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TETRAHEDRON:
*ASYMMETRY* 1

# Asymmetric synthesis and Lewis acid mediated type II carbonyl ene cyclisations of (*R*)-2-isopropyl-5-methylhex-5-enal

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## Abstract

The asymmetric synthesis of (*R*)-2-isopropyl-5-methylhex-5-enal in 98% ee is described. It was discovered that the key alkylation step employing an Evans chiral auxiliary and 3-methylbut-3-en-1-yl trifluoromethanesulphonate as the alkylating agent led to significant competing *O*-alkylation, a phenomenon not previously reported. Type II carbonyl ene cyclisation of the aldehyde with a range of Lewis acids led to either the (*R*,*R*)- or (*R*,*S*)-5-methylidenecyclohexanols without concurrent racemisation of the alpha stereogenic centre of the aldehyde. Conditions for effecting the easy racemisation of a model enantiomerically pure aldehyde, (*S*)-2-methylbutanal, were developed. In an effort to secure a dynamic kinetic resolution procedure, these conditions were applied to (*R*)-2-isopropyl-5-methylhex-5-enal. However, a competing and dominant Prins cyclisation occurred instead leading to a mixture of all possible cycloadducts, all of which were obtained in 98% ee. Any unreacted aldehyde was found to be enantiomerically pure.

## 1. Introduction

We have recently defined the intimate stereochemical course (*cis* vs *trans*) of the type II carbonyl ene cyclisation of (±)-2-isopropyl-5-methylhex-5-enal **1** with various alkylaluminium mediated reagents by recourse to the use of deuterium labelled aldehyde (±)-(*E*)-[$^2$H] **1a**.[1] This study was in agreement with Snider's original model[2] for the transition state **A** leading to the *cis* adduct **2** with sterically undemanding aluminium reagents (e.g. $Me_2AlCl$). Yamamoto's bulky alkylaluminium reagent methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) gives the *trans* adduct **3**[3] via a previously unrecognised boat conformation **B**.[1] A similar boat-like transition state has been proposed for the type I ene cyclisation of citronellal using bulky molybdenum(II) Lewis acid catalysts.[4]

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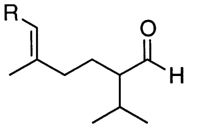
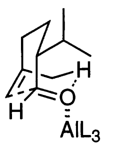
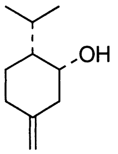


**1**; R = H
**1a**; R = D



**A**



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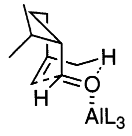

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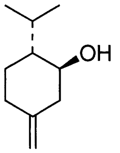
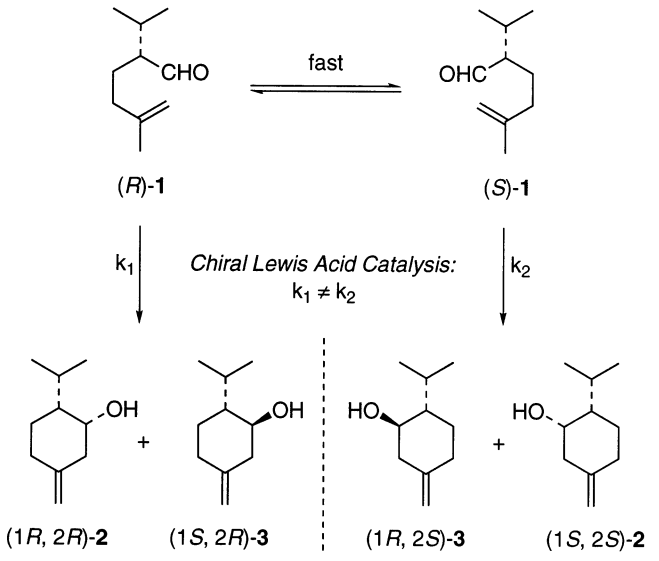
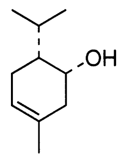


**3**

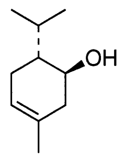
During the course of these studies it became apparent that a fast racemisation of aldehyde **1** coupled to a chiral Lewis acid catalysed asymmetric ene cyclisation would give rise to enantiomerically enriched cyclohexenols (Scheme 1). This provided an incentive to study the feasibility of this dynamic kinetic resolution.[5] Inherent to this is the need to also control diastereoselectivity to provide either the *cis* or *trans* cycloadducts **2** and **3**. Clearly, any proposed racemisation reagent must be compatible with the Lewis acidic catalyst; the solvent system must also be selected with care such as not to destroy the Lewis acid (i.e. a non-protic solvent). Surprisingly, there is very little known about racemisation of α-chiral aldehydes in non-protic solvents[6] and, to the best of our knowledge, no information on the racemisation of α-chiral aldehydes in the presence of Lewis acids. Moreover, asymmetric Lewis acid catalysts for intramolecular type II ene cyclisations are still in the early stages of development.[7,8] To circumvent the need to discover a novel asymmetric Lewis acid catalyst, we therefore chose to examine our postulated dynamic kinetic resolution in the reverse sense: are there conditions under which enantiomerically pure aldehyde **1** can be successfully enolised (and therefore racemised) and also undergo in situ ene cyclisation? Herein we describe the asymmetric synthesis of aldehyde (*R*)-**1**, its stereoselective Lewis acid mediated carbonyl ene cyclisation to either (1*R*,2*R*)-**2** or (1*S*,2*R*)-**3**, and report on our efforts to secure a dynamic kinetic resolution. We also report on the action of catalytic quantities of titanocene ditriflate[9] on (*R*)-**1** to provide enantiomerically pure endocyclic ene adducts (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5**. We also note that all the carbonyl ene cyclisation adducts **2**–**5** may be hydrogenated with high diastereoselectivity using Crabtree's catalyst.[10]



Scheme 1.



(1*R*, 2*R*)-**4**

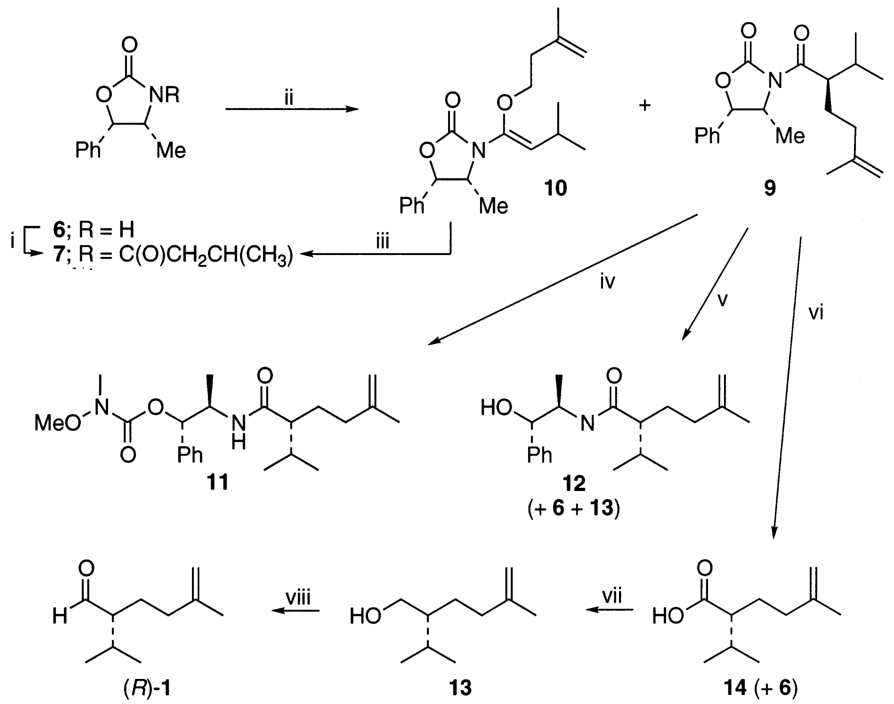


(1*S*, 2*R*)-**5**

## 2. Results and discussion

### 2.1. Synthesis and diastereoselective carbonyl ene cyclisation of aldehyde (R)-1

Enantiomerically pure aldehyde (*R*)-**1** was accessed using Evans chiral auxiliary methodology[11] (Scheme 2). *N*-Acylation of (1*S*,2*R*)-(+)-norephedrine derived oxazolidinone **6**[12] with isovaleryl chloride provided the previously reported *N*-acyloxazolidinone **7**.[13] In the synthesis of racemic aldehyde **1**[14] 4-iodo-2-methylbut-1-ene had served as an effective electrophile in the alkylation of *N*-(3-methylbutylidene)cyclohexylamine (a masked aldehyde equivalent) employing LDA as the base. However, when employed as the electrophile for alkylation of **7** (LDA, THF, −78°C) no carbon–carbon bond formation was observed. Moving to the highly electrophilic triflate derivative **8** and LDA in THF at −78°C, alkylation proceeded smoothly to provide an approximately 3:1 mixture of compounds which could be separated by chromatography. The major compound proved to be the desired *C*-alkylated product **9**, essentially as a single diastereoisomer (>98:2) as judged by $^1$H NMR, with the predicted *R*



Scheme 2. *Reagents and conditions:* (i) *n*-BuLi, isovaleryl chloride, THF, −78°C→0°C, 2 h (86%); (ii) LDA, MeC(=CH$_2$)CH$_2$CH$_2$OTf **8**, THF, −20°C, 2 h (50%; **9**); (iii) rt; (iv) MeO(Me)NH$_2$Cl, Me$_3$Al, CH$_2$Cl$_2$, 0°C, 1 h (82%); (v) LiAlH$_4$, THF, −78°C→0°C (39%; **12**, 33%; **13**); (vi) LiOH, H$_2$O$_2$, THF:H$_2$O 3:1 rt, 16 h (75%); (vii) LiAlH$_4$, Et$_2$O, reflux, 1 h (98%); (viii) DMSO, oxalyl chloride, Et$_3$N, CH$_2$Cl$_2$, −30°C, 0.5 h (71%)

configuration at the newly created stereogenic centre[11] (vide infra). Surprisingly, the minor adduct proved to be the product of *O*-alkylation: enol ether **10**. To the best of our knowledge, competing *O*-alkylation in Evans chiral auxiliary methodology had not previously been observed. The formation of quantities of enol ether **10** can be rationalised by noting that triflate **8** is a hard electrophile thus favouring *O*-alkylation.[15] Fortuitously, enol ether **10** was found to decompose back to *N*-acyloxazolidinone **7** (with concomitant loss of isoprene) on standing ($t_{1/2} \approx 24$ h), which could be recovered and re-alkylated.

Chiral auxiliary removal proved troublesome. Attempted transamination to the Weinreb amide[16] resulted in complete endocyclic ring cleavage leading to amide **11**. Reductive cleavage with LAH[11] led to approximately 1:1:1 mixtures of the recovered auxiliary **6**, endocylic cleaved amide **12** and the desired alcohol **13**, which could be isolated by chromatography (33%, 98% ee[†]). A more satisfactory auxiliary cleavage was achieved with lithium hydroxide and hydrogen peroxide in a THF/water mixture[17] to provide carboxylic acid **14** in 75% yield after distillation in 98% ee.[†] The auxiliary **6** could be recovered in moderate yield (48%) by recrystallisation from toluene. Straightforward functional group manipulation ensued: LAH reduction of acid **14** to alcohol **13** (98% yield, 98% ee[†]) followed by Swern oxidation[18] provided aldehyde (*R*)-**1** in 71% yield, 98% ee.[†]

The action of 1 equivalent of dimethylaluminium chloride on aldehyde (*R*)-**1** in dichloromethane solution at −78°C brought about smooth cyclisation to the cycloadducts **2** and **3** in the same diastereomeric ratio as observed for the racemic case[2] (33:1 **2**:**3**, 98% yield). The two cycloadducts were formed in 98% ee[†] and were assigned as (1*R*,2*R*)-**2** and (1*S*,2*R*)-**3**. This was confirmed by chemical correlation via directed hydrogenation[19] of (1*R*,2*R*)-**2** with Crabtree's catalyst[10] (vide infra).[‡] Similarly, the MABR[3] mediated cyclisation of (*R*)-**1** proceeded with the expected reversal of diastereomeric ratio (1:17 **2**:**3**) yielding both cycloadducts in 98% ee. We have previously shown that a catalytic quantity (4 mol%) of titanocene ditriflate[9] cleanly converts (±)-**1** into the *endocyclic* double bond adducts (±)-**4** and (±)-**5**.[1] When (*R*)-**1** was employed as the substrate the expected cycloadducts (1*R*,2*R*)-**4** and (1*S*,2*R*)-**5** were also obtained in 98% ee.[†] These results firmly establish that the α-stereogenic centre of aldehyde **1** is configurationally stable under the typical Lewis acidic conditions required to bring about type II carbonyl ene cyclisation.

### *2.2. Racemisation studies*

Having established that the α-stereogenic centre in aldehyde **1** is configurationally stable under prototypical Lewis acidic conditions, we set about finding reagents that would induce racemisation, but that would also be compatible with the Lewis acid. Rapid equilibration of the two enantiomeric forms of α-stereogenic carbonyl compounds is well known in polar solvents with either acid[20] or base,[21] but there is little or no literature precedent for this type of process in non-coordinating solvents.

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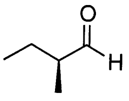
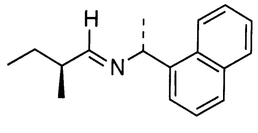
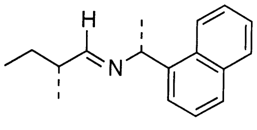
[†] Enantiomeric excesses were determined by chiral GC analysis by comparison with the corresponding racemic compound (Table 3, Section 4).

[‡] The resulting reduction product proved to have an equal and opposite optical rotation {$[\alpha]_D = -17.3$ (*c* 0.70, $CHCl_3$)} to that of the naturally occuring (1*S*,2*S*,5*R*)-neomenthol {$[\alpha]_D = +17.6$ (*c* 0.70, $CHCl_3$)} and was thus assigned as (1*R*,2*R*,5*S*)-neomenthol.


(*S*)-**15**


**16**


**17**

(*S*)-2-Methylbutanal **15**, prepared by oxidation of (*S*)-2-methylbutan-1-ol,[22] was chosen as a model compound for the racemisation studies. Racemic aldehyde (±)-**15** was also prepared in analogous manner from (±)-2-methylbutan-1-ol. Owing to the volatility of aldehyde **15** (bp 88–90°C), an in situ ee determination was developed: diastereomeric imines **16** and **17** were formed rapidly and quantitatively by treating a solution of (±)-**15** in chloroform-*d* with 1.05 equivalents of (*R*)-(+)-α-methylnaphthylamine. Inspection of the $^1$H NMR spectrum obtained at 300 MHz revealed that the triplet resonances for the 4-H methyl protons of the two diastereomers **16** and **17** ($\delta_H$ 0.96 and 0.86 ppm, respectively) were sufficiently separated to allow meaningful integration of these signals. No signals pertaining to the *Z* imines were observed in the $^1$H NMR spectrum. When this method was applied to freshly prepared (*S*)-**15** a 20:1 mixture of imines **16**:**17** was obtained, setting the benchmark at 90% ee prior to racemisation. The major diastereomer **16** was found to epimerise slowly in chloroform-*d* into the minor diastereomer **17** and after 7 days the diastereomeric ratio was found to be 35:65 (**17** major). As a consequence of this finding all NMR acquisitions were performed immediately after imine formation.

The racemisation of (*S*)-**15** in water–dioxane and water–ethanol mixtures with hydrogen chloride has been studied by Badin and Pascu.[20] These aqueous conditions are clearly incompatible with alkyl aluminium Lewis acids, but it was thought that other reagents in non coordinating organic solvents may well bring about the same effect.

Triethylamine and 2,6-di-*tert*-butylpyridine (Table 1, entries 1–2) were found to be ineffective for the racemisation of (*S*)-**15** in chloroform-*d* and the use of nitrogen bases was abandoned. (*S*)-**15** was also found to be stable in the presence of acetic acid in chloroform-*d* for 24 h (entry 3) but with the stronger *p*-toluenesulphonic acid approximately 56% racemisation had occurred after 20 h at room temperature (entry 4). The NMR analysis avoided any evaporative procedure: the mixture was quenched with dilute aqueous base, the organic phase separated, dried and filtered and then treated directly with 1.05 equivalents of (*R*)-(+)-α-methylnaphthylamine. The resulting imine mixture in chloroform-*d* was subjected to $^1$H NMR analysis.

Various commercially available resins with basic and acidic properties were also examined as possible racemisation reagents. The use of the basic Amberlyst 27 resin (entry 5) was found to have no effect on (*S*)-**15**. In contrast, strongly acidic Amberlyst 15 resin resulted in partial racemisation (entry 6) after 4 h at room temperature.

Molecular sieves (MS) are known to be compatible with Lewis acids.[23,24] While 4 Å MS were found to have no effect on (*S*)-**15** (entry 7), the use of 13X MS resulted in slow racemisation (entry 8). A possible rationale invokes the ability of 13X MS (pore size ≈ 10 Å) to accommodate aldehyde **15** in the cavity where the effective proton concentration is much increased, but not in the 4 Å MS cavities. In contrast, 13X MS had no effect on (*R*)-**1** after 24 h at room temperature, where presumably the $C_{10}$-aldehyde is too bulky to enter the molecular framework of the sieves. Control experiments with 4 Å MS gave the same negative and expected result.

Table 1
Racemisation of (*S*)-2-methylbutanal **15**[a]

| Entry | Reagent | Time/h | **16**:**17**[b,c] |
|---|---|---|---|
| 1 | Triethylamine[d] | 48 | 95:5 (0) |
| 2 | 2,6-di-*tert*-Butylpyridine[d] | 48 | 95:5 (0) |
| 3 | Acetic acid[d] | 24 | 95:5 (0) |
| 4 | *p*-Tosic acid[d] | 20 | 67:33 (56) |
| 5 | Amberlyst 27[e] | 24 | 95:5 (0) |
| 6 | Amberlyst 15[e] | 4 | 56:44 (78) |
| 7 | 4 Å MS[e,f] | 24 | 95:5 (0) |
| 8 | 13X MS[e,f] | 24 | 73:27 (44) |

[a] All reactions performed in freshly distilled chloroform-*d* with 0.5 mmol of (*S*)-15.

[b] Imines **16** and **17** formed by addition of 0.53 mmol (*R*)-(+)-α-methylnaphthylamine to the isolated solution of aldehyde **15** and the diastereomeric ratio determined immediately by integration of the 4-H methyl resonances in the $^1$H NMR spectrum.

[c] Figures in parenthesis indicate percentage racemisation of (*S*)-**15**.

[d] 5 mol%.

[e] 200 mg solid reagent.

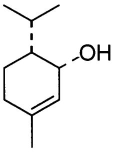
[f] Molecular sieves were powdered and activated prior to use at 300°C under vacuum for 0.5 h.

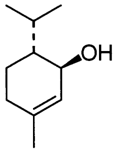
When (±)-aldehyde **1** was treated with *p*-tosic acid or Amberlyst 15 resin in chloroform-*d* a complex mixture of inseparable products resulted with at least seven resonances in the double bond region of the $^1$H NMR spectrum ($\delta_H$ 6.0–4.5 ppm). The relative ratios of products was approximately the same in both cases. The chemical shifts of the resonances and their relative ratios are tabulated below (Table 2). The products were identified as the *exocyclic* adducts **2** and **3** and *endocyclic* adducts **4** and **5**. The two broad singlets resonating at $\delta_H$ 4.71 and 4.68 ppm were tentatively assigned as the 6-H resonances for the alternative internal double bond isomers (1*R**,2*R**)-2-isopropyl-5-methylcyclohex-5-en-1-ol **18** and (1*S**,2*R**)-2-isopropyl-5-methylcyclohex-5-en-1-ol **19**. The appearance of two sets of resonances as apparent AB quartets in this region of the spectrum suggests the formation of conjugated dienes **20** and **21**.

The various cycloadducts are postulated to result from direct intramolecular Prins-addition[1] of the terminus of the double bond to the protonated carbonyl group of (±)-**1**. Non-selective intermolecular β-hydrogen abstraction follows to produce the complex mixture of double bond isomers. The dienes **20** and **21** presumably result from acid-catalysed elimination of water from the already formed cyclohexenols.

(*R*)-**1** was treated with *p*-tosic acid in chloroform-*d* in an attempt to measure the relative rates of Prins-type cyclisation versus acid catalysed enolisation of the α-stereogenic centre. The reaction was monitored by $^1$H NMR and was quenched with aqueous base at approximately 50% conversion. Chiral GC analysis revealed that the unreacted aldehyde **1** had not undergone any racemisation (i.e. 98% ee) and all the cyclohexenols **2**–**5**, **18**, **19** so produced were formed in 98% ee[†] by comparison with the GC traces from the experiment with *p*-tosic acid and (±)-aldehyde **1**.

Table 2
$^1$H NMR analysis of product distribution resulting from effect of *p*-tosic acid on (±)-**1**


**18**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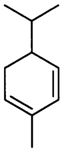
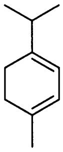

**20**


**21**

| $\delta_H$/ppm | Relative ratio[a] | Assignment |
|---|---|---|
| 5.46 br s | 57 | **4**; 4-H |
| 5.32 br s | 23 | **5**; 4-H |
| 4.85 br s and 4.75 br s | 17 | **2**; 7-H × 2 |
| 4.71 br s | 32 | **18**; 6-H[b,c] |
| 4.68 br s | 31 | **19**; 6-H[b] |
| 6.13 and 5.78 AB quartet; $J$ = 10.2 Hz | 6 | **20**; 3-H, 4-H[d] |
| 5.5.8 2nd order AB quartet | 13 | **21**; 2-H, 3-H[d] |

[a] As determined by integration of the corresponding signals in the $^1$H NMR spectrum.

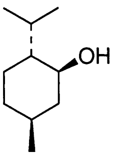
[b] The assignments are interchangeable.

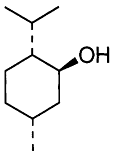
[c] This resonance obscures the expected signal for the 7-H *trans* cycloadduct **3** proton: relative ratio 3 by integration of the 1-H resonance at $\delta_H$ 3.48 ppm.

[d] The assignments are interchangeable.

## *2.3. Diastereoselective hydrogenation*

Yamamoto previously confirmed the relative stereochemistry of the *trans* cycloadduct (±)-**3** obtained from the ene cyclisation of (±)-**1** with MABR by its hydrogenation to (±)-menthol **21** with hydrogen gas over 10% Pd/C in methanol.[3] In our hands, hydrogenation of (±)-**3** under these conditions gave a 2:1 mixture of (±)-menthol **21** and (±)-isomenthol **22** (43% combined yield). Similarly, the hydrogenation of cycloadduct (±)-**2** with palladium-on-carbon gave a 1:1 mixture of (±)-neomenthol **23** and (±)-isoneomenthol **24** (53% combined yield) confirming the *cis* relationship between the hydroxyl and isopropyl groups.


**21**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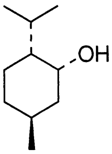
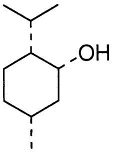

**23**


**24**

Crabtree's catalyst {[PCy$_3$(py)Ir(COD)]PF$_6$} has been used to great effect in hydroxyl-directed hydrogenations of cyclohexenols.[19,25] Hydrogenation of *cis* cycloadduct (±)-**2** in dichloromethane in the presence of 5 mol% of the catalyst was complete within 0.5 h giving (±)-neomenthol **23** as the exclusive product (87% yield). Directed hydrogenation with Crabtree's catalyst of the racemic *cis endocyclic* adduct (±)-**4** was similarly effective again giving rise exclusively to (±)-neomenthol **23**. Furthermore, hydrogenation of the either *exocyclic* or *endocyclic trans* cycloadducts (±)-**3** or (±)-**5** with Crabtree's catalyst gave (±)-isomenthol **22** in 92 and 88% yield, respectively.

Since we have shown that enantiomerically pure cyclohexenols (1*R*,2*R*)-**2** and (1*S*,2*R*)-**3** are available by diastereoselective carbonyl ene cyclisation of (*R*)-**1**, we have thus also completed formal asymmetric syntheses of (1*R*,2*R*,5*S*)-neomenthol **23** and (1*S*,2*R*,5*R*)-isomenthol **22**.

## 3. Conclusion

We have demonstrated that the Lewis acid mediated type II carbonyl ene-cyclisation of the α-stereogenic enantiomerically pure aldehyde (*R*)-**1** proceeds without configurational compromise giving direct access to enantiomerically pure menthol skeletons. We have also used (*R*)-**1** to probe the possibility of effecting a dynamic kinetic resolution process. In these experiments any acid source employed to facilitate enolisation leads instead to competing and dominant Prins reactivity and leaves the original configuration untouched.

## 4. Experimental

### 4.1. Materials and methods

THF, PhMe and $Et_2O$ were distilled from $Na/Ph_2CO$. $CH_2Cl_2$, $NEt_3$ and diisopropylamine were distilled from $CaH_2$. $Tf_2O$ was distilled from $P_2O_5$. DMF, DMSO, $CH_3NO_2$, isovaleric chloride, pyridine and oxalyl chloride were distilled immediately prior to use. *n*-Butyllithium was titrated against freshly recrystallised diphenylacetic acid immediately prior to use.[26] (4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidinone **6** was prepared by the method of Evans.[12] 4-Bromo-2,6-di-*tert*-butylphenol was prepared from 2,6-di-*tert*-butylphenol using $Br_2$ in $CCl_4$. (*S*)-(+)-2-Methylbutanal **15**[22] {$[\alpha]_D$ +27.0 (neat) (lit.,[22] +28.5 (neat))}, pyridinium dichromate,[27] $Cp_2Ti(OTf)_2$[9] and Crabtree's catalyst[10,25] were prepared using published procedures. Racemic samples of alcohol **13**, aldehyde **1** and cycloadducts **2**–**5** were prepared according to our previously published methods.[14] All other materials were used as purchased. All manipulations of air or moisture sensitive materials were carried out under a dry argon atmosphere using standard vacuum line and Schlenk techniques.

Analytical thin layer chromatography (tlc) was performed on Merck plastic-backed plates coated with 0.2 mm silica gel 60 $F_{254}$. Product spots were visualised by quenching of ultraviolet fluorescence ($\lambda_{max}=254$ nm) or by staining with acidic potassium permanganate. Column chromatography was performed on Merck silica gel 60H, 230–300 mesh using the flash chromatographic technique of Still.[28]

Melting points were recorded on a Reichert–Koffler block and are uncorrected. Boiling point values recorded for short path distillations were obtained using a Büchi GKR-51 Kügelrohr oven. The value quoted is the uncorrected pot temperature. Elemental microanalyses were performed by Mrs. V. Lamburn in the Dyson Perrins Laboratory using a Carlo Erba 1106 elemental analyser. Specific rotations ($[\alpha]_D$) were recorded at 24°C on a thermostatted Perkin–Elmer 241 polarimeter. Infrared spectra were recorded on a Perkin–Elmer 1750 Fourier Transform spectrometer. Samples were prepared as thin films on sodium chloride plates or as potassium bromide disks. $^1H$ and $^{13}C$ NMR spectra were recorded on Varian Gemini 200, Bruker WH 300 or Bruker AM 500 spectrometers. Chemical shifts ($\delta$) are quoted in parts per million relative to residual internal chloroform and $J$ values are given in Hz. $^{19}$F spectra were recorded on a Bruker AM 250 (235.2 MHz) spectrometer. Chemical shifts ($\delta_F$) are quoted in ppm and are externally referenced to fluorotrichloromethane [$\delta_F = 0.0$]. Mass spectra were recorded on a Trio-1 GCMS spectrometer.

### 4.2. (4R,5S)-(+)-3-[3-Methyl-1-oxobut-1-yl]-4-methyl-5-phenyl-2-oxazolidinone 7

*n*-Butyllithium (1.6 M in hexanes, 45.2 ml) was added to a solution of oxazolidinone **6** (12.8 g, 72 mmol) in dry THF at −78°C until the red colour persisted. Isovaleryl chloride (9.5 ml, 78 mmol) was added immediately and the colour discharged. The pale yellow solution was allowed to warm to 0°C over 2 h, stirred for 1 h, and quenched with saturated aqueous sodium hydrogen carbonate solution (30 ml). The resulting two phase mixture was stirred vigorously for 1 h and the THF removed under reduced pressure. The organics were extracted with $Et_2O$ (3×100 ml), washed with 1 M NaOH solution (3×100 ml), water (100 ml) and brine (100 ml). The pale yellow solution was dried ($MgSO_4$), filtered and evaporated to give a pale yellow oil. This material solidified on standing and was recrystallised from pentane (two crops) to give the acyloxazolidinone **7** (16.2 g, 86%) as a white solid; mp 53–55°C (lit.,[13] 52–53°C); $[\alpha]_D$ +47.9 ($c$ 1.3 in $CHCl_3$); (found: C, 68.80; H, 7.37; N, 5.33. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36%). $\nu_{max}$ (KBr disk)/cm$^{-1}$ 2962m, 2873m, 1779vs (C=O), 1703s (C=O); $\delta_H$ (500 MHz; $CDCl_3$) 7.47–7.27 (5H, m, Ph), 5.67 (1H, d, $J$ 7.3, PhC*H*), 4.78 (1H, dq, $J$ 7.3, 6.6, NC*H*), 2.92 (1H, dd, $J$ 15.9, 6.7, COCH*H*), 2.79 (1H, dd, $J$ 15.9, 7.2, COC*H*H), 2.22 (1H, ddqq, $J$ 7.2, 6.7, 6.4, 6.4, $(CH_3)_2CH$), 1.02 (3H, d, $J$ 6.4, $CH_3CHCH_3$), 1.01 (3H, d, $J$ 6.4, $CH_3CHCH_3$), 0.91 (3H, d, $J$ 6.6, 4-Me); $\delta_C$ (50.3 MHz; $CDCl_3$) 172.8 ($COCH_2$), 159.3 (OCON), 133.6 (*ipso*-C), 128.9 (Ar–*C*H), 125.9 (Ar–*C*H), 79.9 (Ph*C*H), 54.7 (N*C*HCH$_3$), 44.0 (CO*C*H$_2$), 25.0 ($CH_3CHCH_3$), 22.4 ($CH_3CHCH_3$), 22.3 ($CH_3CHCH_3$), 14.4 ($NCHCH_3$); $m/z$ (CI$^+$; NH$_3$) 279 (M+18$^+$, 95%), 262 (M+1$^+$, 100), 244 (4),.218 (12), 195 (5), 175 (4), 159 (4), 134 (13), 116 (15), 105 (4), 91 (5), 85 (7), 69 (3).

### 4.3. 3-Methylbut-3-en-1-yl trifluoromethanesulphonate 8

Using the general method of Stang[29] a solution of $Tf_2O$ (6.7 ml, 40 mmol) in $CH_2Cl_2$ (50 ml) was added dropwise to a stirred solution of 3-methylbut-3-en-1-ol (4.0 ml, 40 mmol) and pyridine (3.9 ml, 48 mmol) in $CH_2Cl_2$ (50 ml) at −78°C. A white precipitate was formed immediately in a colourless solution. After complete addition of $Tf_2O$ the resulting black solution was stirred at 0°C for a further 2 h, poured onto ice, washed with ice-cold 1 M HCl solution (3×50 ml), water (50 ml), dried ($MgSO_4$), filtered and partially evaporated (ca 20 ml) to give a dilute solution of the thermally sensitive triflate **8** in $CH_2Cl_2$. This solution was stored at −26°C under argon. An aliquot of this solution (1.0 ml) was withdrawn and evaporated to dryness to give a spectroscopically pure black oil (205 mg, 0.94 mmol, 0.94 M solution; 22 ml, 20.6 mmol, 52%); $\nu_{max}$ (thin film)/cm$^{-1}$ 3085w, 2980m, 2923m, 1815w (C=C), 1414s, 1247s, 1208s, 1147s, 946s, 810s; $\delta_H$ (200 MHz; $CDCl_3$) 4.94 (1H, br s, C=CH*H*), 4.83 (1H, br s, C=C*H*H), 4.63 (2H, t, $J$ 6.8, OC*H*$_2$), 2.54 (2H, br t, $J$ 6.8, OCH$_2$C*H*$_2$), 1.79 (3H, br s, 3-Me); $\delta_C$ (50.3 MHz; $CDCl_3$) 138.7 (*C*=CH$_2$), 118.6 (q, $J$ 319, *C*F$_3$), 114.2 (C=*C*H$_2$), 75.2 (O*C*H$_2$), 37.1 (OCH$_2$*C*H$_2$), 22.0 (*C*H$_3$); $\delta_F$ (235.2 MHz; $CDCl_3$) −75.5 (3F, s, C*F*$_3$).

### 4.4. (4R,5S)-(+)-3-[(2R)-2-Isopropyl-5-methyl-1-oxohex-5-en-1-yl]-4-methyl-5-phenyl-2-oxazolidinone **9**

*n*-Butyllithium (1.6 M, 12.4 ml, 19.8 mmol) was added dropwise to a solution of diisopropylamine (3.3 ml, 23.4 mmol) in THF (40 ml) at −20°C and stirred for 0.5 h. The straw yellow solution was cooled to −78°C and added dropwise to a stirred solution of acyloxazolidinone **7** (4.7 g, 18.0 mmol) in THF (80 ml) at −78°C. The bright yellow solution was stirred at −78°C for 0.5 h and a solution of triflate **8** in $CH_2Cl_2$ (0.94 M, 22.0 ml, 20.6 mmol) was added dropwise. The bright yellow colour discharged and the pale yellow solution was warmed to −20°C and stirred for 2 h. The solution was allowed to warm to room temperature and quenched with a phosphate buffer (50 ml, pH 7). The solvent was removed under reduced pressure and the organics extracted with $Et_2O$ (3×100 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a dark orange oil. Purification by flash chromatography on silica gel (5% ethyl acetate in pentane) gave first the title compound **9** (2.95 g, 50%) as a single diastereomer as a colourless oil which solidified on standing mp 66–68°C; $[\alpha]_D$ +23.3 (*c* 1.1 in $CHCl_3$) (found: C, 72.92; H, 8.05; N, 4.04. $C_{20}H_{27}NO_3$ requires C, 72.92; H, 8.26; N, 4.25%); $\nu_{max}$ (thin film)/cm$^{-1}$ 3072w, 2964m, 2878, 1781vs (C=O), 1697vs (C=O), 1650w (C=C); $\delta_H$ (500 MHz; $CDCl_3$) 7.44–7.21 (5H, m, Ph), 5.63 (1H, d, *J* 7.2, PhC*H*), 4.81 (1H, dq, *J* 7.2, 6.6, NC*H*), 4.69 (1H, br s, C=CH*H*), 4.67 (1H, br s, C=CH*H*), 3.76 (1H, ddd, *J* 10.1, 6.8, 3.5, COC*H*), 2.01–1.88 (4H, m, C$H_2$C$H_2$), 1.72–1.67 (1H, m, $CH_3$C*H*$CH_3$), 1.71 (3H, br s, 5′-Me), 1.00 (3H, d, *J* 6.8, C$H_3$CH$CH_3$), 0.98 (3H, d, *J* 6.8, $CH_3$CHC$H_3$), 0.91 (3H, d, *J* 6.6, 4-Me); $\delta_C$ (50.3 MHz; $CDCl_3$) 176.3 (*C*OCH), 159.2 (O*C*ON), 145.7 (*C*=$CH_2$), 135.5 (*ipso*-C), 128.9 (Ar–*C*H), 125.8 (Ar–*C*H), 110.6 (C=*C*$H_2$), 78.7 (Ph*C*H), 55.0 (N*C*H), 48.3 (CO*C*H), 35.4, 30.7, 26.7, 22.1, 20.7, 19.0, 14.3; *m*/*z* ($CI^+$; $NH_3$) 347 ($M+18^+$, 7%), 330 ($M+1^+$, 100), 286 (10), 261 (6), 246 (2), 202 (3), 153 (3), 134 (9), 118 (8), 109 (3) and second (4*R*,5*S*)-(+)-3-[(*Z*)-2,8-dimethyl-5-oxanona-1,6-dien-6-yl]-4-methyl-5-phenyl-2-oxazolidinone **10** as a thermally unstable colourless oil: $\delta_H$ (300 Hz, $CDCl_3$) 7.45–7.28 (5H, m, Ph), 5.65 (1H, d, *J* 7.4, PhC*H*), 4.87 (1H, br s, C=CH*H*), 4.84 (1H, d, *J* 8.5, OC=C*H*), 4.82 (1H, br s, C=CH*H*). 4.27 (1H, dq, *J* 7.4, 6.6, NC*H*), 3.95 (1H, dt, *J* 9.5, 7.4), 3.83 (1H, dt, *J* 9.5, 7.4), 2.78 (1H, dqq, *J* 8.5, 6.8, 6.8,), 2.42 (1H, br t, *J* 7.4), 1.80 (3H, br s), 1.07 (3H, d, *J* 6.8), 1.01 (3H, d, *J* 6.8), 0.80 (3H, d, *J* 6.6, 4-Me).

### 4.5. Attempted transamination of **9**

Following the method of Evans et al.[16] a solution of trimethylaluminium in toluene (2 M, 0.33 ml, 0.66 mmol) was added dropwise to a stirred suspension of *N*,*O*-dimethylhydroxylamine (64 mg, 0.66 mmol) in dry dichloromethane (2 ml) under argon at 0°C. Effervescence occurred and the white suspension solubilised to give a colourless solution in 0.5 h. A solution of oxazolidinone **9** (72 mg, 0.22 mmol) in dry dichloromethane (1 ml) was added via a double ended needle and the yellow solution was stirred at 0°C. After 1 h the mixture was partitioned between ice-cold 1 M HCl (10 ml) and dichloromethane (10 ml). The layers were separated and the aqueous phase extracted with dichloromethane (2×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a pale yellow oil. This material was purified by flash chromatography on silica gel (30% ethyl acetate in pentane) to give (1*S*,2*R*,5*R*)-(+)-*N*,*O*-dimethyl-3-aza-2,8-dimethyl-5-(1-methylethyl)-4-oxo-1-phenyl-8-nonenyl hydroxyl carboxy imide **11** (42 mg, 82%) as a white solid: mp 123–125°C (found: C, 67.39; H, 8.78. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78%); $[\alpha]_D$ +5.9 (*c* 0.38 in $CHCl_3$); $\nu_{max}$ (KBr disk)/cm$^{-1}$ 3317m (NH), 3074w, 2959m, 2873, 1722s (C=O), 1641s (C=O); $\delta_H$ (500 MHz; $CDCl_3$) 7.39–7.28 (5H, m, Ph), 5.78 (1H, d, *J* 4.0, PhC*H*), 5.57 (1H, br d, *J* 8.7, NH), 4.70 (1H, br s, C=C*H*H), 4.64 (1H, br s, C=CH*H*), 4.54 (1H, ddq, *J* 8.7, 6.9, 4.0, NC*H*), 3.75 (3H, s, O*Me*), 3.19 (3H, s, N*Me*), 2.02 (1H, ddd, *J* 15.0, 8.1, 4.7, $CH_2CH$*H*C=C), 1.89 (1H, ddd, *J* 15.0, 7.6, 7.6, $CH_2CH$*H*C=C), 1.77 (1H, dqq, *J* 6.7, 6.7, 6.6, MeC*H*Me), 1.75–1.61 (3H, m, COC*H*C*H*$_2$$CH_2$), 1.69 (3H, br s, C=C*Me*), 1.13 (3H, d, *J* 6.9, NCH*Me*), 0.91 (3H, d, *J* 6.7, MeCH*Me*), 0.86 (3H, d, *J* 6.7, *Me*CHMe); $\delta_C$ (125.6 MHz; $CDCl_3$) 174.6 (NH*C*O), 156.2 (N*C*OO), 145.7 (*C*=$CH_2$), 137.6 (*ipso*-C), 128.7 (Ar–*C*H), 128.3 (Ar–*C*H), 126.5 (Ar–*C*H), 110.6 (C=*C*$H_2$), 79.4 (Ph*C*O), 61.8 (O*C*$H_3$), 54.2 (N*C*HMe), 48.6, 35.6, 35.6, 30.6), 27.5, 22.0, 20.7, 20.2, 15.5; *m*/*z* (CI$^+$; $NH_3$) 391 (M+18$^+$, 12%) 304 (4), 288 (5), 287 (21), 286 (100), 270 (7), 217 (3), 196 (8), 164 (5), 134 (5), 62 (6).

### 4.6. *Attempted reduction of* **9** *to alcohol* **13**

A solution of oxazolidinone **9** (164 mg, 0.5 mmol) in dry THF (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (190 mg, 5 mmol) in dry THF (10 ml) under argon at −78°C. The grey suspension was allowed to warm to 0°C and quenched by the successive addition of water (0.2 ml), 4 M NaOH solution (0.2 ml) and water (1 ml). The resulting white suspension was filtered through a pad of Celite, washed with diethyl ether (3×10 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a yellow oil. The material was purified by flash chromatography on silica gel (30% ethyl acetate in pentane) to give first (2*R*)-*N*-2-((1*S*,2*R*)-2-methyl-1-phenylethoxy)-5-methyl-2-(1-methylethyl)-5-hexenyl amide **12** (60 mg, 39%) as a white solid: $\delta_H$ (300 MHz; $CDCl_3$) 7.38–7.29 (5H, m, Ph), 5.52 (1H, br d, *J* 8.4, NH), 4.89 (1H, d, *J* 4.2, PhC*H*), 4.71 (1H, br s, C=CH*H*), 4.65 (1H, br s, C=C*H*H), 4.38 (1H, ddq, *J* 8.4, 6.9, 4.2, HNC*H*), 3.33 (1H, br s, OH), 2.11–1.55 (6H, m, $Me_2$C*H*C*H*C*H*$_2$C*H*$_2$), 1.69 (3H, br s, C=C*Me*), 1.11 (3H, d, *J* 6.9, NCH*Me*), 0.97 (3H, d, *J* 6.7, MeCH*Me*), 0.96 (3H, d, *J* 6.7, *Me*ChMe); $\delta_C$ (50.3 MHz; $CDCl_3$) 176.3 (*C*=O), 145.6 (*C*=$CH_2$), 141.0 (*ipso*-C), 128.3 (Ar–*C*H), 127.7 (Ar–*C*H), 126.6 (Ar–*C*H), 110.7 (C=*C*$H_2$), 76.5 (Ph*C*H), 54.1 (NH*C*), 50.7 (CO*C*), 35.6, 30.6, 27.5, 22.0, 21.0, 20.2, 14.6; *m*/*z* (CI$^+$; $NH_3$) 304 (M+1$^+$, 11%), 290 (13), 288 (75), 286 (M+1$^+$–$H_20$, 100), 270 (7), 218 (4), 202 (4), 170 (5), 134 (8), 118(3); recovered auxiliary **6** (22 mg, 25%) and alcohol **13** (26 mg, 33%) as a colourless oil, $[\alpha]_D$ +9.04 (*c* 1.2, $CHCl_3$); $\nu_{max}$ (thin film)/cm$^{-1}$ 3600–3100br s (OH), 3074w, 2959s, 2943s, 2874s, 1650m (C=C), 1454m, 1387m, 1370m, 1037m, 886m; $\delta_H$ (500 MHz; $CDCl_3$) 4.72 (1H, br s, C=CH*H*), 4.70 (1H, br s, C=C*H*H), 3.61 (2H, m, HOC*H*$_2$), 2.09 (1H, ddd, *J* 14.7, 10.9, 5.9), 2.03 (1H, ddd, *J* 14.7, 9.3, 6.1), 1.83 (1H, dqq, *J* 6.9, 6.9, 4.7), 1.74 (3H, br s, 5-Me), 1.50 (1H, dddd, *J* 13.8, 10.9, 6.1, 5.0), 1.40 (1H, dddd, *J* 3.8, 9.3, 7.8, 5.9), 1.34 (1H, ddddd, *J* 7.8, 5.0, 5.0, 5.0, 4.7) 0.92 (3H, d, *J* 6.9, $CH_3$CHC*H*$_3$), 0.91 (3H, d, *J* 6.9, C*H*$_3$CH$CH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 146.5 (*C*=$CH_2$), 110.0 (C=*C*$H_2$), 63.4 (HO*C*$H_2$), 46.0, 35.8, 27.7, 25.6, 22.3, 19.6, 19.0; *m*/*z* (CI$^+$; $NH_3$) 174 (M+18$^+$, 7%), 157 (M+1$^+$, 100), 138 (13), 123 (47), 109 (10), 95 (83), 82 (94), 69 (67), 55 (38).

### 4.7. *(*R*)-(+)-2-Isopropyl-5-methylhex-5-ene-1-carboxylic acid* **14**

Hydrogen peroxide (7.6 ml, 30% by volume, 54.0 mmol) was added dropwise to a stirred solution of oxazolidinone **9** (2.95 g, 9.0 mmol) in water (45 ml) and THF (135 ml) followed by lithium hydroxide monohydrate (750 mg, 18 mmol) at 0°C. The solution was allowed to warm to room temperature and stirred for 16 h. Aqueous sodium sulphite solution (1.5 M, 40 ml, 10% excess based on $H_2O_2$) was added to the milky solution to give a colourless alkaline solution (pH 9). The neutral organics were extracted with $CH_2Cl_2$, dried ($MgSO_4$), filtered and the solvent evaporated to give an off-white solid. Recrystallisation from toluene gave white crystals of (4*R*,5*S*)-(+)-4-methyl-5-phenyl-2-oxazolidinone **6** (0.77 g, 48%), $[\alpha]_D$ +168.4 (*c* 1.1 in $CHCl_3$). The aqueous phase was acidified to pH 1 with 1 M HCl, extracted with EtOAc (3×50 ml) dried ($MgSO_4$), filtered and the solvent evaporated to give a pale yellow oil. Purification by short path distillation in base-washed glassware (160°C, 0.1 mmHg) gave carboxylic acid **14** (1.15 g, 75%) as a colourless oil, $[\alpha]_D$ +5.3 (*c* 1.2 in $CHCl_3$); $\nu_{max}$ (thin film)/cm$^{-1}$ 3400–2400s (OH), 3076w, 2965s, 2943s, 2877, 1704s (C=O), 1651m (C=C), 1452m, 1421m, 1391m, 1374m, 1287m, 1229m, 889m; $\delta_H$ (500 MHz; $CDCl_3$) 4.73 (1H, br s, C=CH*H*), 4.70 (1H, br s, C=C*H*H), 2.17 (1H, ddd, *J* 10.6, 7.1, 3.9, $HO_2CCH$), 2.08 (1H, br ddd, *J* 14.8), 2.00 (1H, ddd, *J* 14.8, 9.6, 6.6), 1.93 (1H, dqq, 7.1, 6.8, 6.8, $CH_3CHCH_3$), 1.77 (1H, dddd, *J* 13.9, 10.6, 9.6, 5.4), 1.72 (3H, s, 5-Me), 1.67 (1H, dddd, *J* 13.9, 10.2, 6.6, 3.9), 0.99 (6H, d, *J* 6.8, $CH(CH_3)_2$); $\delta_C$ (50.3 MHz; $CDCl_3$) 182.6 ($HO_2C$), 145.2 ($C$=$CH_2$), 110.6 (C=$CH_2$), 51.9 ($H_2OCCH$), 35.7, 30.3, 26.9, 22.2, 20.2, 19.0; *m*/*z* ($CI^+$; $NH_3$) 188 ($M+18^+$, 20%), 171 ($M+1^+$, 100), 153 (20), 137 (8), 127 (10), 109 (12), 95 (3), 83 (6), 69 (14), 58 (13). Racemic carboxylic acid (±)-**14** for chiral GC analysis (Table 3) was prepared by PDC oxidation of (±)-aldehyde **1**:[14] Pyridinium dichromate (7.52 g, 20 mmol) was added in portions to a stirred solution of (±)-aldehyde **1** (1.54 g, 10 mmol) in DMF (20 ml) under argon at room temperature. After 16 h the dark mixture was poured into water (200 ml) and extracted with $Et_2O$ (3×50 ml). The combined organics were washed with 1 M HCl (3×100 ml), water (3×100 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a dark red oil. Purification by short path distillation (160°C, 0.1 mmHg) gave (±)-**14** (1.3 g, 76%) as a colourless oil identical in all respects to the enantiomerically pure material prepared above.

### *4.8. (*R*)-(+)-2-Isopropyl-5-methylhex-5-en-1-ol* **13**

Carboxylic acid (*R*)-(+)-**14** (800 mg, 4.7 mmol) was dropped as a solution in $Et_2O$ (30 ml) into a finely divided suspension of $LiAlH_4$ (800 mg, 20 mmol) in $Et_2O$ (60 ml) at room temperature. The grey suspension was refluxed for 1 h, cooled to room temperature and quenched by the successive addition of water (1 ml), 4 M NaOH solution (1 ml) and water (3 ml). The white solids were filtered at the pump, the ethereal solution dried ($MgSO_4$), filtered and the solvent evaporated to give alcohol **13** (722 mg, 98%) as a colourless oil, $[\alpha]_D$ +9.12 (*c* 1.2 in $CHCl_3$); all other data identical to the material prepared above. For enantiomeric excess determination, see Table 3.

### *4.9. (*R*)-(−)-2-Isopropyl-5-methylhex-5-enal* **1**

Dimethyl sulphoxide (127 µl, 1.8 mmol) was added as a solution in $CH_2Cl_2$ (2 ml) to a stirred solution of oxalyl chloride (155 µl, 1.8 mmol) in $CH_2Cl_2$ (2 ml) at −78°C. Effervescence occurred, the colourless solution was stirred for 1 h at −78°C and alcohol (*R*)-(+)-**13** (139 mg, 0.89 mmol) was added as a solution in $CH_2Cl_2$ (4 ml). The resulting colourless solution was stirred at −78°C for 1 h. Triethylamine (625 µl, 4.5 mmol) was added and a white precipitate was immediately formed in the colourless solution. The solution was allowed to warm to −30°C over 0.5 h and quenched with 4 M aqueous sodium hydrogen sulphate solution (6.0 ml). The organics were extracted with $CH_2Cl_2$ (3×10 ml), combined, washed with water (10 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a pale yellow oil. Purification by flash chromatography on silica gel (3% ethyl acetate in pentane) gave aldehyde (*R*)-**1** (98 mg, 71%) as a colourless oil, $[\alpha]_D$ −40.9 (*c* 0.43 in $CHCl_3$) (found: C, 77.60; H, 12.06. $C_{10}H_{18}O$ requires C, 77.87; H, 11.76%); $\nu_{max}$ (thin film)/cm$^{-1}$ 3075m, 2963s, 2921s 2837s, 1724s (C=O), 1650m (C=C), 1456s; $\delta_H$ (500 MHz; $CDCl_3$) 9.66 (1H, d, *J* 3.2, C*H*O), 4.74 (1H, br s, C=CH*H*), 4.69 (1H, br s, C=C*H*H), 2.10 (1H, dddd, *J* 9.4, 6.2, 3.6, 3.2, OHCC*H*), 2.03 (1H, dqq, *J* 6.8, 6.8 6.2), 2.02 (1H, br ddd, *J* 14.8, 10.1, 5.5), 1.95 (1H, br ddd *J* 14.8, 9.4, 6.6), 1.81 (1H, dddd, *J* 13.6, 9.4, 9.4, 5.5), 1.72 (3H, br s, 5-Me), 1.61 (1H, dddd, *J* 13.6, 10.1, 6.6, 3.6), 0.99 (3H, d, *J* 6.8, $CH_3CHCH_3$), 0.98 (3H, d, *J* 6.8, $CH_3CHCH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 206.1 (*C*HO), 145.3 (*C*=$CH_2$), 110.7 (C=*C*$H_2$), 57.5 (OHC*C*H), 35.5, 28.2, 23.6, 22.2, 20.1, 19.5; *m*/*z* (CI$^+$; $NH_3$) 172 (M+18$^+$, 23%), 155 (M+1$^+$, 10), 137 (100), 121 (15), 111 (23), 93 (18), 81 (33), 69 (31). For enantiomeric excess determination, see Table 3.

### *4.10. (1*R*,2*R*)-2-Isopropyl-5-methylidenecyclohexan-1-ol* **2**

A solution of dimethylaluminium chloride in hexane (0.33 ml, 1 M, 1.1 mmol) was added dropwise to a solution of aldehyde (*R*)-**1** (46 mg, 0.3 mmol) in $CH_2Cl_2$ (2 ml) at −78°C. The colourless solution was stirred for 0.5 h and then quenched with 1 M sulphuric acid (2 ml). The organics were extracted with $CH_2Cl_2$ (3×5 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a pale yellow oil (44 mg, 98%). Purification by flash chromatography on silica gel (10% ethyl acetate in pentane) gave the title compound **2** (37 mg, 80%) as a colourless oil, $[\alpha]_D$ −18.0 (*c* 0.35 in $CHCl_3$); $\nu_{max}$ (thin film)/cm$^{-1}$ 3700–3100s (OH), 3072w, 2941vs, 2870s, 1654m (C=C stretch); $\delta_H$ (500 MHz; $CDCl_3$) 4.85 (1H, br s, C=CH*H*), 4.75 (1H, br s, C=C*H*H), 4.14 (1H, br s, HOC*H*), 2.40 (1H, br dd, *J* 13.6, 3.4), 2.33 (1H, dddd, *J* 13.2, 4.4, 2.4, 2.2), 2.29 (1H, br dd, *J* 13.6, 2.9), 2.01 (1H, br ddd, *J* 13.3, 13.3, 4.4), 1.81 (1H, br d, *J* 13.3), 1.60 (1H, dqq, *J* 8.9, 6.7, 6.7), 1.30 (1H, dddd, *J* 13.3, 13.2, 12.7, 4.2), 1.28 (1H, d, *J* 8.1, O*H*), 1.09 (1H, dddd, 12.7, 8.9, 3.9, 2.2), 0.99 (3H, d, *J* 6.7, $CH_3CHCH_3$), 0.93 (3H, d, *J* 6.7, $CH_3CHCH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 145.3 (*C*=$CH_2$), 111.2 (C=*C*$H_2$), 68.3 (H*C*OH) 47.9, 42.9, 34.5, 29.1, 25.9, 20.9, 20.8; *m*/*z* (CI$^+$; $NH_3$) 137 (M+1−$H_2O^+$, 58%), 136 (54), 121 (26), 107 (12), 93 (100). For enantiomeric excess determination, see Table 3.

### *4.11. (1*S*,2*R*)-2-Isopropyl-5-methylidenecyclohexan-1-ol* **3**

Following the procedure of Yamamoto[3] a solution of trimethylaluminium in toluene (0.9 ml, 2 M, 1.8 mmol) was added dropwise to a solution of 4-bromo-2,6-di-*tert*-butylphenol (1.0 g, 36 mmol) in toluene (2 ml) with vigorous effervescence at 0°C. After 1 h the red solution was cooled to −78°C and added dropwise to a solution of (*R*)-2-isopropyl-5-methylhex-5-enal **1** (140 mg, 0.9 mmol) in toluene (1 ml). The solution was stirred for 1 h and then allowed to warm to −40°C. After 2 h the mixture was quenched with 1 M sulphuric acid (2 ml), the organics were extracted with $CH_2Cl_2$ (3×5 ml), dried ($MgSO_4$), filtered and the solvent evaporated to give a dark brown residue. Purification by flash chromatography on silica gel (pentane followed by 15% ethyl acetate in pentane) gave the title compound **3** (110 mg, 78%) as a colourless oil; $\nu_{max}$ (thin film)/cm$^{-1}$ 3600–3100m (OH), 3074m, 2937s, 2875s, 1654 (C=C stretch); $\delta_H$ (500 MHz; $CDCl_3$) 4.69 (1H, br s, C=CH*H*), 4.68 (1H, br s, C=C*H*H), 3.46 (1H, ddd, *J* 10.0, 9.6, 4.6, HOC*H*), 2.61 (1H, ddd, 12.5, 4.6, 1.5), 2.27 (1H, ddd, *J* 13.3, 4.1, 3.7, 1.5), 2.17 (1H, dqq, *J* 7.0, 6.9, 3.4), 2.05 (1H, br dd, *J* 12.5, 10.0), 1.95 (1H, br ddd, *J* 13.3, 13.2, 3.7), 1.72 (1H, dddd, *J*

13.0, 3.7, 3.7, 3.4), 1.31 (1H, dddd, *J* 13.1, 9.6, 3.4, 3.4), 1.06 (1H, dddd, *J* 13.2, 13.1, 13.0, 4.1), 0.96 (3H, d, *J* 6.9, $CH_3CHCH_3$), 0.83 (3H, d, *J* 7.0, $CH_3CHCH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 146.9 ($C$=$CH_2$), 108.9 (C=$CH_2$), 72.0 (HO*C*H), 49.8, 44.2, 33.8, 25.6, 23.7, 20.9, 16.2; *m*/*z* ($CI^+$; $NH_3$) 137 ($M+1-H_2O^+$, 32%), 121 (19), 107 (11), 93 (100). 4-Bromo-2,6-bis(1,1-dimethylethyl)phenol was recovered as a bright yellow solid (0.9 g, 86%). For enantiomeric excess determination, see Table 3.

### *4.12. (1*R*,2*R*)-2-Isopropyl-5-methylcyclohex-4-en-1-ol* **4** *and (1*S*,2*R*)-2-isopropyl-5-methylcyclohex-4-en-1-ol* **5**

Aldehyde (*R*)-**1** (198 mg, 1.3 mmol) was added to a solution of titanocene ditriflate (12 mg, 0.03 mmol) in nitromethane (2 ml). After 10 minutes the orange solution was passed through a pad of silica and washed through with $Et_2O$. The combined organics were evaporated and the yellow residue purified by flash chromatography on silica gel (10% ethyl acetate in pentane) to give first (1*R*,2*R*)-**4** (112 mg, 56%) as a colourless oil. $\nu_{max}$ (thin film)/$cm^{-1}$ 3600–3100s (OH), 3070w, 2960s, 2926, 1474m, 1383m, 1215m; $\delta_H$ (500 MHz; $CDCl_3$) 5.46 (1H, br s, C=C*H*), 4.18 (1H, br s, HOC*H*), 2.16 (1H, br d, *J* 16.8), 2.16 (1H, br d, *J* 16.8), 2.06 (1H, d, *J* 17.8), 1.83 (1H, br dd, *J* 16.8, 10.5), 1.68 (3H, br s, 5-Me), 1.62 (1H, dqq, *J* 9.4, 6.7, 6.7), 1.36 (1H, d, *J* 7.5, O*H*), 1.14 (1H, dddd, *J* 10.5, 9.4, 5.8, 1.0), 0.99 (3H, d, *J* 6.7, $CH_3CHCH_3$), 0.93 (3H, d, *J* 6.7, $CH_3CHCH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 129.9 (*C*=CH), 120.7 (C=*C*H), 66.1 (HO*C*H), 44.1, 39.5, 29.3, 25.1, 23.5, 20.8; *m*/*z* ($CI^+$, $NH_3$) 172 ($M+18^+$, 36%), 153 (22), 137 (100), 136 (85), 121 (68), 93 (38), 81 (40); and second (1*S*,2*R*)-**5** (49 mg, 25% as a colourless oil). $\nu_{max}$ (thin film)/$cm^{-1}$ 3600–3100s (OH), 3074w, 2961s, 2943s, 2863, 1463m, 1302m, 1218m; $\delta_H$ (500 MHz; $CDCl_3$) 5.39 (1H, br s, C=C*H*), 3.84 (1H, ddd, *J* 9.6, 8.5, 5.4, HOC*H*), 2.32 (1H, br dd, *J* 17.0, 5.4), 2.13 (1H, dqq, *J* 6.9, 6.9, 4.6), 2.05 (2H, m), 1.89 (1H, br dd, *J* 17.0, 8.5), 1.70 (3H, br s, 5-Me), 1.53 (1H, dddd, *J* 9.8, 9.6, 5.5, 4.6), 0.98 (3H, d, *J* 6.9, $CH_3CHCH_3$), 0.92 (3H, d, *J* 6.9, $CH_3CHCH_3$); $\delta_C$ (50.3 MHz; $CDCl_3$) 131.1 (*C*=CH), 120.4 (C=*C*H), 69.1 (HO*C*H), 45.3, 39.6, 25.9, 23.9), 23.1, 20.6, 16.6; *m*/*z* ($CI^+$, $NH_3$) 172 ($M+18^+$, 19%), 154 (11), 137 (100), 136 (55), 121 (30), 93 (53), 81 (62). For enantiomeric excess determination, see Table 3.

Table 3
Retention times from chiral GC analysis for enantiomeric excess determination[a,b]

| Compound | *T*/°C[c] | Retention time/min[d] |
|---|---|---|
| **14** | 120 | 47.3 (*R*)*, 49.4 (*S*) |
| **13** | 75 | 159.6 (*S*), 169.5 (*R*)* |
| **1** | 50 | 167.5 (*S*), 172.7 (*R*)* |
| **2** | 80 | 77.3 (1*S*,2*S*), 81.4 (1*R*,2*R*)* |
| **3** | 100 | 47.6 (1*R*,2*S*), 50.2 (1*S*,2*R*)* |
| **4** | 85 | 103.7 (1*S*,2*S*), 113.2 (1*R*,2*R*)* |
| **5** | 85 | 157.8 (1*R*,2*S*), 161.9 (1*S*,2*R*)* |

[a] All runs were performed on a Fisons GC 8130 gas chromatograph fitted with a flame ionisation detector and a 3390A Hewlett Packard Integrator. Helium was used as the carrier gas at a pressure of 10 psi using a 25QC2/Cydex-b 0.25 column (SGE).

[b] All runs utilised racemic compounds to establish retention times, followed by a separate injection with the corresponding compound in the chiral series; in all cases the chiral compounds displayed a 98% ee.

[c] Oven temperature.

[d] Major enantiomer marked with an asterisk.

### *4.13. Reaction of (±)-2-methylbutanal* ***15*** *with (*R*)-(+)-1-methyl-1-(1-naphthyl)ethylamine*

(*R*)-(+)-1-Methyl-1-(1-naphthyl)ethylamine (85 mg, 0.53 mmol) was added dropwise to a solution of (±)-2-methylbutanal **15** (43 mg, 0.50 mmol) stirring in $CDCl_3$ (0.5 ml). The solution immediately turned milky to give a 1:1 mixture of the diastereomeric imines **16** and **17**, which were analysed directly by $^1H$ NMR; $\delta_H$ (300 MHz; $CDCl_3$) 8.14 (2H, d, *J* 8.2, Ar–*H*, **16** and **17**), 7.89 (1H, d, *J* 7.3, Ar–*H*, **16**), 7.86 (1H, d, *J* 7.3, Ar–*H*, **17**), 7.75 (2H, d, *J* 8.1, Ar–*H*, **16** and **17**), 7.72 (2H, d, *J* 8.2, Ar–*H*, **16** and **17**), 7.62 (1H, d, *J* 6.0, *H*C=N, **16**), 7.61 (1H, d, *J* 6.1, *H*C=N, **17**), 7.51 (4H, m, Ar–*H*, **16** and **17**), 5.13 (1H, q, *J* 7.1, C=NC*H* **16**), 5.12 (1H, q, *J* 7.1, C=NC*H* **17**), 2.33 (2H, dddq, *J* 7.3, 7.1, 6.9, 6.0), 1.67 (6H, d, *J* 7.1), 1.53 (2H, ddq, *J* 14.0, 7.4, 7.3, 8), 1.41 (2H, ddq, *J* 14.0, 7.4, 7.1), 1.11 (3H, d, *J* 6.9, 2-Me **17**), 1.08 (3H, d, *J* 6.9, 2-Me **16**), 0.96 (3H, t, *J* 7.4, $CH_3CH_2$ **16**), 0.86 (3H, t, *J* 7.4, $CH_3CH_2$ **17**); $\delta_C$ (50.3 MHz; $CDCl_3$) 168.8 (*C*=N, **16** and **17**), 141.4 (Ar–*C*, **16** and **17**), 134.2 (Ar–*C*, **16** and **17**), 130.1 (Ar–*C*, **16** and **17**), 129.2 (Ar–*C*H, **16** and **17**), 127.5 (Ar–*C*H, **16** and **17**), 126.0 (Ar–*C*H×2, **16** and **17**), 125.6 (Ar–*C*H, **16** and **17**), 124.0 (Ar–*C*H, **16** and **17**), 123.7 (Ar–*C*H, **16** and **17**), 65.1 (C=N*C*H, **16** and **17**), 41.0, 27.0, 24.5, 24.4, 17.1 (2-Me, **16** and **17**).

### *4.14. Reaction of (*S*)-(+)-2-methylbutanal* ***15*** *with (*R*)-(+)-1-methyl-1-(1-naphthyl)ethylamine*

As for the method above for the reaction of (±)-2-methylbutanal (**15**) with 1-methyl-1-(1-naphthyl)ethylamine to give a 95:5 ratio of **16**:**17**, respectively, by integration of the 4-H diasteromeric resonances in the $^1H$ NMR spectrum ($\delta_H$ 0.96, 0.86 ppm; **16**,**17**).

### *4.15. General procedure for the attempted racemisation of (*S*)-(+)-2-methylbutanal* ***15*** *with organic bases (Table 1, entries 1–2)*

(*S*)-(+)-2-Methylbutanal **15** (43 mg, 0.50 mmol) was treated with an organic base (5 mol%) for 48 h in dry $CDCl_3$ (1 ml). The mixture was quenched with saturated aqueous ammonium chloride solution (1 ml) and extracted with $CDCl_3$ (2×1 ml). The combined organics were dried ($MgSO_4$), filtered and then treated with (*R*)-(+)-1-methyl-1-(1-naphthyl)ethylamine (85 mg, 0.53 mmol). The mixture was analysed directly by integration of the 4-H diasteromeric imine resonances in the $^1H$ NMR spectrum ($\delta_H$ 0.96, 0.86 ppm; **16**,**17**).

### *4.16. General procedure for the attempted racemisation of (*S*)-(+)-2-methylbutanal* ***15*** *with organic acids (Table 1, entries 3–4)*

(*S*)-2-Methylbutanal **15** (43 mg, 0.50 mmol) was treated with an organic acid (5 mol%) for 20–24 h in dry $CDCl_3$ (1 ml). The mixture was quenched with saturated aqueous sodium hydrogen carbonate solution (1 ml) and extracted with $CDCl_3$ (2×1 ml). The combined organics were dried ($MgSO_4$), filtered and then treated with (*R*)-(+)-1-methyl-1-(1-naphthyl)ethylamine (85 mg, 0.53 mmol). The mixture was analysed directly by integration of the 4-H diasteromeric imine resonances in the $^1H$ NMR spectrum ($\delta_H$ 0.96, 0.86 ppm; **16**,**17**).

### *4.17. General procedure for the attempted racemisation of* (S)*-(+)-2-methylbutanal with solid reagents (Table 1, entries 5–8)*

(*S*)-2-Methylbutanal (**15**) (43 mg, 0.50 mmol) and activated molecular sieves (200 mg) or an Amberlyst resin (200 mg) were stirred vigorously for 24 h in dry $CDCl_3$ (1 ml). The mixture was filtered and (*R*)-(+)-1-methyl-1-(1-naphthyl)ethylamine (85 mg, 0.53 mmol) was added. The mixture was analysed directly by integration of the 4-H diasteromeric imine resonances in the $^1$H NMR spectrum ($\delta_H$ 0.96, 0.86 ppm; **16**,**17**).

### *4.18. General procedure for hydrogenations with Crabtree's catalyst*

A vigorously stirred mixture of cycloadduct **2**, **3**, **4** or **5** (154 mg, 1 mmol) and Crabtree's catalyst[10,26] (41 mg, 5 mol%) in degassed $CH_2Cl_2$ (2 ml) was exposed to hydrogen gas (1 atmosphere). The extent of reaction was monitored by the uptake of hydrogen on a gas burette. The hydrogen atmosphere was removed and the solvent was evaporated under reduced pressure. The residue was triturated with hot pentane, and the combined organics filtered. The solvent was removed under reduced pressure and the products analysed by $^1$H NMR and GCMS. In all cases the menthol isomer produced was identical to an authentic sample.

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