Tetrahedron 66 (2010) 1489–1495

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

L-Threonine-catalysed asymmetric α-hydroxymethylation of cyclohexanone: application to the synthesis of pharmaceutical compounds and natural products

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ARTICLE INFO

Article history:
Received 10 September 2009
Received in revised form 11 November 2009
Accepted 20 November 2009
Available online 2 December 2009

Keywords:
Hydroxymethylation
Formaldehyde
Threonine
Aldol reaction
Rociverine

ABSTRACT

L-Threonine has been found to be an efficient catalyst for the asymmetric α-hydroxymethylation of cyclohexanone with formalin. Reducing the amount of water in the reaction by the addition of magnesium sulfate as a dehydrating additive significantly improves the yield. Applications of (*S*)-2-hydroxymethyl cyclohexanone and the chiral building blocks derived therefrom for the synthesis of pharmaceutical compounds and natural products have been explored.

1. Introduction

Optically active α-hydroxymethyl cyclohexanone and chiral building blocks derived therefrom are high value and versatile chiral intermediates for synthetic applications. For example, (*S*)-2-hydroxymethyl cyclohexanone (*S*)-**1** (Fig. 1) is a key building block for a potent spasmolitic agent (*R*,*R*)-rociverine **2**.[1] Chiral 6-hydroxyl heptanoates **3a**–**b** obtainable from (*S*)-**1** are present in many pharmaceutical compounds and natural products.[2]

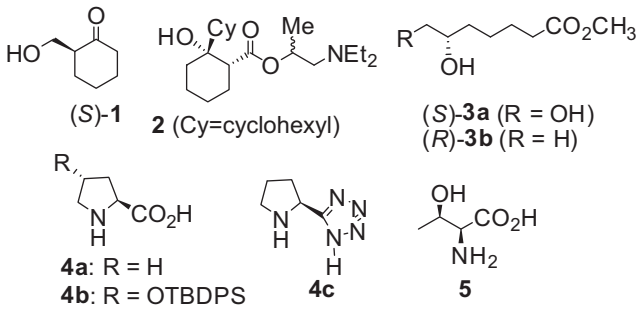

Figure 1. Structure of compound **1**–**5**.

As such, several methods have been developed for the synthesis of (*S*)-**1** and its derivatives. Lipase-mediated resolution of (±)-**1** using vinyl acetate provided (*S*)-**1** in 42% yield and 87% ee.[3] Lewis acid-catalysed aldol reaction of cyclohexyl silyl enol ether with formalin in the presence of (*R*)-BINAP afforded (*S*)-**1** in 31% yield and 57% ee.[4] More recently, organocatalytic direct aldol reactions have been developed for the synthesis of (*S*)-**1**. For example, the reaction of cyclohexanone with formalin in the presence of L-proline (**4a**)[5a] or its derivatives **4b**–**c**[5b–c] provided (*S*)-**1** in 37–47% yield and 96–99% ee. L-Threonine **5**, which contains a primary amine group, has also been reported to catalyse this aldol reaction, providing (*S*)-**1** in 63% yield and 93% ee.[6]

Our interest in optically active α-hydroxymethyl cyclohexanone arose from the recognition that these are high value intermediates for the pharmaceutical industry and in natural product syntheses due to the scope of downstream transformations. We report herein our independent work on the identification of L-threonine as an efficient organocatalyst for the asymmetric α-hydroxymethylation of cyclohexanones with formalin as well as the use of (*S*)-**1** and the chiral building blocks obtained therefrom for the synthesis of pharmaceutical compounds and natural products.

2. Results and discussion

2.1. L-Threonine-catalysed asymmetric α-hydroxymethylation of cyclohexanone

Our studies on the organocatalytic α-hydroxymethylation of cyclohexanone commenced with a reported procedure[5a] wherein

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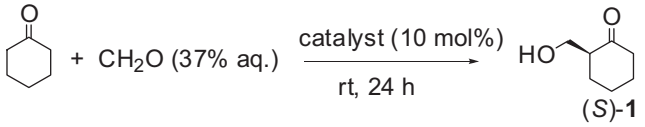
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.100

cyclohexanone was treated with formalin using proline **4a** as the catalyst and the desired product (*S*)-**1** was obtained in 47% yield and 99% ee. In our hands, the desired product could only be obtained in low yields (<20%) in ca. 94% ee in spite of numerous attempts to reproduce as well as to optimise the conditions. These disappointing results prompted us to search for a more effective catalyst for the reaction.

The catalyst for this purpose should ideally be readily available and inexpensive while providing the hydroxymethyl compounds in both good yield and optical purity. Thus a number of L-amino acids were screened for the reaction of cyclohexanone with formalin (Table 1). Most of these showed either no catalytic activity (entries 6–8) or afforded products in very poor yields (entries 1–4) after 24 h at room temperature. Amino acids with either an acidic or basic residue (entries 7–8) were found to be ineffective. Surprisingly, L-threonine, which has not often been reported as a catalyst for the aldol reaction, gave the best yield of the desired product in 33% yield and 90% ee (entry 5).

Table 1
Screening of catalysts[a]



Entry	Catalyst	Yield[b] (%)	ee[d] (%)
1	L-Tryptophan	<8	n.d.[e]
2	L-*trans*-4-Hydroxy-proline	<7	n.d.[e]
3	L-Serine	12	n.d.[e]
4	L-Proline	18	94
5	L-Threonine	33	90
6	L-Leucine	—[c]	—
7	L-Lysine	—	—
8	L-Glutamic acid	—	—

[a] The reactions were performed with CH_2O (37% aq solution, 1.0 mmol) and cyclohexanone (2.0 mmol) in DMSO (1 mL) with the catalyst (10 mol%) at rt for 24 h.
[b] Determined by ^1H NMR spectroscopic analysis of the crude product.
[c] Not detectable by ^1H NMR spectroscopic analysis.
[d] Determined by chiral GC analysis after trifluoroacetylation.
[e] Not determined.

With this encouraging result, the reaction was further optimised. From screening for the best solvents for the reaction (Table 2), DMSO and THF were found to give comparable yields (entries 1–2) and ee whereas reactions carried out in other solvents or in the absence of a solvent (neat) afforded lower yields and/or lower enantioselectivity of the desired hydroxymethylated product. For convenience and ease of work-up, THF was chosen as the solvent of choice in subsequent optimisation studies.

Table 2
Screening of solvents[a]

Entry	Solvent	Yield[c] (%)	ee[d] (%)
1	DMSO	33	90
2	THF	37	91
3	—[b]	22	n.d.[e]
4	DMF	11	n.d.[e]
5	Toluene	14	n.d.[e]
6	DCM	25	16
7	CH_3CN	29	69
8	Ethyl acetate	33	9

[a] The reactions were performed with CH_2O (37% aq solution, 1.0 mmol) and cyclohexanone (2.0 mmol) in the solvents (1 mL) with L-threonine (10 mol%) at rt for 24 h.
[b] Neat reaction.
[c] Determined by ^1H NMR spectroscopic analysis of the crude product.
[d] Determined by chiral GC analysis after trifluoroacetylation.
[e] Not determined.

First, the relationship between catalyst loading and the product yields was examined (Table 3). It was found that 10 mol% loading (entry 2) was optimal as further increase in the amount of catalyst resulted in slightly decreased yields due to catalyst precipitation. Considering the fact that formaldehyde is strongly hydrated,[7] which results in a low concentration of the reactive form, we envisioned that removal of water by the addition of a dehydrating agent as an additive would shift the equilibrium to the free formaldehyde and thus facilitate the reaction.

Table 3
Optimisation of conditions[a]

Entry	Catalyst (mol%)	Additive (equiv)	Time (h)	Yield[b] (%)
1	5	—	24	15
2	10	—	24	37
3	15	—	24	36
4	20	—	24	33
5	10	$MgSO_4$ (0.5)	24	43
6	10	$MgSO_4$ (1)	24	54
7	10	$MgSO_4$ (1.5)	24	46
8	10	$MgSO_4$ (2)	24	39
9	10	$MgSO_4$ (1)	48	62
10	10	$MgSO_4$ (1)	72	74
11	10	$MgSO_4$ (1)	96	82
12	10	$MgSO_4$ (1)	120	85

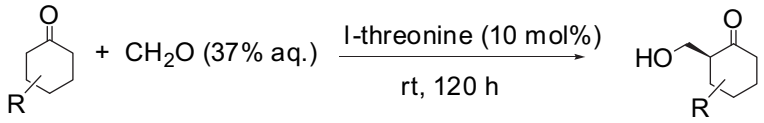
[a] The reactions were performed with CH_2O (37% aq solution, 1.0 mmol) and cyclohexanone (2.0 mmol) in THF (1 mL) with L-threonine (5–20 mol%) and $MgSO_4$ (0.5–2.0 equiv) at rt for 24–120 h.
[b] Determined by ^1H NMR spectroscopic analysis of the crude product.

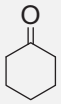
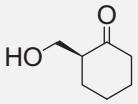
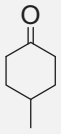
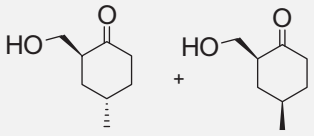
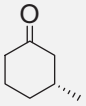
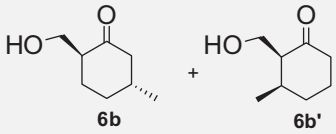
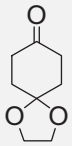
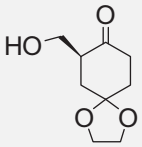
Screening several dehydrating additives, including Na_2SO_4, $MgSO_4$, 4 Å molecular sieves and $CaCl_2$, it was found that the addition of 1 equiv of $MgSO_4$ (Table 3, entry 6) afforded the best yield of 54% in 24 h. However, further increase in the amount of $MgSO_4$ (entries 7–8) resulted in a decreased yield. This adverse effect could be attributed to the over removal of water as some water is needed in order to release the catalyst bound to the aldol adduct.[8,9] Therefore, a fine balance of the amount of water seems paramount to the success of the reaction. The dual roles of water in the acceleration and deceleration of an organocatalytic aldol reaction have been studied for L-proline catalysed aldol reaction.[8] In addition, the presence of water has also been found to be essential for primary amino acid-catalysed aldol reactions.[9a] With $MgSO_4$ being identified as a beneficial additive, the reaction time was extended to maximise the conversion. It was found that the yield increased to 82% in 96 h but the increase in yields is less significant thereafter.

The optimised conditions were applied to a few substituted cyclohexanones (Table 4), providing the hydroxymethyl products in 55–74% yield and in 60–98% ee (entries 1–4). For (*R*)-3-methyl cyclohexanone (entry 3), the regioisomeric products **6b** and **6b′** are each formed as a pair of diastereomers with the major isomers shown, and the isomeric excess is expressed as diastereomeric excess (de).

The *S*-configuration of the hydroxymethyl products, predicted on the basis of a generally accepted model of stereochemical induction for primary amino acid-catalysed aldol reactions,[6,9] was verified by optical rotation measurement (for (*S*)-**1**).[10] This was further confirmed by single crystal X-ray analysis of compound **6b**, obtained from (*R*)-3-methyl cyclohexanone (entry 3), after derivatisation to its (1*S*)-(−)-camphanate **7** using (1*S*)-(−)-camphanic chloride. The crystal structure (Fig. 2) clearly revealed the *trans* relationship of the 2-hydroxymethyl to the 5-methyl group and its (2*S*,5*R*)-configuration.[11] In addition, we have observed that the stereochemical induction is predominantly governed by the configuration of the amino acid motif and less influenced by the hydroxyl group as L-allo-threonine (**8**) catalysed reaction of cyclohexanone provided the product (*S*)-**1** with the same configuration despite in a lower ee of 75%.

Table 4
L-Threonine-catalysed asymmetric α-hydroxymethylation of cyclohexanones[a]



Entry	Ketone	Product	Yield[b] (%)	ee/de (%)
1		 (*S*)-**1**	74	90[c]
2		 **6a** + **6a'**	72 (**6a**: **6a**′)=5:4	**6a** (96)[d] **6a**′ (42)[d]
3		 **6b** + **6b'**	55 (**6b**: **6b**′=7.5:1)	**6b** (98)[d, e] **6b**′ (67)[d, e]
4		 **6c**	56	70[d]

[a] The reactions were carried out with a cyclohexanone (8.0 mmol), CH_2O (37% aq solution, 4.0 mmol) and $MgSO_4$ (4.0 mmol) in THF (4 ml) with L-threonine (10 mol %) at rt for five days.
[b] Isolated yields after silica gel column chromatography.
[c] Determined by chiral GC analysis after trifluoroacetylation.
[d] Determined by direct chiral GC analysis.
[e] Diastereomeric excess (de, see text).

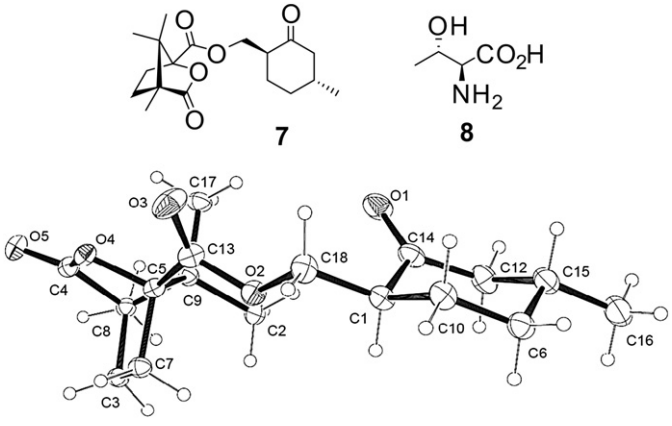
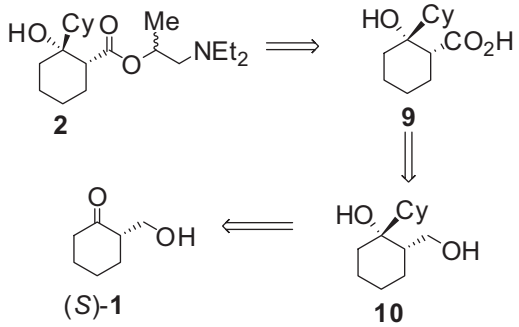


Figure 2. Structure of **7**–**8** and X-ray structure of **7** with displacement ellipsoids drawn at the 30% probability level.

2.2. Synthetic application of (*S*)-(2-hydroxymethyl) cyclohexanone

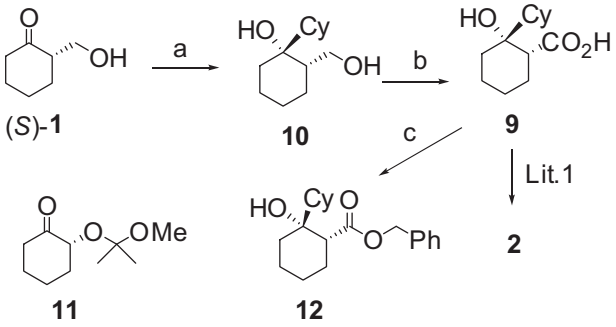
The optimised conditions were applied to the multigram synthesis of (*S*)-**1**. At ~10 °C, the enantiomeric excess of the product was further improved to 98% although the yield was lower (~42%) by vacuum distillation (see Experimental Section). With quantities of (*S*)-**1** in hand, its synthetic application was explored. (*R*,*R*)-Rociverine (**2**), the most potent muscarinic antagonist among the four stereoisomers[12] whose activity resides in the chirality of the cyclohexane ring, has previously only been obtained by chemical resolution.[1] No enantioselective synthesis of **2** has been achieved to date. We envisioned that a formal synthesis of **2** can be achieved concisely via intermediate 9 from (*S*)-**1**. This would involve two key steps, which include a stereo-controlled *anti*-addition of a cyclohexyl Grignard reagent to the carbonyl group of (*S*)-**1** and selective oxidation of the primary alcohol within **10** to provide the carboxylic acid **9** (Scheme 1).

It has been shown[13] that it was necessary to protect the hydroxyl group as methoxyisopropyl (MIP) ketal to facilitate a chelation-controlled, *anti*-selectivity Grignard addition and to



Scheme 1. Retrosynthesis of **2** from (*S*)-**1**.

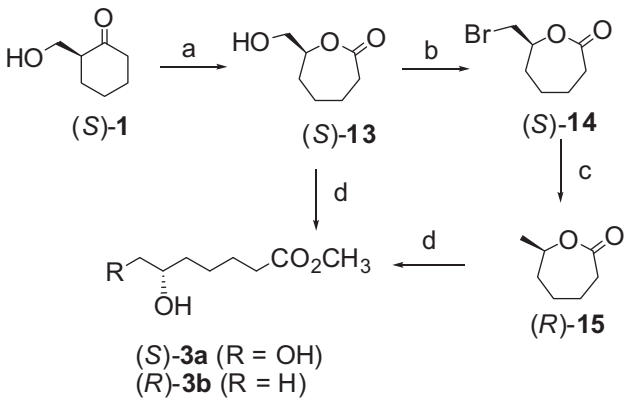
avoid enolisation of the β-hydroxyl ketone. In our hands, the MIP ketal **11** was found to be unstable to chromatographic purification on silica gel. Consequently, a one-pot, three-step procedure was developed for the synthesis of **10**. Thus, protection of the hydroxyl group with 2-methoxypropene in the presence of PPTS led to the ketal intermediate **11**, which was reacted with cyclohexylmagnesium chloride at −10 °C to introduce the cyclohexyl group diastereoselectively. Acidic workup resulted in the deprotection of the MIP protecting group, providing the desired diol **10** in 76% yield. The selective oxidation of the primary alcohol within **10** to the carboxylic acid **9** was not as straightforward as it appeared. As the tertiary alcohol is prone to elimination, conventional strongly acidic oxidation conditions, such as $H_2Cr_2O_7/H^+$, $KMnO_4/H^+$, were avoided. After screening a few milder oxidation methods including $CuCl/^tBuOOH$,[14] O_2-Pt/C,[15] it was found that a one-pot, two-step sequence, involving TEMPO/NaOCl to the intermediate aldehyde followed by further oxidation using $NaClO_2/NaH_2PO_4$ in a biphasic solvent system (DCM:H_2O ~ 7:1) in the presence of 2-methyl-2-butene,[16] provided the required acid **9** in 87% yield (Scheme 2).



Scheme 2. Formal synthesis of **2** from (*S*)-**1**. a. (i) 2-methoxypropene, PPTS (3 mol %), Et_2O, −10 °C, 30 min; (ii) *c*-$C_6H_{11}MgCl$, Et_2O, −10–0 °C, 1 h; (iii) 0.2 M HCl, rt, 4 h, 76%; b. (i) NaOCl, TEMPO (30 mol %), $^nBu_4NBr$, DCM/H_2O (7:1), 0 °C to rt, 3 h; (ii). $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH, rt, 3 h, 87%; c. $NaHCO_3$, $^nBu_4NBr$, $PhCH_2Br$, DCM, rt, 4 h, 88%.

The optical purity of the product was determined by converting the acid **9** to its benzyl ester **12**, which was analysed by chiral HPLC and shown to be 98% ee. The retention of optical purity from (*S*)-**1** highlighted the Grignard reaction proceeded in a highly diastereoselective manner and racemisation did not occur under the mild oxidation conditions. As (±)-**9** has previously been converted to (±)-**2** by reacting with 2-chloro-1-diethylaminopropane,[12] this concise route constitutes a highly efficient and stereoselective formal synthesis of (*R*,*R*)-Rociverine (**2**).

Having achieved a formal synthesis of **2**, the synthetic application of (*S*)-**1** was further demonstrated by its downstream transformation to chiral building blocks with general synthetic application (Scheme 3). Bayer–Villiger oxidation of (*S*)-**1** afforded 6-hydroxymethyl-ε-caprolactone (*S*)-**13** in 89% yield. It is worth noting that aqueous workup should be avoided to prevent loss of the product due to its water solubility. The hydroxymethyl lactone (*S*)-**13** was converted to the bromide (*S*)-**14**, which was further debrominated under free radical conditions ($^nBu_3SnH$/AIBN) to provide (*R*)-6-methyl-ε-caprolactone (*R*)-**15**,[17] which has been used for the synthesis of a chiral polymer.[18] Finally, both optically active caprolactones, (*S*)-**13** and (*R*)-**15**, were ring-opened with sodium methoxide in methanol, providing two novel optically active 6-hydroxyl heptanoate (*S*)-**3a** and (*R*)-**3b**, which are valuable chiral building blocks for the synthesis of natural products, such as pyranicin,[2a] cladospolides[2d] and daumone.[2e]



Scheme 3. Downstream transformation of (*S*)-**1** to chiral building blocks. a. *m*-CPBA, $NaHCO_3$, DCM, rt, 3 h, 98%; b. CBr_4, PPh_3, DCM, 0 °C to rt, 5 h, 58%; c. $^nBu_3SnH$, AIBN (30 mol %), toluene, 100 °C, 3 h, 77%; d. NaOMe, MeOH, rt, 2 h, 85% for (*S*)-**3a**, 84% for (*R*)-**3b**.

3. Conclusion

In conclusion, we have independently identified L-threonine as an efficient catalyst for the stereoselective hydroxymethylation of cyclohexanones. The addition of $MgSO_4$ as a dehydrating additive has been found to promote the hydroxymethylation reaction. The hydroxymethyl compounds were obtained in 55–74% yield and 60–98% ee. The synthetic application of (*S*)-**1** has been demonstrated in a formal synthesis of pharmaceutical compound (*R*, *R*)-rociverine and chiral building blocks with general synthetic applications.

4. Experimental

4.1. General

Melting points were measured on a Büchi B-540 capillary melting point apparatus. $^1H/^{13}C$ NMR spectra were recorded at 400/100 MHz on a Bruker Advance 400 spectrometer in $CDCl_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference. IR spectra were recorded on a Bio-Rad FTS 3000MX FTIR spectrometer as liquid film or evaporated film (EF). Optical rotations were measured using a JASCO P-1030 polarometer. Mass spectra were run by the electro spray ionization time-of-flight (ESI-TOF) mode on an Agilent 6210 mass spectrometer. Chiral GC and HPLC analyses were performed on an Agilent Technologies 6890N Network GC system or Agilent 1100 HPLC system. Solvents for moisture sensitive reactions were taken from a Glasscontour solvent purification system under nitrogen. Commercially available reagents were used as received unless otherwise indicated. Reactions Flash column chromatography purification was carried out either manually or by using a Biotage SP1™ purification system by gradient elution.

4.2. General procedure for the optimisation of reaction conditions

4.2.1. Procedure for the screening of catalysts for the α-hydroxymethylation of cyclohexanone. To a vial containing a catalyst (0.1 mmol, 10 mol % to CH_2O) was added formalin (37% aqueous solution, 75 μL, 1.0 mmol). The mixture was stirred at rt for 10 min before DMSO (1 mL) and cyclohexanone (210 μL, 2.0 mmol) were added. The vial was sealed and the mixture was stirred at rt for 24 h. The reaction was quenched by the addition of saturated NH_4Cl aqueous solution (1.0 mL) and stirred for 5 min. The mixture was extracted with ethyl acetate (3×10 mL). The combined extracts

were washed with brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the yield of the reaction was obtained by ^1H NMR spectroscopic analysis of a weighed sample dissolved in $CDCl_3$ (0.50 mL containing 0.01 mmol DMF as the internal reference). The enantiomeric excess of the product was determined by chiral GC analysis on a Chiraldex G-TA column after conversion to the trifluoroacetate. The results are given in Table 1.

4.2.2. Procedure for the screening of solvents. To a vial containing L-threonine (12 mg, 0.1 mmol, 10 mol % to CH_2O) was added formalin (37% aqueous solution, 75 μL, 1.0 mmol). The mixture was stirred at rt for 10 min before the solvent (1 mL) and cyclohexanone (210 μL, 2.0 mmol) were added. The vial was sealed and the mixture was stirred at rt for 24 h. The solvent was evaporated under reduced pressure and the yield was obtained by ^1H NMR spectroscopic analysis of a weighed sample dissolved in $CDCl_3$ (0.50 mL containing 0.01 mmol DMF as the internal reference). The enantiomeric excess of the product was determined by chiral GC analysis on a Chiraldex G-TA column after conversion to the trifluoroacetate. The results are given in Table 2.

4.2.3. Procedure for the optimisation of catalyst loading. To a vial containing L-threonine (0.05–0.2 mmol, 5–20 mol % to CH_2O) was added formalin (37% aqueous solution, 75 μL, 1.0 mmol). The mixture was stirred at rt for 10 min before THF (1 mL) and cyclohexanone (210 μL, 2.0 mmol) were added. The vial was sealed and the mixture was stirred at rt for 24 h. The solvent was evaporated under reduced pressure and the yield was obtained by ^1H NMR spectroscopic analysis of a weighed sample dissolved in $CDCl_3$ (0.50 mL containing 0.01 mmol DMF as the internal reference). The results are given in Table 3.

4.2.4. Procedure for the study of the effect of $MgSO_4$. To a vial containing L-threonine (12 mg, 0.1 mmol, 10 mol % to CH_2O) was added formalin (37% aqueous solution, 75 μL, 1.0 mmol). The mixture was stirred at rt for 10 min before THF (1 mL), cyclohexanone (210 μL, 2.0 mmol) and $MgSO_4$ (0–2.0 mmol) were added. The vial was sealed and the mixture stirred at rt for 24 h. The mixture was filtered through a cotton wool plug and the solid residue washed with ethyl acetate (5 mL). The solvents were evaporated under reduced pressure and the yield was obtained by ^1H NMR spectroscopic analysis of a weighed sample dissolved in $CDCl_3$ (0.50 mL containing 0.01 mmol DMF as the internal reference). The results are given in Table 3.

4.3. General procedure for the α-hydroxymethylation of cyclohexanones

To a vial containing L-threonine (48 mg, 0.4 mmol, 10 mol % to CH_2O) was added formalin (37% aqueous solution, 300 μL, 4.0 mmol). The mixture was stirred at rt for 10 min before THF (4 mL), the cyclohexanone (8.0 mmol) and $MgSO_4$ (480 mg, 4.0 mmol) were added. The vial was sealed and the mixture was stirred at rt for five days. The mixture was filtered and the solid residue washed with ethyl acetate (10 mL). Saturated aqueous NH_4Cl solution (5 mL) was added to the filtrates and the solution was stirred for 10 min. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2×15 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvents were evaporated under reduced pressure and the crude product was purified by silica gel column chromatography by gradient elution with ethyl acetate in petroleum ether to provide the hydroxymethyl cyclohexanones (Table 4). The enantiomeric excess of the products was determined by chiral GC analysis on a Chiraldex G-TA column: injection temperature: 180 °C; detector temperature: 250 °C; flow rate: 1.0 mL/min (except for **1** at 0.8 mL/min).

*4.3.1. (S)-2-(Hydroxymethyl)cyclohexanone ((S)-**1**).* The compound (*S*)-**1** was obtained as a colourless liquid (380 mg, 74%) in 90% ee; $[\alpha]_D^{22}$ +11.4 (*c* 1.0, $CHCl_3$) {lit.[19] $[\alpha]_D^{26}$ −8.5 (*c* 0.41, $CHCl_3$) for (*R*)−1, 78% ee}; GC: after trifluoroacetylation, t_{major}=27.4 min, t_{minor}= 27.8 min; IR (film) 3406 (OH), 2937, 2865, 1703 (C=O), 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (dd, *J*=11.3, 7.3 Hz, 1H), 3.57 (dd, *J*=11.3, 3.7 Hz, 1H), 2.72 (br s, 1H), 2.53–2.45 (m,1H), 2.41–2.25 (m, 2H), 2.12–1.97 (m, 2H), 1.92–1.86 (m, 1H), 1.73–1.56 (m, 2H), 1.50–1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 62.8, 52.3, 42.2, 30.1, 27.5, 24.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{12}O_2Na$ $[M+Na]^+$ 151.0730, found 151.0726.

*4.3.2. (2S,4R)-2-(Hydroxymethyl)-4-methylcyclohexanone (**6a**) and (2S,4S)-2-(hydroxymethyl)-4-methylcyclohexan-one (**6a′**).* The two isomeric products were obtained as a mixture in a ratio of 5:4 (by ^1H NMR spectroscopic analysis) as a colourless liquid (410 mg, 72%). Separation of the mixture by silica gel column chromatography provided the *trans*-isomer **6a**, which was analysed by chiral GC to be 96% ee; $[\alpha]_D^{22}$ −28.1 (*c* 1.0, $CHCl_3$); GC: t_{major}=46.4 min, t_{minor}= 47.2 min; IR (film) 3410 (OH), 2955, 2928, 2872, 1701 (C=O), 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (ddd, *J*=12.2, 7.7, 5.2 Hz, 1H), 3.60 (ddd, *J*=12.2, 8.2, 4.2 Hz, 1H), 2.71–2.63 (m, 1H), 2.54 (dd, *J*=8.2, 5.2 Hz, 1H), 2.51–2.44 (m, 1H), 2.32–2.24 (m, 1H), 2.16–2.11 (m, 1H), 1.95–1.87 (m, 1H), 1.80–1.71 (m, 3H), 1.18 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 63.1, 48.1, 37.8, 35.5, 32.9, 26.7, 18.4; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0882.

The *cis*-isomer **6a′** was partially separated from **6a** and analysed to be 42% ee; GC: t_{major}=39.8 min, t_{minor}=40.6 min; IR (film) 3410 (OH), 2955, 2928, 2872, 1701 (C=O), 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (ddd, *J*=12.2, 7.3, 5.3 Hz, 1H), 3.57 (ddd, *J*=12.2, 8.5, 3.8 Hz, 1H), 2.65 (dd, *J*=8.5, 5.3 Hz, 1H), 2.59–2.52 (m, 1H), 2.39–2.36 (m, 2H), 2.06–1.91 (m, 3H), 1.42–1.31 (m, 1H), 1.26–1.17 (m, 1H), 1.00 (d, *J*=8.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 62.7, 51.2, 41.5, 38.1, 35.4, 31.5, 21.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0887.

*4.3.3. (2S,5R)-2-(Hydroxymethyl)-5-methylcyclohexanone (**6b**) and (2S,3R)-2-(hydroxymethyl)-3-methylcyclohexan-one (**6b′**).* The two isomeric products were obtained as a mixture in a ratio of 7.5:1 (by ^1H NMR spectroscopic analysis) as a colourless liquid (313 mg, 55%). Separation of the mixture by silica gel column chromatography provided the major isomer **6b**, which was analysed to be 98% ee by chiral GC; $[\alpha]_D^{22}$ +33.0 (*c* 1.0, $CHCl_3$); GC: t_{major}=36.0 min, t_{minor}= 39.0 min; IR (film) 3410 (OH), 2954, 2928, 2872, 1703 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.71 (m, 1H), 3.59 (m, 1H), 2.68 (t, *J*=6.5 Hz, 1H), 2.48–2.41 (m, 1H), 2.40–2.34 (m, 1H), 2.05–1.95 (m, 2H), 1.90–1.79 (m, 2H), 1.51–1.34 (m, 2H), 1.03 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 62.6, 51.3, 50.4, 35.3, 33.4, 28.9, 22.3. HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0890.

The isomer **6b′** was partially separated from **6b** and analysed to be 67% ee; GC: t_{major}=45.5 min, t_{minor}=42.7 min; IR (film) 3421 (OH), 2955, 2934, 2875, 1701, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (t, *J*=10.2 Hz, 1H), 3.41 (br s, 1H), 2.73–2.68 (m, 1H), 2.44–2.20 (m, 4H), 1.97–1.82 (m, 2H), 1.78–1.63 (m, 1H), 0.81 (d, *J*=7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.6, 61.2, 56.5, 41.8, 34.2, 32.0, 22.3, 14.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{14}O_2Na$ $[M+Na]^+$ 165.0886, found 165.0882.

*4.3.4. (S)-7-(Hydroxymethyl)-1,4-dioxaspiro[4.5]decan-8-one (**6c**).* The compound **6c** was obtained as a colourless liquid (417 mg, 56%) in 70% ee; $[\alpha]_D^{22}$ −3.0 (*c* 1.0, $CHCl_3$); GC: t_{major}=69.8 min,

t_{minor}=68.5 min; IR (film) 3425 (OH), 2959, 2889, 1710 (C=O), 1143, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07–3.99 (m, 4H), 3.66 (t, J=5.9 Hz, 2H), 2.88–2.80 (m, 1H), 2.68 (td, J=13.5, 5.8 Hz), 2.58 (br d, 1H), 2.38 (dt, J=13.5, 4.0 Hz), 2.08–1.97 (m, 3H) 1.94–1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2, 107.2, 64.9, 64.7, 62.2, 48.3, 38.5, 36.9, 34.4; HRMS (ESI-TOF) m/z calcd for $C_9H_{14}O_4Na$ $[M+Na]^+$ 209.0784, found 209.0791.

*4.3.5. Larger scale synthesis of (S)-**1**.* To a flask containing L-threonine (1.49 g, 0.0125 mol) was added formalin (37% aqueous solution, 9.5 mL, 0.125 mol). The mixture was stirred at rt for 30 min until the catalyst fully dissolved. THF (250 mL) was added and the solution was cooled to 10 °C using a chiller circulator before cyclohexanone (20.0 mL, 0.19 mol) and powdered anhydrous $MgSO_4$ (15.0 g, 0.125 mol) were added. The reaction was stirred at 10–12 °C for five days. After, which time, it was filtered and the solid residue washed with ethyl acetate (2×50 mL). Saturated aqueous NH_4Cl solution (40 mL) was added to the filtrates and the solution was stirred for 20 min. The organic phase was separated, dried ($MgSO_4$) and the solvent was evaporated. Vacuum distillation of the crude product provided (*S*)-**1** (6.67 g, 41.7%, 107–109 °C/0.15 mbar) as a colourless oil. The optical purity of the product (98% ee) was determined by chiral GC analysis as described in 4.3.1.

*4.3.6. Synthesis of camphanate (**7**).* To a solution of the alcohol **6b** (50 mg, 0.352 mmol) in dry DCM was added DMAP (215 mg, 1.76 mmol) and then (−)-(*S*)-camphanic chloride (99 mg, 0.458 mmol) at rt. The mixture was stirred at rt for 4 h and then concentrated under reduced pressure. The crude product was purified by column chromatography using 0–25% EtOAc in petroleum ether to afford pure product (45 mg, 40% yield) as a white solid, which was then *re*-crystallized from EtOAc/pentane to afford colourless single crystals suitable for X-ray analysis. Mp: 111–112 °C; IR (EF) 2974, 2877, 1784, 1710, 1640, 1279, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, J=11.3, 5.6 Hz, 1H), 4.20 (dd, J=11.3, 6.4 Hz, 1H), 2.66 (m, 1H), 2.43–2.37 (m, 2H), 2.22–2.16 (m, 2H), 2.07–1.98 (m, 2H), 1.93–1.82 (m, 3H), 1.70–1.64 (m, 1H), 1.52–1.36 (m, 2H), 1.11 (s, 3H), 1.05 (d, J=5.4 Hz, 3H), 1.04 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 178.3, 167.4, 91.2, 64.3, 54.8, 54.2, 50.2, 48.3, 35.3, 33.3, 30.6, 29.8, 28.9, 22.3, 16.7, 16.7, 9.7; HRMS (ESI-TOF) m/z calcd for $C_{18}H_{26}O_5Na$ $[M+Na]^+$ 345.1673, found 345.1684.

4.4. Synthesis of (1*R*, 2*R*)-1-hydroxy-1,1′-bicyclohexyl-2-carboxylic acid (9)

*4.4.1. Synthesis of (1R,2S)-1-hydroxy-1,1′-bicyclohexyl-2-methanol (**10**).* To a solution of (*S*)-**1** (98% ee, 128 mg, 1.0 mmol) and PPTS (8 mg, 3 mol %) in anhydrous Et_2O (2 mL) was added 2-methoxypropene (377 μL, 4 mmol) dropwise at −10 °C. After stirring for 30 min at −10 °C, Et_2O (3 mL) was added, followed by the addition of cyclohexylmagnesium chloride (2 M in Et_2O, 1.4 mL, 2.8 mmol) over 20 min at −10 °C. The reaction mixture was allowed to warm to 0 °C and continued stirring at this temperature for 1 h before being quenched by the addition of aqueous NH_4Cl solution (2 mL) and water (1 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2×10 mL). The combined extracts were evaporated under reduced pressure to give a viscous residue to which was added saturated NH_4Cl (5 mL) and 0.2 M HCl until pH 4. The mixture was stirred at rt for 4 h and then extracted with Et_2O (3×20 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The crude white solid was washed with ~5% Et_2O in petroleum ether and dried under vacuum to afford the diol (**9**) as a white solid (162 mg, 76%). Mp: 168–169 °C; $[\alpha]_D^{24}$ +27.9 (*c* 1.2, EtOH) {lit.[13] $[\alpha]_D^{24}$ −10.66 (*c* 1.22, EtOH) for (1*S*, 2*R*)-**10**, ee unspecified}; IR (EF) 3305 (OH), 2926, 2853, 1448, 1017; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09 (dt, J=11.0, 2.9 Hz, 1H), 3.54 (ddd, J=11.0, 6.2, 2.9 Hz, 1H), 2.63 (dd, J=6.2, 2.9 Hz, 1H), 2.33 (s, 1H), 1.98–1.47 (m, 13H), 1.30–0.93 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 76.8, 64.7, 45.5, 41.3, 31.3, 27.9, 26.9 (2C), 26.7, 26.2, 25.73, 25.67, 21.5; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{24}O_2Na$ $[M+Na]^+$ 235.1669, found 235.1671.

*4.4.2. Synthesis of (1R,2R)-1-hydroxy-1,1′-bicyclohexyl-2- carboxylic acid (**9**).* To a solution of the diol (**10**) (191 mg, 0.9 mmol) in CH_2Cl_2 (20 mL) and H_2O (3 mL) was added sequentially aqueous solutions of NaBr (1 M, 0.5 mL) and $^nBu_4NBr$ (1 M, 1 mL), saturated aqueous $NaHCO_3$ (2.5 mL), TEMPO (44 mg, 0.3 mmol) and aqueous NaOCl (13%, 2 mL) with stirring at 0 °C. The reaction mixture was stirred at rt for 3 h. After, which time, the mixture was acidified to pH 7 with 2 N HCl aqueous solution, followed by sequential addition of ^tBuOH (14 mL), 2-methyl-2-butene (2 M in THF, 28 mL, 56 mmol) and an aqueous solution of $NaClO_2$ (1.2 g, 13 mmol) and NaH_2PO_4 monohydrate (800 mg, 5.8 mmol) in H_2O (4 mL). The mixture was stirred vigorously at rt for 3 h. The solvents were removed under reduced pressure and the residue was diluted with EtOAc (20 mL) and H_2O (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×30 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography by gradient elution with 0–50% EtOAc in petroleum ether with 0.05% formic acid to provide the acid **9** (177 mg, 87%) as a white solid. Mp: 128–129 °C (lit.[1]130–132 °C); $[\alpha]_D^{25}$ +12.4 (*c* 1.0, 0.5 N NaOH) {lit.[1] $[\alpha]_D$ +10.3, (*c* 1.0, 0.5 N NaOH), temperature unspecified}; IR (EF) 3345 (OH), 2928, 1695 (C=O), 1446, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (dd, J=12.1, 4.4 Hz, 1H), 2.01 (s, 1H), 1.95–1.052 (m, 12H), 1.48–1.39 (m, 1H), 1.30–0.94 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 73.9, 48.1, 47.8, 29.9, 28.2, 26.9, 26.7, 26.5, 26.33, 26.26, 25.0, 20.6; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{21}O_3$ $[M-H]^-$ 225.1496, found 225.1489.

*4.4.3. Synthesis of benzyl (1R,2R)-1-hydroxy-1,1′-bicyclo-hexyl-2-carboxylate (**12**).* To a solution of carboxylic acid **9** (40 mg, 0.177 mmol) in DCM (2 mL) was added $^nBu_4NI$ (78 mg, 0.212 mmol), saturated aqueous $NaHCO_3$ (1 mL) and benzyl bromide (32 μL, 0.266 mmol). The mixture was stirred at rt for 4 h, followed by addition of saturated aqueous NH_4Cl solution (1 mL) and DCM (3 mL). The phases were separated and the aqueous phase was extracted with DCM (2×5 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography by gradient elution with 0–10% EtOAc in petroleum ether to afford the benzyl ester **12** (49 mg, 88%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 5.23 (d, J=12.1 Hz, 1H), 5.06 (d, J=12.1 Hz, 1H), 3.25 (d, J=2.6 Hz, 1H), 2.63 (dd, J=12.4, 3.6 Hz, 1H), 1.98–1.87 (m, 2H), 1.78–1.57 (m, 8H), 1.53–1.46 (m, 1H), 1.22–0.85 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 135.7, 128.7 (2C), 128.4, 128.3 (2C), 73.5, 66.2, 48.1, 48.0, 29.9, 28.3, 26.79, 26.77, 26.6, 26.3, 26.2, 25.1, 20.7; HPLC: 98% ee, t_{major}=11.0 min (1*R*, 2*R*), t_{minor}=13.7 min (1*S*, 2*R*); 0.5% IPA in hexane; Chiralpak AS-H column (4.6×250 mm); flow rate: 1 mL/min.

4.5. Synthesis of compounds 3, 13–15

*4.5.1. Synthesis of (S)-7-(hydroxymethyl)oxepan-2-one ((S)-**13**).* To a solution of (*S*)-**1** (98% ee, 1.02 g, 7.97 mmol) in dry DCM (40 mL) was added $NaHCO_3$ (1.0 g, 12 mmol) followed by *m*-CPBA (77%, 2.14 g, 9.6 mmol) at 0 °C. The resulting mixture was allowed to warm to rt and stirred for 3 h. The reaction was diluted with DCM (20 mL) and quenched by the addition of solid sodium thiosulphate

(0.63 g, 4 mmol). The mixture was stirred for 10 min, filtered and the solid residues were washed with DCM (30 mL). The filtrates were evaporated under reduced pressure and the crude product was purified by silica gel column chromatography by gradient elution with 50–100% EtOAc in petroleum ether to afford the lactone (*S*)-**13** as a colourless oil (1,03 g, 89%); $[\alpha]_D^{24}$ +41.2 (*c* 1.3, $CHCl_3$); IR (film) 3420 (OH), 2939, 2866, 1717 (C=O), 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33–4.28 (m, 1H), 3.65 (dd, *J*=12.0, 7.3 Hz, 1H), 3.55 (dd, *J*=12.0, 4.0 Hz, 1H), 3.31 (br s, 1H), 2.67–2.54 (m, 2H), 1.97–1.82 (m, 3H), 1.62–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 81.0, 65.0, 34.7, 30.4, 27.7, 22.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{12}O_3Na$ $[M+Na]^+$167.0679, found 167.0687; GC: 96% ee (Chiraldex G-TA), t_{major}=10.7 min, t_{minor}=13.7 min; flow rate: 2.0 mL/min.

*4.5.2. Synthesis of (S)-7-(bromomethyl)oxepan-2-one ((S)-**14**).* To the solution of the hydroxymethyl lactone (*S*)-**13** (144 mg, 1.0 mmol) in dry DCM (5 mL) was added PPh_3 (525 mg, 2.0 mmol) and CBr_4 (663 mg, 2.0 mmol) at 0 °C under argon. The mixture was stirred at rt for 5 h, followed by concentration under reduced pressure. The residues was purified by silica gel column chromatography by gradient elution with 0–20% EtOAc in petroleum ether to afford the bromide (*S*)-**14** (120 mg, 58%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.47–4.42 (m, 1H), 3.54 (dd, *J*=10.6, 5.8 Hz, 1H), 3.41 (dd, *J*=10.8, 6.2 Hz, 1H), 2.76–2.70 (m, 1H), 2.63–2.55 (m, 1H), 2.24–2.17 (m, 1H), 2.05–1.94 (m, 2H), 1.73–1.59 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 79.3, 34.8, 34.2, 33.0, 27.9, 22.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{11}BrO_2Na$ $[M+Na]^+$ 228.9840 (^{79}Br), found 228.9831.

*4.5.3. Synthesis of (R)-7-methyloxepan-2-one ((R)-**15**).* To a solution of bromide (*S*)-**14** (100 mg, 0.69 mmol) in dry toluene (5 mL) was added AIBN (35 mg, 0.2 mmol) and $^nBu_3SnH$ (368 μL, 1.38 mmol) under argon. The mixture was heated at 100 °C for 3 h. After cooled to rt, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography by gradient elution with 0–30% EtOAc in petroleum ether to afford the lactone (*R*)-**15** (69 mg, 77%) as a colourless oil; $[\alpha]_D^{24}$ +27.4 (*c* 1.0, $CHCl_3$) {lit.[17] $[\alpha]_D^{23}$ +25.0 (*c* 1.8, $CHCl_3$)}; IR (film) 2936, 2864, 1727 (C=O), 1179, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47–4.40 (m, 1H, CHO), 2.70–2.56 (m, 2H, CH_2CO), 1.95–1.86 (m, 3H), 1.69–1.55 (m, 3H), 1.35 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 76.8, 36.2, 35.0, 28.3, 22.9, 22.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{12}O_2Na$ $[M+Na]^+$ 151.0730, found151.0734.

*4.5.4. Synthesis of (S)-methyl 6,7-dihydroxyheptanoate (S)-**3a**.* To a solution of lactone (*S*)-**15** (144 mg, 1.0 mmol) in dry MeOH (5 mL) was added sodium methoxide (216 mg, 4.0 mmol) and the mixture was stirred at rt for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by removal of MeOH under reduced pressure. The residue was diluted with EtOAc (10 mL) and water (2 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2×8 mL). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography by gradient elution with 5–10% MeOH in DCM to afford the methyl ester (*S*)-**3a** (150 mg, 85%) as a colourless oil. $[\alpha]_D^{26}$ −20.1 (*c* 1.07, EtOH); IR (film) 3393 (OH), 2943, 2867, 1734 (C=O), 1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74–3.68 (m, 1H), 3.66 (s, 3H), 3.64(dd, *J*=11.0, 2.9 Hz, 1H), 3.43 (dd, *J*=11.0, 7.3 Hz, 1H), 2.33 (t, *J*=7.3 Hz, 1H), 1.70–1.60 (m, 2H), 1.53–1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 71.9, 66.8, 51.6, 33.9, 32.7, 25.0, 24.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{16}O_4Na$ $[M+Na]^+$ 199.0941, found 199.0938.

*4.5.5. Synthesis of (R)-methyl 6-hydroxyheptanoate ((R)-**3b**).* Compound (*R*)-**3b** (53 mg, 84% yield) was similarly prepared from lactone (*R*)-**15** (50 mg, 0.391 mmol) as a colourless oil; $[\alpha]_D^{25}$ −12.7 (*c* 1.0, $CHCl_3$); IR (film) 3410 (OH), 2936, 2865, 1739 (C=O), 1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.84–3.75 (m, 1H), 3.65 (s, 3H), 2.32 (t, *J*=7.4 Hz, 2H), 1.75 (br s, 1H), 1.68–1.59 (m, 2H), 1.51–1.26 (m, 4H), 1.17 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 67.8, 51.5, 38.8, 34.0, 25.3, 24.8, 23.5; HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_{16}O_3Na$ $[M+Na]^+$ 183.0992, found 183.0983.

Acknowledgements

We are most grateful to our scientific advisors Professor Brian Cox (AstraZeneca) and Professor Richard Taylor (University of York) for their valuable discussions. We also thank Drs Murugapillai Venugopal and Shanti Thavaneswaran for their contributions at the early stage of this study, Ms Sze Chen Chia and Dr. Cun Wang for their assistance on the X-ray structure analysis, and the Agency for Science, Technology and Research (A*STAR), Singapore for supporting this work.

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10. (*S*)-**1** {$[\alpha]_D^{23}$ +11.4 (*c* 1.0, $CHCl_3$)} has the same sign of rotation as the (*S*)-enantiomer obtained from enzymatic resolution.[3]
11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 742698. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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