100), 133 (10), 105 (30) (Found M$^+$ 190.0994. $C_{12}H_{14}O_2$ requires 190.0994).

70% ee, determined by chiral GC (see supporting information).

(*S*)-5-Propyl-5-phenyl dihydro-furan-2-one 6

As for general procedure A. Reaction of butyrophenone (26 μL, 0.18 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.57 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **6** (15.9 mg, 43%) as a pale yellow oil: $[\alpha]_D$ −33.0 (*c* 0.01 in MeOH); ν_{max} (neat)/cm^{-1} 2960s, 2873m, 1780s (C=O), 1448m, 1324m, 1297m, 1228s; δ_H (400 MHz, $CDCl_3$) 7.32–7.20 (5H, m, Ar*H*), 2.55–2.33 (4H, m, 2 × CH_2), 1.91–1.81 (2H, m, CH_2), 1.34–1.25 (1H, m, 1H from CH_2) 1.08–0.97 (1H, m, 1H from CH_2), 0.77 (3H, t, *J* 7.4, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 177.1 (*C*=O), 143.4 (Ar*C*), 128.9 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 125.0 (Ar*C*H), 89.9 (*C*O), 45.1 (*C*H$_2$), 35.5 (*C*H$_2$), 29.1 (*C*H$_2$C=O), 17.6 (*C*H$_2$CH$_3$), 14.4 (*C*H$_3$C); *m*/*z* (EI$^+$ mode) 204 (M$^+$, 2.5%), 161 (100), 149 (2.5), 105 (25), 77 (15) (Found M$^+$ 204.1148. $C_{13}H_{16}O_2$ requires 204.1150).

74% ee, determined by chiral GC (see supporting information).

(*R*)-5-*n*-Pentyl dihydro-furan-2-one 7[5]

As for general procedure A. Reaction of hexanal (25 μL, 0.21 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.66 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **7** (11.9 mg, 37%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 4.48 (1H, apparent q, *J* = 7.6, C*H*), 2.53 (2H, dd, *J* 6.3, 8.4, CH_2C=O), 2.32 (1H, dt, *J* 6.6, 13.7, 1H from CH_2CH$_2$C=O), 1.90–1.24 (9H, m, 4 × CH_2CH$_2$ and 1H from CH_2CH$_2$C=O), 0.90 (3H, t, *J* 6.9, CH_3C); δ_C (100 MHz, $CDCl_3$) 177.7 (*C*=O), 81.5 (*C*HO), 35.9 (*C*H$_2$CH), 31.9 (*C*H$_2$C(O)), 29.3 (*C*H$_2$), 28.4 (*C*H$_2$), 25.3 (*C*H$_2$), 22.9 (*C*H$_2$), 14.3 (*C*H$_3$); *m*/*z* (EI$^+$ mode) 156.2 (M$^+$, 2), 138 (3), 128 (5), 100 (5), 84 (100), 49 (10) (Found M$^+$ 156.1143. $C_9H_{16}O_2$ requires 156.1150).

71% ee, determined by chiral GC (see supporting information).

(*R*)-5-*n*-Butyl dihydro-furan-2-one 8[20]

As for general procedure A. Reaction of pentanal (18 μl, 0.17 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.54 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **8** (12.4 mg, 52%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 4.49 (1H, quintet, *J* 7.6, C*H*OC(O)), 2.59–2.51 (2H, m, CH_2C(O)), 2.33 (1H, apparent sextet, *J* 6.8, 1H from CH_2CH$_2$C(O)), 1.91–1.83 (1H, m, 1H from CH_2CH$_2$C(O)), 1.76–1.73 (1H, m, 1H from CH_2CH), 1.64–1.57 (1H, m, 1H from CH_2CH), 1.48–1.32 (4H, m, 2 × CH_2), 0.92 (3H, t, *J* 7.2, CH_3); δ_C (100 MHz, $CDCl_3$) 177.3 (*C*(O)), 81.0 (*C*H), 35.3 (*C*H$_2$CH), 28.9 (*C*H$_2$C(O)), 28.0 (*C*H$_2$CH$_2$C(O)), 27.3 (*C*H$_2$), 22.4 (*C*H$_2$), 13.9 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutane) 143 ((M + H)$^+$, 100), 81 (8) (Found (M + H)$^+$ 143.1074. $C_8H_{15}O_2$ requires 143.1072).

66% ee, determined by chiral GC (see supporting information).

(*S*)-5-Isopropyl dihydro-furan-2-one 9[5]

As for general procedure A. Reaction of isobutyraldehyde (23 μL, 0.25 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.78 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **9** (17.6 mg, 56%) as a pale yellow oil: $[\alpha]_D$ +26.9 (*c* 0.02 in MeOH); lit.,[5] (93% ee) $[\alpha]_D$ +35.6 (*c* 0.2–1.0 in MeOH); δ_H (400 MHz, $CDCl_3$) 4.20 (1H, td, *J* 8.5, 7.0, C*H*O), 2.60–2.52 (2H, m, CH_2C=O), 2.26 (1H, apparent sextet, *J* 6.5, 1H from CH_2CH$_2$C=O), 1.96–1.79 (2H, m, 1H from CH_2CH$_2$C=O and C*H*(CH$_3$)$_2$), 1.03 (3H, d, *J* 6.7, CH(CH_3)$_2$), 0.94 (3H, d, *J* 6.8, CH(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 177.3 (*C*=O), 85.8 (*C*HO), 33.0 (*C*H), 29.1 (*C*H$_2$C=O), 25.6 (*C*H$_2$CH$_2$C=O), 18.4 (*C*H$_3$), 17.3 (*C*H$_3$); *m*/*z* (EI$^+$ mode) 128 (M$^+$, 25%), 95 (15), 85 (100), 69 (22), 57 (30), 56 (25) (Found M$^+$ 128.0834. $C_7H_{12}O_2$ requires 128.0837).

70% ee, determined by chiral GC (see supporting information).

(*S*)-5-*tert*-Butyl dihydro-furan-2-one 10[5]

As for general procedure A. Reaction of pivalaldehyde (27 μL, 0.25 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.78 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **10** (19.3 mg, 56%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 4.19 (1H, dd, *J* 6.9, 8.8, C*H*), 2.55–2.50 (2H, m, CH_2C=O), 2.16–2.08 (1H, m, 1H from CH_2), 2.02–1.94 (1H, m, 1H from CH_2), 0.95 (9H, s, 3 × (CH_3)C); δ_C (100 MHz, $CDCl_3$) 177.8 (*C*=O), 88.6 (*C*–O), 34.2 (*C*), 29.7 (*C*H$_2$C=O), 25.3 (3 × CH_3), 23.3 (*C*H$_2$); *m*/*z* (CI$^+$ mode) 143 ((M + H)$^+$, 30%), 57 (100) (Found (M + H)$^+$, 143.1073. $C_8H_{15}O_2$ requires 143.1072).

81% ee, determined by chiral GC (see supporting information).

(*S*)-5-Cyclohexyl dihydro-furan-2-one 11[5]

As for general procedure A. Reaction of cyclohexane-carboxaldehyde (29 μL, 0.23 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.75 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **11** (26.0 mg, 66%) as a pale yellow oil: $[\alpha]_D$ +29.8 (*c* 0.01 in MeOH); lit.[5] (96% ee) $[\alpha]_D$ +26.2 (*c* 0.2–1.0 in MeOH); δ_H (400 MHz, $CDCl_3$) 4.14 (1H, dt, *J* 8.0, 7.4, C*H*O), 2.54–2.50 (2H, m, CH_2C=O), 2.25 (1H, apparent sextet, *J* 6.7, 1H from CH_2CH$_2$C=O), 1.98–1.90 (2H, m, 1H from CH_2CH$_2$C=O and 1H from CH_2), 1.80–1.76 (2H, m, CH_2), 1.72–1.65 (2H, m, CH_2), 1.57–1.51 (1H, m, C*H*), 1.29–1.16 (3H, m, CH_2), 1.06–1.00 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 177.3 (*C*=O), 85.1 (*C*O), 42.7 (*C*H), 29.0 (*C*H$_2$), 28.9 (*C*H$_2$), 27.7 (*C*H$_2$), 26.2 (*C*H$_2$), 25.7 (*C*H$_2$), 25.6 (*C*H$_2$), 25.5 (*C*H$_2$); *m*/*z* (EI$^+$ mode) 168 (M$^+$, 8%), 140 (10), 111 (15), 85 (100), 67 (10), 55 (28), 41 (16) (Found M$^+$ 168.1149. $C_{10}H_{16}O_2$ requires 168.1150).

76% ee, determined by chiral GC (see supporting information).

(4*R*,5*S*)-5-*tert*-Butyl-4-methyl dihydro-furan-2-one 12[5]

As for general procedure A. Reaction of pivalaldehyde (16.5 μl, 0.15 mmol, 1 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.49 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **12** (13.2 mg, 56%) as a yellow oil: ν_{max} (neat)/cm^{-1} 2924s, 2854m, 1736m (C=O), 1458m; δ_H (400 MHz, $CDCl_3$) 4.09 (1H, d, *J* 4.9, C*H*O), 2.76 (1H, dd, *J* 7.5, 16.6, 1H of CH_2C=O), 2.69–2.64 (1H, m, C*H*CH$_3$), 2.20 (1H, dd, *J* 1.6, 16.6, 1H of CH_2C=O), 1.14 (3H, d, *J* 7.1, CH_3CH), 1.08 (9H, s,

(3 × CH_3)$_3$C); δ_C (100 MHz, $CDCl_3$) 177.6 (*C*=O), 90.6 (*C*H–O), 40.1 (*C*H_2C=O), 34.6 (*C*HCH$_3$), 34.2 (*C*), 26.9 (3 × (*C*H$_3$)$_3$C), 16.3 (*C*H$_3$CH); *m*/*z* (EI$^+$ mode) 141 (M–CH$_3^+$, 10%), 99 (100), 83 (63), 71 (44), 57 (100) and 41 (39) (Found (M − CH$_3$)$^+$, 141.0917. $C_8H_{13}O_2$ requires 141.0916).

93% ee, determined by chiral GC (see supporting information).

(4*R*,5*S*)-5-Cyclohexyl-4-methyl dihydro-furan-2-one 13[5]

As for general procedure A. Reaction of cyclohexane carboxaldehyde (18.4 µl, 0.15 mmol, 1 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.49 mmol, 3.2 equiv.) and purification by column chromatography on silica (eluting with 10% EtOAc/petroleum ether (40–60 °C)) gave **13** (18.2 mg, 66%) as a pale yellow solid: $[\alpha]_D$ +53.9 (*c* 0.5 in MeOH); lit.,[5] $[\alpha]_D$ +56.2 (*c* 1.0 in MeOH); ν_{max} (Golden Gate)/cm^{-1} 2927s, 1747s (C=O), 1456w, 1174s; δ_H (400 MHz, $CDCl_3$) 3.95 (1H, dd, *J* 4.7, 9.8, C*H*O), 2.65 (1H, dd, *J* 7.4, 16.9, 1H of C*H*$_2$C=O), 2.50–2.47 (1H, m, C*H*CH$_3$), 2.12 (1H, dd, *J* 1.1, 16.9, 1H of C*H*$_2$C=O), 2.00–1.96 (1H, m, 1H of C*H*$_2$ of cyclohexane ring), 1.71–1.62 (4H, m, 2 × C*H*$_2$ cyclohexane ring), 1.58–1.53 (2H, m, 1H of C*H*$_2$ of cyclohexane ring and C*H*CHO), 1.22–1.07 (2H, m, C*H*$_2$ of cyclohexane ring), 1.00–0.99 (1H, m, 1H of C*H*$_2$ of cyclohexane ring), 0.95 (3H, d, *J* 12.9, C*H*$_3$CH), 0.92–0.83 (1H, m, 1H of C*H*$_2$ of cyclohexane ring); δ_C (100 MHz, $CDCl_3$) 177.4 (*C*=O), 88.1 (*C*HO), 39.2 (*C*H$_2$C=O), 37.8 (*C*HCHO), 32.4 (*C*HCH$_3$), 30.7 (*C*H$_2$ of cyclohexane ring), 28.4 (*C*H$_2$ of cyclohexane ring), 26.5 (*C*H$_2$ of cyclohexane ring), 25.8 (*C*H$_2$ of cyclohexane ring), 25.7 (*C*H$_2$ of cyclohexane ring), 13.9 (*C*H$_2$ of cyclohexane ring); *m*/*z* (EI$^+$ mode) 182 (M$^+$, 13%), 154 (28), 99 (100), 84 (41), 83 (29) and 49 (34) (Found M$^+$ 182.1306. $C_{11}H_{18}O_2$ requires 182.1307).

96% ee, determined by optical rotation.

(4*R*,5*R*)-5-Isopropyl-4-methyl dihydro-furan-2-one 14[21]

As for general procedure A. Reaction of isobutyraldehyde (20.6 µl, 0.23 mmol, 1 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.73 mmol, 3.2 equiv.) and purification by column chromatography on silica (eluting with 10% EtOAc/petroleum ether (40–60 °C)) gave **14** (17.9 mg, 55%) as a yellow oil: $[\alpha]_D$ +11.8 (*c* 0.4 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2926s, 2875s, 2362m, 1751s (C=O), 1594m, 1457m; δ_H (400 MHz, $CDCl_3$) 3.94 (1H, dd, *J* 4.8, 10.2, C*H*O), 2.74 (1H, dd, *J* 7.4, 16.9, 1H of C*H*$_2$C=O), 2.58–2.53 (1H, m, C*H*CH$_2$C=O), 2.21 (1H, dd, *J* 1.1, 16.9, 1H of C*H*$_2$C=O), 1.93–1.86 (1H, m, C*H*(CH$_3$)$_2$), 1.09 (3H, d, *J* 6.5, C*H*$_3$CHCH$_3$), 1.00 (3H, d, *J* 7.0, C*H*$_3$CHCH$_2$), 0.91 (3H, d, *J* 6.6, C*H*$_3$CHCH$_3$); δ_C (100 MHz, $CDCl_3$) 177.0 (*C*=O), 89.1 (*C*HO), 39.0 (*C*H$_2$C=O), 31.9 (*C*HCH$_2$C=O), 28.1 (*C*H(CH$_3$)$_2$), 20.1 (*C*H$_3$CHCH$_3$), 18.4 (*C*H$_3$CHCH$_3$), 13.4 (*C*H$_3$CHCH$_2$); *m*/*z* (EI$^+$ mode) 142 (M$^+$, 5%), 114 (16), 99 (70), 84 (100), 71 (37) and 43 (27) (Found M$^+$ 142.0996. $C_8H_{14}O_2$ requires 142.0994).

91% ee, determined by chiral GC (see supporting information).

(4*R*,5*R*)-5-*n*-Butyl-4-methyl dihydro-furan-2-one 15[5]

As for general procedure A. Reaction of pentanal (14 µl, 0.12 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.39 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **15** (9.6 mg, 50%) as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 4.46–4.41 (1H, m, C*H*O), 2.70 (1H, dd, *J* 16.9, 7.8, 1H from C*H*$_2$C=O), 2.63–2.54 (1H, m, C*H*CH$_3$), 2.21 (1H, dd, *J* 16.9, 3.9, 1H from C*H*$_2$C=O), 1.70–1.61 (1H, m, 1H from C*H*$_2$), 1.58–1.45 (2H, m, C*H*$_2$), 1.42–1.36 (3H, m, C*H*$_2$), 0.95 (3H, d, *J* 7.0, CHC*H*$_3$), 0.93 (3H, t, *J* 7.3, C*H*$_3$CH$_2$); δ_C (100 MHz, $CDCl_3$) 176.9 (*C*=O), 83.7 (*C*HO), 37.6 (*C*H$_2$C=O), 33.0 (*C*HCH$_3$), 29.6 (*C*H$_2$), 28.1 (*C*H$_2$), 22.5 (*C*H$_2$), 13.9 (*C*H$_3$), 13.8 (*C*H$_3$); *m*/*z* (CI$^+$ mode) 157 ((M + H)$^+$, 100%), 113 (6), 81 (8) (Found (M + H)$^+$ 157.1231. $C_9H_{17}O_2$ requires 157.1229).

91% ee, determined by chiral GC (see supporting information).

(4*R*,5*S*)-5-Cyclopentyl-4-methyl dihydro-furan-2-one 16

As for general procedure A. Reaction of cyclopentane carboxaldehyde (19.6 µl, 0.18 mmol, 1 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.57 mmol, 3.2 equiv.) and purification by column chromatography on silica (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **16** (13 mg, 43%) as a colourless oil: ν_{max} (neat)/cm^{-1} 2958s, 1775s (C=O), 1454m, 1421m, 1383m, 1326m; δ_H (400 MHz, $CDCl_3$) 4.15 (1H, dd, *J* 10.1, 5.1, C*H*O), 2.74 (1H, dd, *J* 17.0, 7.6, 1H from C*H*$_2$C=O), 2.58–2.52 (1H, m, C*H*CH$_3$), 2.21 (1H, dd, *J* 17.0, 1.9, 1H from C*H*$_2$C=O), 2.16–2.12 (1H, m, C*H*), 1.96–1.91 (1H, m, 1H from C*H*$_2$), 1.79–1.73 (1H, m, 1H from C*H*$_2$), 1.68–1.56 (4H, m, C*H*$_2$), 1.50–1.43 (1H, m, 1H from C*H*$_2$), 1.26–1.17 (1H, m, 1H from C*H*$_2$), 1.03 (3H, d, *J* 7.1, C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 177 (*C*=O), 88.2 (*C*HO), 39.5 (*C*H), 38.5 (*C*H$_2$C=O), 32.8 (*C*HCH$_3$), 30.9 (*C*H$_2$), 27.8 (*C*H$_2$), 25.4 (*C*H$_2$), 25.3 (*C*H$_2$), 14.2 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutane) 169 ((M + H)$^+$, 100%) (Found (M + H)$^+$ 169.1231. $C_{10}H_{17}O_2$ requires 169.1229).

88% ee, determined by chiral GC (see supporting information).

(5*R*,4*R*)-5-*n*-Butyl-4,5-dimethyl dihydrofuran-2-one 17

As for general procedure A except, due to the lower reactivity of the ketone, 2-hexanone (3 equiv.) was reacted with the resin (1 equiv.). Reaction of 2-hexanone (78 µl, 0.62 mmol, 3.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl crotonate **3** (0.21 mmol, 1.0 equiv.) and purification by column chromatography on silica gel (eluting with 20% EtOAc/petroleum ether (40–60 °C)) gave **17** (12.7 mg, 36%) as a pale yellow oil and as an inseparable 3 : 1 mixture of diastereoisomers: For the major diastereoisomer: ν_{max} (neat)/cm^{-1} 2959s, 2872s, 1772s (C=O), 1460m, 1382m; δ_H (400 MHz, $CDCl_3$) 2.59 (1H, dd, *J* 16.6, 7.5, 1H from C*H*$_2$C=O), 2.39–2.24 (2H, m, 1H from C*H*$_2$C=O and C*H*CH$_3$), 1.66–1.31 (6H, m, 3 × C*H*$_2$), 1.39 (3H, s, C*H*$_3$), 1.00 (3H, d, *J* 6.8, CHC*H*$_3$), 0.93 (3H, t, *J* 7.1, CH$_2$C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 176.1 (*C*=O), 88.7 (*C*O), 41.3 (*C*HCH$_3$), 36.9 (*C*H$_2$C=O), 34.5 (*C*H$_2$), 25.6 (*C*H$_2$), 24.3 (*C*H$_3$), 23.2 (*C*H$_2$), 14.0 (*C*H$_3$), 13.9 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutene) 171 (M + H$^+$, 100%), 113 (3), 85 (5), 71 (4) (Found (M + H)$^+$ 171.1384. $C_{10}H_{19}O_2$ requires 171.1385).

Major (89% ee) and *minor* (76% ee), the *cis*-product was assumed to be the major diastereoisomer, determined by chiral GC (see supporting information).

5-Methyl-hexane-1,5-diol 18[17]

To a solution of δ-valerolactone (1.46 g, 14.6 mmol, 1.0 equiv.) in THF at −78 °C was added MeLi (1.5 M in Et_2O, 29.2 mL, 43.8 mmol, 3.0 equiv.) dropwise. The solution was allowed to stir at −78 °C for 30 min before being allowed to warm to room temperature overnight. The reaction was then quenched by dropwise addition of acetic acid (1.4 mL, 25.0 mmol, 1.7 equiv.) to the reaction solution. A white suspension resulted and this was stirred at room temperature for 4 h before filtration. The precipitate was washed with THF (3 × 50 mL) and the combined filtrate and washings were concentrated *in vacuo* to afford a crude oil. Purification by dry flash chromatography on silica (90% EtOAc/petroleum ether (40–60 °C) to 20% MeOH/EtOAc) gave **18** (1.27 g, 66%) as a colourless oil: ν_{max}(neat)/cm^{-1} 3350s, 2968s, 2934s, 2867s, 1468m, 1379m, 1201m, 1155m; δ_H (400 MHz, $CDCl_3$) 3.66 (2H, t, *J* 6.4, C*H*$_2$OH), 1.74 (2H, br s, 2 × O*H*), 1.58 (2H, quintet, *J* 6.4, C*H*$_2$CH$_2$OH), 1.52–1.41 (4H, m, 2 × C*H*$_2$), 1.22 (6H, s, 2 × C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 71.0 (*C*), 62.6 (*C*H$_2$OH), 43.3 (*C*H$_2$), 33.0 (*C*H$_2$CH$_2$OH), 29.2 (2 × *C*H$_3$), 20.4 (*C*H$_2$); *m*/*z* (FAB$^+$ mode) 133 ((M + H)$^+$, 25%), 115 (100), 97 (28), 60 (8), 56 (8) (Found (M + H)$^+$ 133.1229. $C_7H_{17}O_2$ requires 133.1230).

5-Methyl-5-trimethylsilyloxy-hexan-1-ol 19

To a solution of diol **18** (90 mg, 0.69 mmol, 1.0 equiv.) in CH_2Cl_2 (8 mL) was added triethylamine (3.8 mL, 27.3 mmol, 40 equiv.) and trimethylsilyl chloride (1.74 mL, 13.7 mmol, 20 equiv.) and the reaction was allowed to stir at room temperature for 3 days. The reaction

was quenched with water (2 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to afford the crude product. Purification by column chromatography on silica (30% EtOAc/petroleum ether (40–60 °C)) gave a colourless oil (171.0 mg, 90%) that was shown to be composed mainly of bis-TMS protected compound by ^{1}H NMR. To this product (144 mg, 0.52 mmol, 1 equiv.) was added potassium carbonate (144 mg, 1.04 mmol, 2.0 equiv.) and anhydrous methanol (2.0 mL). The solution was stirred at 0 °C for 2.5 h before quenching with acetic acid (0.06 mL, 1.04 mmol, 2.0 equiv.) and water (2 mL). The aqueous solution was then extracted with CH_2Cl_2 (3 × 15 mL) and the combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to afford **19** (108 mg, 92% overall) as a colourless oil, which was used without further purification: ν_{max}(neat)/cm^{-1} 3348s, 1468m, 1379m, 1201m, 1155m; δ_H (400 MHz, $CDCl_3$) 3.66 (2H, t, *J* 6.5, CH_2OH), 1.57 (2H, quintet, *J* 6.5, CH_2CH$_2$OH), 1.54–1.37 (4H, m, 2 × CH_2), 1.21 (6H, s, 2 × CH_3), 0.11 (9H, s, 3 × CH_3Si); δ_C (100 MHz, $CDCl_3$) 74.0 (*C*), 63.0 (*C*H$_2$OH), 44.5 (*C*H$_2$), 33.2 (*C*H$_2$CH$_2$OH), 29.8 (2 × *C*H$_3$), 20.5 (*C*H$_2$), 2.6 (3 × *C*H$_3$Si); *m*/*z* (FAB$^+$ mode) 189 ((M − CH$_3$)$^+$, 7%), 131 (100), 84 (12), 73 (50), 55 (16), 43 (15) (Found (M − CH$_3$)$^+$ 189.1311. $C_9H_{21}O_2Si$ requires 189.1308).

5-Methyl-5-trimethylsilyloxy-hexanal 20

To Dess–Martin periodinane (470 mg, 1.11 mmol, 1.1 equiv.) in CH_2Cl_2 (4.6 mL) was added alcohol **19** (206 mg, 1.01 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) *via* cannula. The light orange coloured solution was then stirred at room temperature for 2 h before dilution with diethyl ether (25 mL) and addition to an aqueous saturated $NaHCO_3$ (1 mL)/aqueous saturated $Na_2S_2O_3$ (8 mL) solution. The mixture was stirred for a few minutes before the organic layer was separated. The organic layer was extracted with aqueous $NaHCO_3$ (10 mL) and water (12 mL). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo* to afford **20** (199.6 mg, 98%) as a pale orange oil which was used without further purification: ν_{max}(neat)/cm^{-1} 2960s, 2715w, 1728s (C=O), 1460m, 1412m, 1383m, 1365m, 1250s; δ_H (400 MHz, $CDCl_3$) 9.67 (1H, t, *J* 1.8, C*H*=O), 2.33 (2H, td, *J* 7.3, 1.8, CH_2CH=O), 1.75–1.67 (2H, m, CH_2CH$_2$CH=O), 1.46–1.39 (2H, m, CH_2), 1.23 (6H, s, 2 × CH_3), 0.11 (9H, s, 3 × CH_3Si); δ_C (100 MHz, $CDCl_3$) 202.9 (*C*H=O), 73.6 (*C*), 44.3 (*C*H$_2$CH=O), 44.2 (*C*H$_2$), 29.8 (2 × *C*H$_3$), 17.1 (*C*H$_2$CH$_2$CH=O), 2.6 (3 × CH$_3$Si); *m*/*z* (EI$^+$ mode) 187 ((M − CH$_3$)$^+$, 8%), 131 (100), 129 (18), 95 (12), 73 (65), 69 (23) (Found (M − CH$_3$)$^+$ 187.1154. $C_9H_{19}O_2Si$ requires 187. 1154).

5-(4-Hydroxy-4-methyl-pentyl) dihydro-furan-2-one 21

As for general procedure A. Reaction of aldehyde **20** (48.6 mg, 0.24 mmol, 1.0 equiv.) with (1*R*,2*S*)-*N*-Wang bound ephedrinyl acrylate **2** (0.77 mmol, 3.2 equiv.) and purification by column chromatography on silica gel (30% EtOAc/petroleum ether (40–60 °C) to ethyl acetate) gave **21** (22.6 mg, 50%) as a pale yellow oil: $[\alpha]_D$ +29.5 (*c* 0.01 in MeOH). lit.[16] $[\alpha]_D$ +42.0 (*c* 1.0 in MeOH); ν_{max}(neat)/cm^{-1} 3450s, 2968s, 1767s (C=O), 1462m, 1421m, 1363m, 1298w; δ_H (400 MHz, $CDCl_3$) 4.55–4.48 (1H, m, C*H*OC(O)), 2.55 (2H, m, CH_2CH$_2$C(O)), 2.38–2.30 (1H, m, 1H from CH_2C(O)), 1.92–1.85 (1H, m, 1H from CH_2C(O)), 1.77–1.74 (1H, m, 1H from CH_2), 1.73–1.48 (5H, m, 1H from CH_2, 2 × CH_2), 1.65 (6H, s, 2 × CH_3); δ_C (100 MHz, $CDCl_3$) 177.2 (*C*=O), 80.9 (*C*H), 70.8 (*C*), 43.4 (*C*H$_2$), 36.1 (*C*H$_2$), 29.4 (*C*H$_3$), 29.2 (*C*H$_3$), 28.8 (*C*H$_2$C(O)), 28.0 (*C*H$_2$CH$_2$C(O)), 20.3 (*C*H$_2$); *m*/*z* (CI$^+$ mode, isobutene) 187 (M$^+$, 5%), 169 (100), 151 (10), 69 (5) (Found M$^+$ 187.1337. $C_{10}H_{18}O_3$ requires 187.1334).

73% ee, determined by chiral GC (see supporting information).

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