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An asymmetric Maitland–Japp reaction: a highly enantioselective synthesis of tetrahydropyran-4-ones

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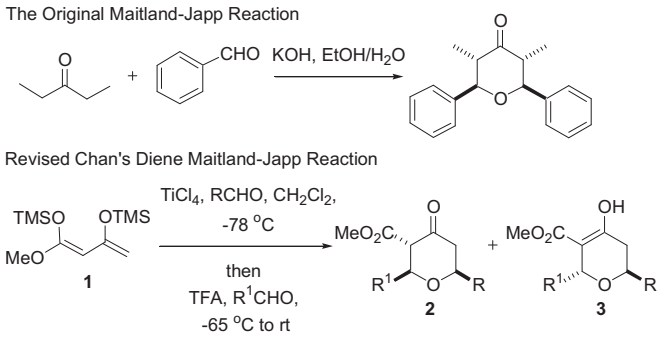
ABSTRACT

A highly enantioselective synthesis of functionalized tetrahydropyran-4-ones has been achieved by the development of a catalytic asymmetric Maitland–Japp reaction using Chan's diene as the nucleophile. This reaction has been used to synthesize the tetrahydropyran ring of (−)-centrolobine and the C9–C19 tetrahydropyran ring of (+)-phorboxazole B.

1. Introduction

Natural products containing highly substituted tetrahydropyrans continue to be targets of interest to synthetic organic chemists.[1] This interest can be attributed to two main reasons: (i) the structures of these natural products present a number of non-trivial synthetic challenges, which need to be overcome and, (ii) these natural products have, more often than not, potent bioactivity in a number of cell assays and may provide new treatments for a number of different diseases. This interest has led to a number of reactions being developed for the enantioselective synthesis of substituted tetrahydropyrans. Such strategies include hetero-Diels–Alder cyclizations,[2] Prins cyclizations,[3] Petasis–Ferrier rearrangements,[4] intramolecular oxy-Michael reactions,[5] cyclization onto epoxides[6] and the reduction of cyclic hemi-ketals,[7] to name a few. Our own group has a continuing interest in the synthesis of tetrahydropyran containing natural products, and in 2005 we reported an updated variation of the Maitland–Japp reaction.[8] The original Maitland–Japp reaction[9] was the condensation of pentan-3-one with benzaldehyde to give a symmetrical tetrahydropyran-4-one in a low yield (Scheme 1). However, this reaction could never be made into a general synthesis of tetrahydropyran-4-ones due to the symmetrical nature of the products produced by the restriction of using aromatic aldehydes and a symmetrical ketone. In our report in 2005, we replaced pentan-3-one with the bis-silyl enolether of methyl acetoacetate (Chan's diene[10] **1**), as the different reactivity of the α- and γ-positions of the diene would allow us to introduce different aldehyde partners and thus expand the range of the tetrahydropyran-4-ones formed (Scheme 1). The utility of this procedure was demonstrated at the time by the shortest, highest yielding synthesis of (±)-centrolobine.[11] However, this synthesis did highlight the need to develop an asymmetric version of the reaction.



Scheme 1. The original and revised Maitland–Japp reactions.

In order to achieve this we turned our attention to the use of diketene instead of Chan's diene as a nucleophile. This enabled us to develop an asymmetric Maitland–Japp reaction[12] (Scheme 2), where enantioselective addition of diketene to the aldehyde generated enantioenriched δ-hydroxy-β-ketoesters, which could be cyclized to the tetrahydropyran-4-one with no loss of enantiomeric

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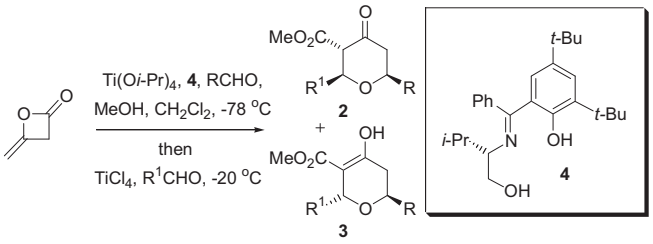
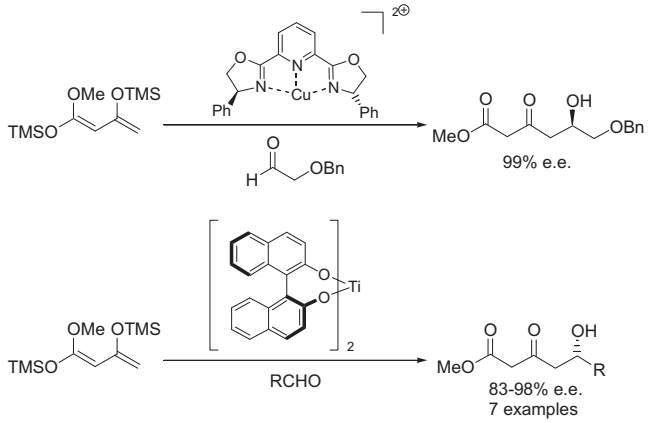
integrity. While this did allow us to complete an asymmetric synthesis of the C1–C19 bis-pyran fragment of phorboxazole B,[13] it became clear that the long reaction times (>5 days) and the moderate enantioselectivities (56–85%) did require further work. It was for these reasons that we refocused our attentions back to the use of Chan's diene as a nucleophile, and in this paper we report the successful development of a highly enantioselective Maitland–Japp synthesis of tetrahydropyran-4-ones.



Scheme 2. Asymmetric diketene Maitland–Japp reaction.

2. Results and discussion

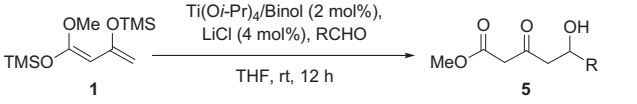
There are a couple of reports in the literature of the asymmetric addition of Chan's diene to aldehydes to generate δ-hydroxy-β-ketoesters.[14] The most notable is the procedure of Evans, which uses a Cu(*S*,*S*-pybox) complex.[14a] However, this reaction only generates high enantioselectivities when benzyloxy acetaldehyde is the electrophile, thus limiting its usefulness. A procedure, which offered to obviate this problem was reported by Soriente, who demonstrated that the Keck reagent (Ti(Binol)$_2$) could be used to catalyze the asymmetric addition of Chan's diene to a wider range of aldehyde electrophiles[14b,c] (Scheme 3).



Scheme 3. Asymmetric addition of Chan's diene to aldehydes.

In our hands application of the Soriente conditions led to disappointing results as the δ-hydroxy-β-ketoesters were formed in low yields (<20%) and low enantioselectivities (0–85% ee). Frustratingly, on most occasions the results of repeated reactions were irreproducible, suggesting that there was some variable we were unaware of which was crucial to the reaction success, and that we were failing to control. We noted that the presence or absence of 4 Å molecular sieves did have a dramatic influence on the outcome of the reaction. In their absence, or if dried by exhaustive heating, the product δ-hydroxy-β-ketoesters were racemic, however, when they were dried by heating at 180 °C for 12 h under a stream of nitrogen, the δ-hydroxy-β-ketoester product was formed in a variable, but low, enantiomeric excess.[15] We were therefore very interested in a report, which appeared contemporaneously to our own studies, which examined the effect of achiral additives on the outcome of the Soriente reaction.[16] This report indicated that the addition of 2 equiv of LiCl resulted in reproducibly excellent yields and enantioselectivities. Test reactions we carried out on both an aromatic and aliphatic aldehyde indicated that this was indeed the case, with the δ-hydroxy-β-ketoesters products being formed in good yields and excellent enantioselectivities (Table 1).

Table 1
Asymmetric addition of Chan's diene to aldehydes



	R	Catalyst	Yield (%)	% ee[a]
a	Ph	(*R*)-Binol	89	97 (*R*)
b	Pr	(*S*)-Binol	83	99 (*R*)[b]

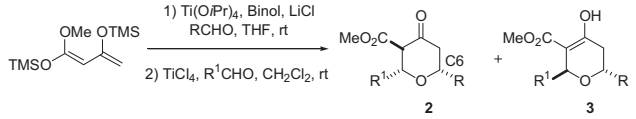
[a] Determined by chiral shift ^{1}H NMR with Eu(hfc)$_3$.
[b] (*R*)-Binol and (*S*)-Binol give products in the opposite enantiomeric series, however, the absolute configuration of **5a** and **5b** are both assigned as (*R*) due to the priorities of the CIP rules.

We believe that the discrepancy between Soriente's report[14b,c] and those of later workers trying to repeat it arises from the manner in which Chan's diene was prepared. We prepared Chan's diene from methyl acetoacetate by first forming the α-mono silyl enolether with Et_3N and TMSCl, removing the precipitated ammonium salts by filtration. The α-mono silyl enolether was then treated with LDA at −78 °C followed by TMSCl. After 1 h the solvents were removed in vacuo and the salts removed by trituration with hexane, followed by Kügelrohr distillation (0.1 Torr, <80 °C) of the crude Chan's diene product to remove any unreacted starting material. This procedure also effectively removes all of the LiCl generated in the formation of the second silyl enolether. In their original report Soriente makes no mention of the procedure used for the synthesis of Chan's diene and it is entirely possible that they used the method in Chan's original reports,[10] which do not advocate purification by Kügelrohr distillation. We therefore believe that in the work of Soriente, the Chan's diene used was unknowingly contaminated with adventitious LiCl leading to the impressive, yet irreproducible results reported.

With the problem of the asymmetric addition of Chan's diene to aldehydes solved, we next turned our attention to the inclusion of this step in the asymmetric Maitland–Japp reaction (Table 2). Chan's diene was added to a range of aldehydes using the Ti(O*i*-Pr)$_4$/Binol/LiCl conditions discussed above, and the resulting δ-hydroxy-β-ketoesters were subjected to our established cyclization conditions to generate tetrahydropyran-4-ones **2** and **3** in moderate to good yields. As Ti(O*i*-Pr)$_4$/Binol complex does not catalyze the Knoevenagel/Michael steps of the Maitland–Japp reaction, $TiCl_4$ is used when an equivalent of the second aldehyde is added. The reaction mixture is then slowly warmed to rt, with pyran formation occurring at temperatures above −65 °C. Our earlier work had shown that the cyclization of δ-hydroxy-β-ketoesters to tetrahydropyran-4-ones **2** and **3** proceeded without erosion of the enantiomeric integrity of the tetrahydropyran-4-ones.[8b,12] We even demonstrated that **2** and **3** could also be separated and re-equilibrated under the cyclization reaction conditions without erosion in their enantiomeric excesses.[13] As can be seen from Table 2 a range of aromatic, aliphatic and heteroatom-containing aldehydes can be used either as the aldol acceptor or as the second aldehyde in the cyclization reaction. The enantiomeric excess of the products are uniformly excellent. In the cases of entries a and e the enantiomeric excess of the THP product appears to have been enhanced in the cyclization reaction. In actuality this is due to the fact that these THPs are solids and preferential crystallization of the major enantiomer may have occurred during purification to give products with an enhanced enantiomeric excess. In the case of entry d some erosion of the

enantiomeric excess did occur. *para*-Anisaldehdye is problematic in the Maitland–Japp reaction[11] as it tends to undergo Knoevenagel condensation/cyclization slowly and in lower yields than the other aldehydes investigated. We believe that this is due to it being less electrophilic than the other aldehydes studied. This reduction in reactivity led to a prolonged reaction time, which resulted in some loss of the enantiomeric integrity of the product. The mechanism for this erosion of enantiomeric integrity is probably the $TiCl_4$ mediated formation of a carbocation, which is stabilized by delocalization into the phenyl ring. It is reassuring to note that this erosion is only seen when extended cyclization times are required.

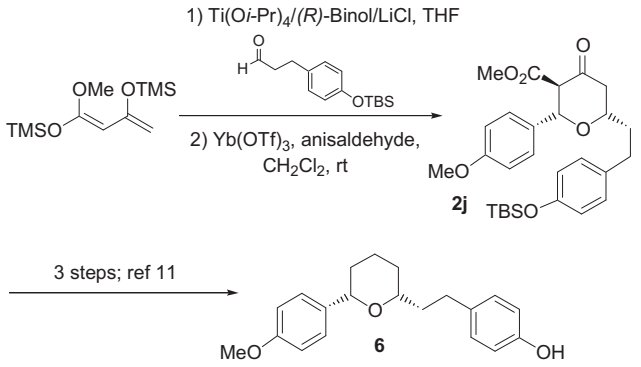
Table 2
Asymmetric Maitland–Japp reaction[a]



Entry	R	R^1	Yield (%)	Ratio **2**/**3**	%ee[b]
a[c]	Ph	Ph	86	1:2	99[g]
b[c]	Ph	*i*-Pr	69	10:1	97[h]
c[c]	Ph	2-furyl	36	1:10	97[g]
d[c]	Ph	4-$MeOC_6H_4$	40	1:3.8	93[i]
e[c]	Ph	4-$NO_2C_6H_4$	70	1:2	99[h]
f[e]	Pr	4-$MeOC_6H_4$	77	1:1	99[i]
g[d]	*i*-Pr	Ph	90	1:2.8	99[g]
h[c]	CH_2OBn	Ph	30	0:1	97[i]
i[c]	cy-Hex	Ph	70	1:1.5	99[g]
j[f]	4-TBSO $C_6H_4(CH_2)_2$	4-$MeOC_6H_4$	55	2:1	91[g]
k[f]	$BnO(CH_2)_2$	2-Me-oxazole	69	2:1	84[g]

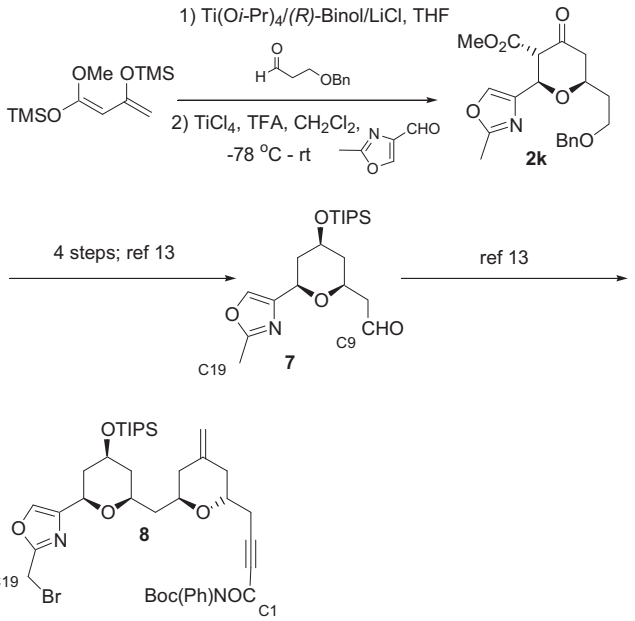
[a] Reaction scheme shows relative stereochemistry only.
[b] Determined either by chiral shift ^1H NMR with $Eu(hfc)_3$ or chiral HPLC. See Experimental section for details.
[c] (*R*)-Binol used; absolute stereochemistry of C6 centre is (*R*).
[d] (*S*)-Binol used; absolute stereochemistry of C6 centre is (*S*).
[e] (*S*)-Binol used; absolute stereochemistry of C6 centre is (*R*).
[f] (*R*)-Binol used; absolute stereochemistry of C6 centre is (*S*).
[g] %ee of both **2** and **3** determined.
[h] %ee of **2** determined.
[i] %ee of **3** determined.

Entries j and k in Table 2 are particularly interesting as they are key compounds on route to our syntheses of (±)-centrolobine **6** and the C1–C19 bis-pyran unit **8** of (+)-phorboxazole B, respectively. Our earlier synthesis of centrolobine **6** was racemic, but did provide the natural product in only four steps and in a 50% overall yield.[11] With the development of an asymmetric Maitland–Japp reaction we now have a formal total synthesis of (−)-centrolobine **6** (Scheme 4).



Scheme 4. Formal synthesis of (−)-centrolobine.

Our first generation synthesis of the C1–C19 fragment of phorboxazole B **8** was asymmetric.[13] However, the C9–C19 THP **7** was synthesized via the diketene version of the Maitland–Japp reaction. The diketene Maitland–Japp reaction generated the C9–C19 THP **7** with an enantiomeric excess of only 73%, which required the development of a resolving second Maitland–Japp reaction to install the second THP unit. This strategy did provide the bis-pyran unit **8** enantiomerically pure, but in a reduced yield due to loss of material in the form of an unwanted diastereomer formed by the reaction of enantiomerically pure δ-hydroxy-β-ketoester with the minor enantiomer of **7**. The asymmetric Chan's diene Maitland–Japp reaction which generated **2k** in a higher 84% ee, will obviate this loss of material, thus a more efficient second generation synthesis of the C1–C19 unit of phorboxazole B **8** can now be realized (Scheme 5).



Scheme 5. Formal synthesis of the C9–C19 unit of (+)-phorboxazole B.

3. Conclusions

We have developed a highly enantioselective Maitland–Japp reaction for the synthesis of functionalized tetrahydropyran-4-ones. The reaction has a wide scope and can accommodate aryl, alkyl, branched alkyl and heteroatom-containing aldehydes as either the first or second aldehyde reaction partner. The yields of the tetrahydropyran-4-ones are moderate to good and the enantiomeric excesses are excellent, ranging between 91 and 99% for most substrates investigated. The utility of this reaction has been demonstrated by the asymmetric synthesis of tetrahydropyran units present in the natural products (−)-centrolobine **6** and (+)-phorboxazole B, and mark an improvement over the group's previously described routes.

4. Experimental section

4.1. General

All reactions were carried out under N_2 unless otherwise specified. IR analyses were carried out on ThermoNicolet Avatar 370 FT-IR and ThermoNicolet IR100 spectrometer using NaCl plates or caesium fluoride solution cell. Nuclear magnetic resonance spectra were recorded on a Jeol ECX-400 MHz, a Jeol ECS-400 MHz and Bruker AV-500 MHz spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-*d*, δ_H 7.26 ppm; chloroform-*d*, δ_C 77.0 ppm,

benzene-*d*, δ_H 7.16 ppm; benzene-*d*, δ_C 128.02 ppm. Mass spectrometry was performed by the University of York mass spectrometry service using ESI, EI or CI ionization techniques. Microanalysis was performed by the microanalytical unit at The University of Nottingham. Melting points were determined using a Stuart SMP3 apparatus and remain uncorrected. Optical rotations were recorded at ambient temperature using a JASCO DIP-370 digital polarimeter. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F_{254}, and developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma–Aldrich. Dichloromethane was distilled from calcium hydride; THF and diethyl ether were distilled from sodium/benzophenone ketyl; toluene was dried over sodium wire prior to use. All other solvents and reagents were used as received from commercial suppliers.

4.2. General procedure for the asymmetric addition of Chan's diene to aldehydes (5a and 5b)

Neat Ti(O*i*-Pr)$_4$ (28 mg, 0.1 mmol) was added to a solution of Binol (29 mg, 0.1 mmol) in THF (10 ml) and stirred for 20 min at rt under a N_2 atmosphere. After this time dry LiCl (8 mg, 0.2 mmol) was added and the reaction mixture was stirred for a further 30 min. After this time a solution of aldehyde (5 mmol) in THF (3 ml) was added and the reaction mixture was stirred at rt for 20 min. A solution of Chan's diene (2.6 g, 10 mmol) in THF (3 ml) was added slowly via a syringe pump at a rate of 30 ml/h. When the addition was complete the reaction mixture was stirred at rt for 12 h. The solvent was removed in vacuo and the residue dissolved in dry MeOH (10 ml), to which was added PPTS (255 mg, 1 mmol) and the mixture was stirred at −12 °C for 2 h. After this time the volatiles were removed in vacuo and the residue was dissolved in EtOAc and washed successively with aqueous solutions of saturated $NaHCO_3$ solution and brine. The organics were then dried with $MgSO_4$ and concentrated in vacuo to give a brownish oil. The residue was purified by flash column chromatography (1:10→1:1 EtOAc/petroleum ether mixtures) to give the δ-hydroxy-β-ketoester **5a** or **5b**.

*4.2.1. (R)-Methyl 5-hydroxy-3-oxo-5-phenylpentanoate (**5a**).* Spectroscopic data identical to that reported in the literature.[17,18] $[\alpha]_{D^{23}}$ 27.3 (*c* 2.9, $CHCl_3$), 97% ee, as determined by ^{1}H NMR (400 MHz, $CDCl_3$) shift reagent experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) (15 mol %).

*4.2.2. (R)-Methyl 5-hydroxy-3-oxooctanoate (**5b**).* Spectroscopic data identical to that reported in the literature.[17,18] $[\alpha]_{D^{23}}$ −16.5 (*c* 2.38, $CHCl_3$), 99% ee, as determined by ^{1}H NMR (400 MHz, $CDCl_3$) shift reagent experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) (17 mol %).

4.3. General procedure for the asymmetric Maitland–Japp reaction (2a–i,k/3a–i/k)

Neat Ti(O*i*-Pr)$_4$ (28 mg, 0.1 mmol) was added to a solution of Binol (29 mg, 0.1 mmol) in THF (10 ml) and stirred for 20 min at rt under a N_2 atmosphere. After this time dry LiCl (8 mg, 0.2 mmol) was added and the reaction mixture was stirred for a further 30 min. After this time a solution of aldehyde (5 mmol) in THF (3 ml) was added and the reaction mixture was stirred at rt for 20 min. A solution of Chan's diene (2.6 g, 10 mmol) in THF (3 ml) was added slowly via a syringe pump at a rate of 30 ml/h. When the addition was complete the reaction mixture was stirred at rt for 12 h. The solvent was removed in vacuo and the residue dissolved in dry MeOH (10 ml), to which was added PPTS (255 mg, 1 mmol) and the mixture was stirred at −12 °C for 2 h. After this time the volatiles were removed in vacuo and the residue was dissolved in EtOAc and washed successively with aqueous solutions of saturated $NaHCO_3$ solution and brine. The organics were then dried with $MgSO_4$ and concentrated in vacuo to give a brownish oil.

Neat $TiCl_4$ (60 mg, 0.32 mmol) was added to a stirred solution of aldol product (0.3 mmol) and second aldehyde (0.32 mmol) in dry CH_2Cl_2 (1.5 ml) and the reaction mixture was stirred for 1.5 h. After this time, the reaction mixture was diluted with diethyl ether and the organics washed successively with saturated aqueous sodium bicarbonate solution, brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 10:1 to 1:1) to yield both trans and cis diastereomers.

*4.3.1. (2S,3R,6R)-2,6-Diphenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2a**).* White solid; mp: 133–135 °C; $[\alpha]_{D^{23}}$ +17.3 (*c* 0.4, $CHCl_3$); ν_{max} (film) 2953, 2921, 1747, 1717, 1496, 1455, 1274, 1067, 757, 699 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.50–7.30 (10H, m), 5.13 (1H, d, *J*=10.6 Hz), 4.95 (1H, dd, *J*=11.3, 3.0 Hz), 3.77 (1H, dd, *J*=10.6, 0.8 Hz), 3.70 (3H, s), 2.86 (1H, dd, *J*=14.3, 3.0 Hz), 2.79 (1H, ddd, *J*=14.3, 11.2, 0.8 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 201.1, 167.8, 139.9, 138.6, 128.8, 128.8, 128.6, 128.1, 126.8, 125.6, 81.0, 78.9, 64.6, 52.1, 48.9 ppm; *m/z* (CI^+) 310 (62%, M^+), 293 (100%, M^+−OH); HRMS: found (M^+) 310.1195. $C_{19}H_{18}O_4$ requires (M^+) 310.1205. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.22; H, 5.95%; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, *T*=20 °C, t_R, (major)=86.9 min.

*4.3.2. (2S,6R)-2,6-Diphenyl-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3a**).* White solid; mp: 118–120 °C; $[\alpha]_{D^{23}}$ +37.2 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2955, 2918, 2849, 1745, 1662, 1443, 1269, 1219, 1063, 698 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.38 (1H, s), 7.57–7.28 (10H, m), 5.80 (1H, d, *J*=1.0 Hz), 4.59 (1H, dd, *J*=10.8, 3.9 Hz), 3.67 (3H, s), 2.73 (1H, ddd, *J*=18.1, 10.8, 1.0 Hz), 2.60 (1H, dd, *J*=18.1, 3.9 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.2, 165.8, 141.0, 140.8, 128.8, 128.4, 128.0, 127.9, 126.9, 126.0, 98.7, 73.7, 68.3, 52.2, 35.6 ppm; *m/z* (CI^+) 310 (50%, M^+), 279 (10%, M^+−OMe), 233 (77%, M^+−Ph); HRMS: found (M^+) 310.1205. $C_{19}H_{18}O_4$ requires (M^+) 310.1205. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.32; H, 5.75%; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, *T*=20 °C, t_R, (major)=70.4 min.

*4.3.3. (2R,3R,6R)-2-(2-Methyl-ethyl)-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2b**).* White solid; mp 99–101 °C; $[\alpha]_{D^{25}}$ +64.9 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2966, 2934, 1746, 1715, 1454, 1361, 1132, 1073 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.43–7.32 (5H, m), 4.73 (1H, dd, *J*=11.7, 2.5 Hz), 4.00 (1H, dd, *J*=10.8, 2.9 Hz), 3.79 (3H, s), 3.53 (1H, dd, *J*=10.8, 1.0 Hz), 2.75 (1H, dd, *J*=14.2, 2.5 Hz), 2.52 (1H, ddd, *J*=14.2, 11.7, 1.0 Hz), 1.84 (1H, d septets, *J*=6.8, 2.9 Hz), 1.10 (3H, d, *J*=6.8 Hz), 1.05 (3H, d, *J*=6.8 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.4, 168.6, 140.8, 128.5, 127.9, 125.2, 82.3, 77.9, 60.5, 52.1, 48.8, 31.5, 19.7, 15.3 ppm; *m/z* (CI^+) 276 (5%, M^+), 233 (100%, M^+−$(CH_3)_2CH$); HRMS: found (M^+) 276.1360. $C_{16}H_{20}O_4$ requires (M^+) 276.1362; 97% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, *T*=20 °C, t_R (minor)=45.2 min, t_R (major)=49.4 min.

*4.3.4. (2S,3R,6R)-2-Furyl-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2c**).* White solid; mp 88–90 °C; $[\alpha]_{D^{23}}$ +20.2 (*c* 0.35, $CHCl_3$); ν_{max} (film) 2950, 2920, 2845, 1745, 1716, 1657, 1440, 1345, 1264, 1217 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.44 (1H, dd, *J*=1.8, 0.6 Hz), 7.43–7.30 (5H, m), 6.44 (1H, d, *J*=3.2 Hz), 6.37 (1H,

dd, J=3.2, 1.8 Hz), 5.20 (1H, d, J=11.1 Hz), 4.89 (1H, dd, J=10.8, 3.4 Hz), 4.03 (1H, dd, J=11.1, 0.9 Hz), 3.73 (3H, s), 2.83 (1H, dd, J=14.6, 3.4 Hz), 2.77 (1H, ddd, J=14.6, 10.8, 0.9 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 200.7, 183.2, 150.7, 143.3, 128.7, 128.6, 126.1, 125.9, 110.4, 109.1, 78.6, 73.8, 60.6, 52.4, 48.7 ppm; m/z (CI^+) 318 (62%, M^++NH_4), 301 (22%, M^++H), 283 (28%, M^+−OH), 222 (58%), 205 (52%, M^++H−furfural); HRMS: found (M^++NH_4) 318.1342. $C_{17}H_{16}O_5$ requires (M^++NH_4) 318.1341; 96% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R (minor)=68.8 min, t_R (major)=79.0 min.

*4.3.5. (2R,6R)-2-Furyl-4-hydroxy-6-phenyl-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3c**).* White solid; mp 81–83 °C; $[\alpha]_{D^{23}}$ +35.9 (c 1.2, $CHCl_3$); ν_{max} (film) 2958, 2930, 1729, 1466, 1275, 1124, 1073 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.16 (1H, s), 7.42 (1H, dd, J=1.8, 0.9 Hz), 7.37–7.28 (5H, m), 6.35 (1H, dd, J=3.2, 1.8 Hz), 6.26 (1H, ddd, J=3.2, 0.9, 0.6 Hz), 5.77 (1H, br s), 4.74 (1H, dd, J=10.8, 4.1 Hz), 3.71 (3H, s), 2.69 (1H, ddd, J=18.1, 10.8, 0.9 Hz), 2.58 (1H, dd, J=18.1, 4.1 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.0, 170.7, 153.3, 142.8, 140.6, 128.5, 127.9, 125.9, 110.0, 109.8, 97.1, 69.2, 67.0, 51.7, 35.5 ppm; m/z (EI^+) 300 (23%, M^+), 268 (100%), 250 (43); HRMS: found (M^+) 300.0994. $C_{17}H_{16}O_5$ requires (M^+) 300.0998; 98% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R (minor)=66.7 min, t_R (major)=81.0 min.

*4.3.6. (2S,6R)-2-(4-Methoxyphenyl)-4-hydroxy-6-phenyl-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3d**).* White solid; mp 112–114 °C; $[\alpha]_{D^{23}}$ +38.9 (c 1.3, $CHCl_3$); ν_{max} (solution, $CHCl_3$) 3012, 2931, 1660, 1624, 1510, 1444, 1271, 1250, 1221, 1174, 1062, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 12.32 (1H, s), 7.32–7.22 (7H, m), 6.89–6.85 (2H, m), 5.73 (1H, s), 4.56 (1H, dd, J=11.0, 4.0 Hz), 3.80 (3H, s), 3.64 (3H, s), 2.70 (1H, dd, J=18.0, 11.0 Hz), 2.57 (1H, dd, J=18.0, 4.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.9, 159.2, 140.9, 132.8, 129.7, 128.4, 127.8, 125.9, 113.5, 98.8, 72.7, 67.9, 55.2, 51.6, 35.4 ppm; m/z (ESI^+) 341 (M^++H), 363 (M^++Na); HRMS: found (M^++Na) 363.1189. $C_{20}H_{20}NaO_5$ requires (M^++Na) 363.1203; 93% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R, (minor)=68.9, t_R (major)=90.7 min.

*4.3.7. (2R,3R,6R)-2-(4-Nitro-phenyl)-6-phenyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2e**).* Oil; $[\alpha]_{D^{23}}$ +1.1 (c 1.11), $[\alpha]_{D^{23}}$ +1.1 (c 1.1, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 3019, 1746, 1720, 1526, 1438, 1350, 1213, 1129 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.24 (2H, br d, J=9.0 Hz), 7.68 (2H, br d, J=9.0 Hz), 7.42–7.34 (5H, m), 5.25 (1H, d, J=11.0 Hz), 4.97 (1H, dd, J=11.5, 2.5 Hz), 3.68 (3H, s), 3.67 (1H, d, J=11.0 Hz), 2.91 (1H, dd, J=14.5, 2.5 Hz), 2.81 (1H, dd, J=14.5, 11.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 167.5, 148.1, 145.6, 139.4, 128.9, 128.6, 127.8, 125.6, 123.9, 79.8, 79.2, 64.2, 52.4, 48.8 ppm; m/z (ESI^+) 378 (100%, M^++Na); HRMS: found (M^++Na) 378.0948. $C_{19}H_{17}NNaO_6$ requires (M^++Na) 378.0954; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R (major)=22.6 min.

*4.3.8. (2R,6R)-2-(4-Methoxyphenyl)-6-propyl-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3f**).* Oil; $[\alpha]_{D^{23}}$ +9.8 (c 2.5, $CHCl_3$); ν_{max} (film) 3417, 2932, 1661, 1623, 1510, 1443, 1247, 1218, 823 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.28 (1H, s), 7.24 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 5.58 (1H, d, J=1.0 Hz), 3.83 (3H, s), 3.64 (3H, s), 3.48 (1H, m), 2.32 (1H, ddd, J=18.1, 10.3, 1.0 Hz), 2.24 (1H, dd, J=18.1, 4.4 Hz), 1.52–1.13 (4H, m), 0.76 (3H, t, J=6.9 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.4, 171.1, 159.0, 133.2, 129.5, 113.2, 98.8, 72.1, 65.8, 55.1, 51.5, 37.6, 34.7, 18.2, 13.7 ppm; m/z (CI^+) 306 (84%, M^+), 275 (50%, M^+−OMe), 247 (80%, M^+−CO_2Me); HRMS: found (M^+) 306.1454. $C_{17}H_{22}O_5$ requires (M^+) 306.1467; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R, (major)=58.6 min.

*4.3.9. (2R,3S,6S)-2-Phenyl-6-(2-methyl-ethyl)-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2g**).* White solid; mp 59–61 °C; $[\alpha]_{D^{23}}$ +7.8 (c 1.0, $CHCl_3$); ν_{max} (film) 3031, 2964, 1746, 1717, 1250 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40–7.29 (5H, m), 4.90 (1H, d, J=10.4 Hz), 3.62 (1H, ddd, J=11.6, 6.7, 2.4 Hz), 3.61 (3H, s), 3.57 (1H, d, J=10.4 Hz), 2.57 (1H, dd, J=14.0, 11.6 Hz), 2.45 (1H, dd, J=14.0, 2.4 Hz), 1.91 (1H, octet, J=6.7 Hz), 0.99 (3H, d, J=6.7 Hz), 0.97 (3H, d, J=6.7 Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.6, 168.1, 139.2, 128.6, 128.6, 126.7, 81.9, 80.6, 52.1, 43.9, 33.1, 18.8, 17.8 ppm; m/z (CI^+) 276 (72%, M^+), 199 (100%, M^+−Ph), 167 (75%); HRMS: found (M^+) 276.1359, $C_{16}H_{20}O_4$ requires (M^+) 276.1362; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R (major)=42.1 min.

*4.3.10. (2R,6S)-2-Phenyl-6-(2-methyl-ethyl)-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3g**).* White solid; mp: 57–58 °C; $[\alpha]_{D^{23}}$ +22.4 (c 1.66, $CHCl_3$); ν_{max} (film) 2957, 1661, 1624, 1442, 1269, 1223 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.32 (1H, s), 7.38–7.30 (5H, m), 5.65 (1H, s), 3.65 (3H, s), 3.14 (1H, ddd, J=10.8, 6.8, 3.9 Hz), 2.38 (1H, dd, J=18.1, 10.8 Hz), 2.25 (1H, dd, J=18.1, 3.9 Hz), 1.63 (1H, oct, J=6.8 Hz), 0.83 (3H, d, J=6.8 Hz), 0.80 (3H, d, J=6.8 Hz) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.8, 171.0, 140.9, 128.4, 127.9, 127.6, 98.5, 72.5, 71.4, 51.5, 32.6, 32.2, 18.3, 17.7 ppm; m/z (CI^+) 276 (65%, M^+), 199 (100%, M^+−Ph), 167 (82%); HRMS: found (M^+) 276.1360. $C_{16}H_{20}O_4$ requires (M^+) 276.1362; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 99:1, flow rate=0.1 ml/min, T=20 °C, t_R (major)=43.7 min.

*4.3.11. (2S,6R)-2-Phenyl-6-((benzyloxy)methyl)-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3h**).* Oil; $[\alpha]_{D^{23}}$ +9.5 (c 1.0, $CHCl_3$); ν_{max} (solution, $CHCl_3$) 3016, 1718, 1496, 1446, 1439, 1348, 1282, 1217, 1106, 1056 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 12.23 (1H, s), 7.39–7.21 (10H, m), 5.60 (1H, s), 4.44 (1H, d, J=12.0 Hz), 4.37 (1H, d, J=12.0 Hz), 3.69–3.64 (1H, m), 3.55 (3H, s), 3.37 (2H, dd, J=4.4, 2.1 Hz), 2.53 (1H, dd, J=18.2, 1.0 Hz), 2.17 (1H, dd, J=18.2, 3.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 140.5, 137.9, 128.5, 128.3, 128.1, 127.9, 127.6, 98.5, 73.3, 72.8, 71.9, 65.9, 51.6, 30.9, 29.7 ppm; m/z (ESI^+) 355 (M+H)$^+$, 377 (M+Na)$^+$; HRMS: found (M+Na)$^+$ 377.1357. $C_{21}H_{22}NaO_5$ requires (M+Na)$^+$ 377.1359; 90% ee, as determined by ^{1}H NMR (400 MHz, $CDCl_3$) shift reagent experiments with tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato] europium(III) (17 mol %).

*4.3.12. (2S,3R,6R)-2-Phenyl-6-cyclohexyl-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2i**).* Oil; $[\alpha]_{D^{23}}$ +11.3 (c 0.9, $CHCl_3$); ν_{max} (film) 2927, 2854, 1748, 1716, 1453, 1338, 1136, 1066, 1030, 760, 699 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.30 (5H, m), 4.89 (1H, d, J=10.5 Hz), 3.63 (1H, ddd, J=11.4, 6.1, 2.6 Hz), 3.61 (3H, s), 3.57 (1H, dd, J=10.5, 0.6 Hz), 2.58 (1H, dd, J=14.0, 2.6 Hz), 2.46 (1H, ddd, J=14.0, 11.4, 0.6 Hz), 1.91 (1H, m), 1.80–1.55 (5H, m), 1.27 (5H, m) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 202.7, 168.1, 139.2, 128.7, 128.6, 126.8, 81.5, 80.7, 64.9, 52.1, 44.4, 43.0, 28.6, 28.2, 26.4, 26.0 ppm; m/z (ES^+) 380 (100%, M^++Na+CH_3CN), 339 (77%, M^++Na), 211 (46%); HRMS: found (M^++Na+CH_3CN) 380.1866. $C_{19}H_{24}O_4$ requires (M^++Na+CH_3CN) 380.1838. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found C, 72.12; H, 7.72%; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 90:10, flow rate=0.1 ml/min, T=20 °C, t_R (major)=22.6 min.

*4.3.13. (2S,6R)-2-Phenyl-6-cyclohexyl-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3i**).* Oil; $[\alpha]_{D^{23}}$ +31.2 (c 2.1, $CHCl_3$); ν_{max} (film) 2924, 2852, 1661, 1624, 1443, 1361, 1277, 1242,

1218, 1051 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 12.28 (1H, s), 7.35–7.28 (5H, m), 5.60 (1H, s), 3.63 (3H, s), 3.14 (1H, ddd, *J*=10.8, 7.3, 3.9 Hz), 2.36 (1H, dd, *J*=17.6, 10.8 Hz), 2.23 (1H, dd, *J*=17.6, 3.9 Hz), 1.86 (1H, m), 1.70–1.47 (4H, m), 1.36–1.01 (4H, m), 0.85 (1H, ddd, *J*=24.5, 12.7, 3.9 Hz), 0.66 (1H, ddd, *J*=24.5, 12.7, 3.9 Hz) ppm; ^{13}C NMR (67.8 MHz; $CDCl_3$) δ 171.9, 140.9, 128.5, 127.9, 127.6, 98.5, 72.5, 70.6, 51.5, 42.3, 32.3, 28.6, 26.3, 25.9, 25.6 ppm; *m*/*z* (CI^+) 334 (100%, M^++NH_4), 317 (55%, M^++H); HRMS: found (M^++NH_4) 334.2013. $C_{19}H_{24}O_4$ requires (M^++NH_4) 334.2013. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found C, 71.93; H, 7.72%; 99% ee as determined by HPLC analysis: CHIRACEL OD-H, hexane/isopropanol 90:10, flow rate=0.1 ml/min, *T*=20 °C, t_R (major)=29.1 min.

*4.3.14. (2S,3S,6R)-2-(2-Methyloxazol-4-yl)-6-(2-benzyloxyethyl)-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2k**).* Oil; mp 80–82 °C; $[\alpha]_{D^{25}}$ −0.5 (*c* 0.90, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 3018, 2954, 2867, 1746, 1717, 1584, 1437, 1358, 1341, 1322, 1217, 1106, 755 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 7.50 (1H, s), 7.34–7.26 (5H, m), 4.92 (1H, d, *J*=10.5 Hz), 4.50 (1H, d, *J*=12.0 Hz), 4.46 (1H, d, *J*=12.0 Hz), 4.04 (1H, dddd, *J*=11.5, 9.5, 4.5, 2.5 Hz), 3.90 (1H, d, *J*=10.5 Hz), 3.69 (3H, s), 3.62 (1H, m), 3.55 (1H, m), 2.57 (1H, dd, *J*=14.5, 2.5 Hz), 2.46 (1H, dd, *J*=14.5, 11.5 Hz), 2.44 (3H, s), 2.05 (1H, m), 1.87 (1H, m) ppm; ^{13}C NMR (125 MHz; $CDCl_3$) δ 201.3, 167.9, 162.2, 138.2, 138.0, 136.0, 128.4, 127.6, 127.6, 74.6, 73.0, 72.9, 65.8, 61.1, 52.2, 47.0, 36.2, 14.0 ppm; *m*/*z* (ESI^+) 374 (100%, M^++H); HRMS: found (M^++H) 374.1598. $C_{20}H_{24}NO_6$ requires (M^++H) 374.1604; 81% ee as determined by ^1H NMR experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) (C_6D_6, 400 MHz, 17 mol %).

*4.3.15. (2S,6R)-2-(2-Methyloxazol-4-yl)-6-(2-benzyloxyethyl)-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3k**).* Oil; $[\alpha]_{D^{25}}$ +1.6 (*c* 1.31, $CHCl_3$); ν_{max} (solution; $CHCl_3$) 3016, 1717, 1662 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 12.25 (1H, s), 7.34 (1H, s), 7.33–7.20 (4H, m), 7.18 (2H, br d, *J*=7.5 Hz), 5.50 (1H, s), 4.39 (1H, d, *J*=12.0 Hz), 4.37 (1H, d, *J*=12.0 Hz), 3.94 (1H, dddd, *J*=11.0, 6.5, 4.0, 4.0 Hz), 3.67 (3H, s), 3.54 (2H, br t, *J*=6.0 Hz), 2.37 (1H, dd, *J*=18.0, 11.0 Hz), 2.34 (3H, s), 2.27 (1H, dd, *J*=18.0, 4.0 Hz), 1.85–1.75 (2H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.7, 161.8, 140.7, 138.4, 136.8, 128.3, 127.5, 127.3, 97.8, 73.0, 66.3, 66.2, 64.3, 51.6, 35.3, 34.4, 13.9 ppm; MS (ESI): *m*/*z* 374 (M^++H); HRMS: found (M^++H) 374.1598. $C_{20}H_{24}NO_6$ requires (M^++H) 374.160; 81% ee as determined by ^1H NMR experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) (C_6D_6, 400 MHz, 25 mol %).

4.4. Procedure for the Maitland–Japp cyclization to give the (−)-centrolobine precursor (2j/3j)

To a solution of Ti(O*i*-Pr)$_4$ (11.8 mg, 0.04 mmol) in THF (10 ml) stirring at rt under a N_2 atmosphere was added (*R*)-Binol (11.5 mg, 0.04 mmol). The solution was stirred for 20 min then treated with dry LiCl (3.4 mg, 0.08 mmol) and stirred for a further 30 min. The solution was treated with 3-(4-tertbutyldimethylsilyloxyphenyl)-propanal (528 mg, 2.00 mmol) over a 10 min period followed by Chan's diene (1.04 g, 4.00 mmol) over a 10 min period. The reaction mixture was stirred for 16 h then concentrated in vacuo to give an orange oil. The crude material was taken up in MeOH (10 ml) and charged with PPTS (50 mg, 0.20 mmol). The orange slurry was stirred for 2 h then concentrated in vacuo to give an orange oil that was dissolved in EtOAc (100 ml) and washed with a saturated aqueous solution of $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in vacuo to give an orange oil. Purification by flash column chromatography using a 9:1 to 8:2 petroleum ether/EtOAc gradient afforded a yellow oil (624 mg, 82%).

Oil; $[\alpha]_{D^{25}}$ +6.6 (*c* 1.0, $CHCl_3$); ν_{max} (solution, $CHCl_3$) 3051, 2901. 2887, 1752, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (2H, d, *J*=7.0 Hz, Ph), 6.75 (2H, d, *J*=7.0 Hz), 4.07 (1H, m, H-5), 3.74 (3H, s, H-14), 3.47 (2H, s, H-2), 2.80 (1H, br s, O–H), 2.76–2.57 (4H, m, H-3+H-7), 1.84–1.75 (1H, m, H-6), 1.71–1.63 (1H, m, H-6), 0.97 (9H, s, H-13), 0.18 (6H, s, H-11) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 167.7, 153.8, 129.6, 129.3, 120.0, 62.3, 52.5, 34.5, 31.3, 30.3, 25.8, 18.3, −4.3 ppm; MS (ESI): *m*/*z* 381 (M^++H); HRMS: found 381.2091. $C_{20}H_{33}O_5Si$ requires 381.2097; 91% ee as determined by ^1H NMR experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) ($CDCl_3$, 400 MHz, 25 mol %).

To a slurry of Yb(OTf)$_3$ (162 mg, 0.262 mmol) in CH_2Cl_2 (0.5 ml) stirring at −78 °C under a N_2 atmosphere was added a solution of δ-hydroxy-β-ketoester (from above procedure) (100 mg, 0.262 mmol) in CH_2Cl_2 (1.0 ml) followed by a solution of anisaldehyde (43 mg, 0.315 mmol) in CH_2Cl_2 (1 ml). After 5 min the mixture was warmed to rt and stirred for 18 h. The mixture was then diluted with Et_2O (20 ml) and washed with a 5% aqueous solution of $NaHCO_3$ (2×20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by flash column chromatography using a 10:1 petroleum ether/EtOAc gradient afforded the tetrahydropyrans **2j** (53 mg, 41%) and **3j** (18 mg, 14%) as colourless oils.

*4.4.1. (2S,3R,6S)-2-(4-Methoxyphenyl)-6-(2-(4-tert-butylbimethylsilanyloxy)-phenyl-ethane)-4-oxo-tetrahydro-pyran-3-carboxylic acid methyl ester (**2j**).* Oil; $[\alpha]_{D^{23}}$ −22.6 (*c* 0.25, $CHCl_3$); ν_{max} (film) 2955, 2930, 1744, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, *J*=8.5 Hz), 7.00 (2H, d, *J*=8.5 Hz), 6.89 (2H, d, *J*=8.5 Hz), 6.74 (2H, d, *J*=8.5 Hz), 4.81 (1H, d, *J*=10.5 Hz), 3.81 (3H, s), 3.78 (1H, m), 3.60 (3H, s), 3.59 (1H, d, *J*=10.5 Hz), 2.68 (2H, m), 2.53 (1H, dd, *J*=14.5, 2.5 Hz), 2.43 (1H, dd, *J*=14.5, 11.5 Hz), 2.02 (1H, m), 1.83 (1H, m), 0.97 (9H, s), 0.18 (6H, s) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 202.1, 168.2, 159.9, 133.8, 131.2, 129.4 128.3, 120.1, 114.6, 80.5, 76.3, 64.7, 55.4, 52.3, 47.2, 37.9, 31.7, 30.5, 25.8, 18.3, −4.2 ppm; *m*/*z* (ESI) 499 (M^++H); HRMS: found (M^++H) 499.2505. $C_{28}H_{39}O_6Si$ requires 499.2516; 91% ee as determined by ^1H NMR experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) ($CDCl_3$, 400 MHz, 15 mol %).

*4.4.2. (2S,6S)-2-(4-Methoxyphenyl)-6-(2-(4-tert-butylbimethylsilanyloxy)-phenyl-ethane)-4-hydroxy-3,4-dihydro-2H-pyran-3-carboxylic acid methyl ester (**3j**).* Oil; $[\alpha]_{D^{23}}$ −29.5 (*c* 0.30, CH_2Cl_2); ν_{max} (film) 3354, 2924, 2853, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.25 (1H, s), 7.24 (2H, d, *J*=7.0 Hz), 6.88 (2H, d, *J*=7.0 Hz), 6.64 (2H, d, *J*=6.5 Hz), 6.57 (2H, d, *J*=6.5 Hz), 5.59 (1H, s), 3.84 (3H, s), 3.62 (3H, s), 3.45 (1H, m), 2.57 (1H, ddd, *J*=13.5, 8.5, 5.0 Hz), 2.32 (2H, m), 2.18 (1H, dd, *J*=18.0, 4.0 Hz), 1.75 (1H, dddd, *J*=17.0, 14.0, 8.5, 5.0 Hz), 1.59 (1H, m), 0.96 (9H, s), 0.15 (3H, s), 0.07 (3H, s) ppm; ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.3, 171.0, 159.5, 133.3, 133.1, 129.4, 129.2, 120.1, 114.6, 113.5, 99.1, 72.0, 64.7, 55.5, 52.3, 37.9, 34.8, 30.5, 25.7, 18.3, −4.2 ppm; *m*/*z* (ESI) 499 (M^++H); HRMS: found (M^++H) 499.2521. $C_{28}H_{39}O_6Si$ requires 499.2516; 91% ee as determined by ^1H NMR experiments with tris[3-(heptafluoropropylhydroxy-methylene)-D-camphorato]europium(III) ($CDCl_3$, 400 MHz, 20 mol %).

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