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Asymmetric conjugate additions to 1,1′-diactivated cyclic enones—a comparative study

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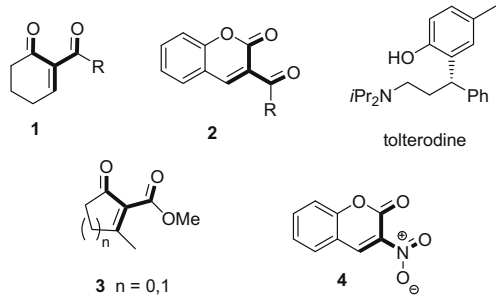
ABSTRACT

A study of copper-phosphoramidite-catalysed ZnR_2 and AlR_3 additions to 1,1′-dicarbonyl-activated cyclic Michael acceptors has revealed high enantioselectivities for AlR_3 (R = Me, Et) 1,4-addition to a range of 3-acylcoumarins (85–98% ee, *trans*:*cis* ~90:10) using commercial or readily available ligands. Large substituents at the 6-position, and to some extent at the 5-position, of the coumarin are less well tolerated, nor is truncation of the coumarin motif to a comparable 2-acylcyclohexenone (ee values up to 78%).

1. Introduction

Asymmetric conjugate addition (ACA) reactions of organozinc and organoalane reagents using unsaturated malonic ester as substrate have been described,[1a] however, the use of cyclic enone substrates bearing two 1,1′-related activating carbonyl groups has scarcely been reported.[1] Such substrate architectures are exemplified by the 2-acylcyclohex-2-enones **1** and coumarin derivatives **2** (Scheme 1).



Scheme 1. Exemplary 1,1′-dicarbonyl-activated cyclic substrates and the related structures of 3-nitrocoumarin and tolerodine.

In particular, the 3,4-dihydrocoumarin ACA products constitute potentially valuable fragments for the construction of enantiopure bioactive compounds. For example, recent routes to tolterodine (a muscarinic receptor drug marketed by Pfizer) are reported to use Rh-catalysed 1,4-addition of arylboronic acids to coumarin precursors.[2] The only enantioselective 1,4-addition of ZnR_2 to substrates closely related to **1**–**2** that we are aware is that of Hoveyda[3] (additions to **3**; 70–98% ee) using 10 mol % of a peptidic amine catalyst) and that of Feringa[4] (who studied nitro derivative **4**; 16–92% ee) using a his phosphoramidite ligand. No 1,4-alane additions to **1**–**2**, or any related substrates, appear to have been disclosed. To more fully define the catalyst system requirements for ACA reactions to 1,1′-dicarbonyl-activated substrates we have carried out a study focussing on enones **1** and in particular, coumarin **2** (with R = Ph). In general, there is a shortage of highly selective approaches to enantioenriched 3,4-dihydrocoumarin cores. Aside from the catalytic studies mentioned above, only two auxiliary-based approaches have been described.[5,6] As a result most medicinal chemistry studies on these molecules have used mixtures of stereoisomers; clearly this situation is undesirable and the attainment of general selective ACA catalysts for substituted coumarins is desirable.

2. Results and discussion

2.1. Synthesis of Michael acceptors

Samples of 2-benzoyl-cyclohex-2-enone **1a** were attained from cyclohex-2-enone via oxidation of the known alcohol **5**[7] (Scheme 2). Dess–Martin periodinane is the preferred oxidant giving a completely clean conversion to **1a**. The use of other oxidants led to an impure product and associated decomposition. The 3-acylcoumarins **2** are attractive starting materials as they are attained easily from mixtures of salicylaldehydes and 1,3-dicarbonyls as crystalline, easily purified, solids. Good literature procedures are available, but most of them rely on piperidine catalysis,[8] whose use is now associated with regulatory restrictions. In our experience, the use of pyrrolidine results in broadly equivalent yields while the use of either amine leads to the small collection **2a**–**j** encompassing a range of steric and electronic factors at all available coumarin substation positions (Scheme 2).

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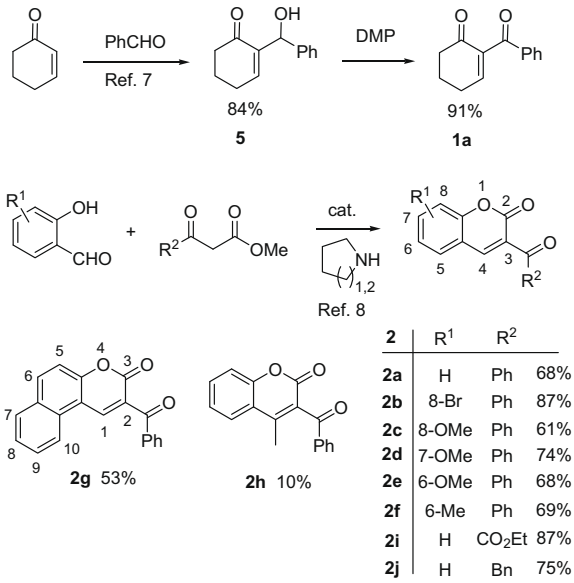


2	R^1	R^2	
2a	H	Ph	68%
2b	8-Br	Ph	87%
2c	8-OMe	Ph	61%
2d	7-OMe	Ph	74%
2e	6-OMe	Ph	68%
2f	6-Me	Ph	69%
2i	H	CO_2Et	87%
2j	H	Bn	75%

Scheme 2. Preparation of the Michael acceptors used in this study.

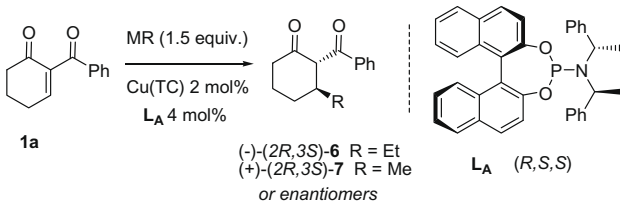
2.2. Studies using 2-benzoyl-cyclohex-2-enone 1a

As simple cyclohex-2-enone is known to give exceptionally high levels of enantioselectivity for the ACA reaction of $ZnEt_2$ using (*R,S,S*)-phosphoramidite $\mathbf{L_A}$[9] this seemed an appropriate point to begin our studies. However, screening of a range of solvents and copper(I) precursor salts (17 variations) revealed a system that optimised to only moderate stereoselectivities ($ee_{max.}$ 77%) for additions to **1a**. Some representative results are given in Table 1; the best being attained in toluene ($ZnMe_2$), THF ($ZnEt_2$) or Et_2O ($AlMe_3$) using Cu(TC) (TC = 2-thiophenecarboxylate). In all cases, complete (>99% by GC) conversion was attained and, in general, $AlMe_3$ gave the most selective ACA reactions.

The absolute stereochemistry of products **6**–**7** has been assigned on the basis of Feringa's synthesis of a 3-bromophenyl analogue of **6** [with a (2*R*,3*S*)-configuration and $[\alpha]_D = -26.4$ for a 93% ee sample] using *ent*-$\mathbf{L_A}$.[9] This 3-BrPh analogue was itself secured on the basis of an X-ray structure of its precursor ACA-aldol cascade product isolated in 32% yield from cyclohex-2-enone, $ZnEt_2$ and 3-BrPhCHO. A pure sample of **6** (Run 3) also showed negative rotations indicating that the (2*R*,3*S*) configuration corresponded to the second eluting stereoisomer on a Chiralpak OJ-H column in our studies. This is exactly the same facial selectivity [when using (*R,S,S*)-$\mathbf{L_A}$] as delineated explicitly by X-ray studies in coumarin analogies (see later). The reversal of the sign of the specific rotation between the ethyl **6** and methyl **7** ACA products is also identical to the behaviour in the analogous crystallographically defined dihydrocoumarin products (see next Section). Although in our route from **1a**, a lower stereoselectivity is attained for **6**, the isolated yields of the equivalent products are much higher. The most intriguing result from Table 1 is the very low enantioselectivity associated with the use of dichloromethane (Run 10). The use of this solvent resulted in a very significant rate acceleration of the background reaction for reasons that are not at present clear to us.

In light of the results of Table 1, we speculated that the poorer performance of the 2-benzoyl-cyclohex-2-enone **1a** might be due to the similar size of the phenyl and cyclohex-2-enone substituents in the substrate. We proposed to combat this in two ways. Firstly, by increasing the steric profile of the cyclohex-2-enone group through buttressing to a phenylene group (i.e., use of the coumarin **2**); and secondly, by diversifying the ligand structure of the phosphoramidite used to promote the asymmetric reaction.

Table 1
ACA studies of ZnR_2 (R = Et, Me) and $AlMe_3$ to 2-benzoyl-cyclohex-2-enone **1a**[a]

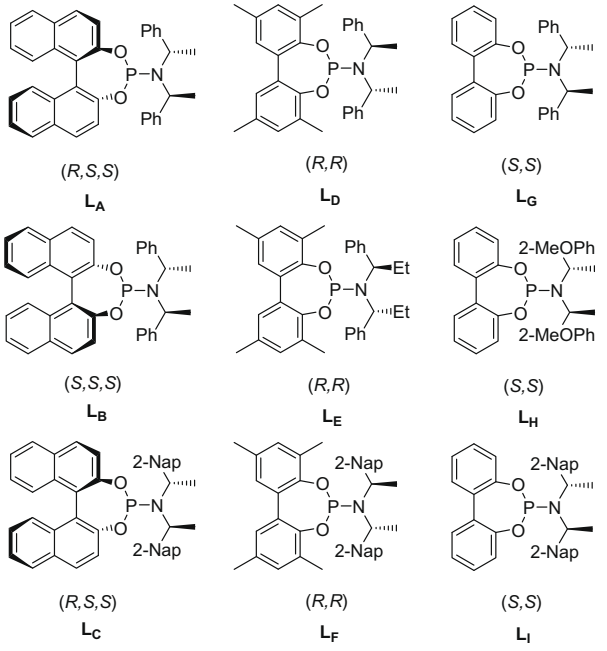


Run	MR	Solvent	Temp. (°C)	Time (h)	*trans*:*cis*	ee[b] (%)
1	$ZnEt_2$	DMF	−30	2	40:60	36 (2*S*,3*R*)
2	$ZnEt_2$	THF	−50	4	58:42	57 (2*S*,3*R*)
3	$ZnEt_2$	Et_2O	−30	2	78:22	18 (2*R*,3*S*)
4	$ZnEt_2$	Toluene	−30	2	64:36	24 (2*S*,3*R*)
5	$ZnMe_2$	THF	−30	3	—[c]	—
6	$ZnMe_2$	Et_2O	−30	2	86:14	62 (2*R*,3*S*)
7	$ZnMe_2$	Toluene	−30	2	82/18	73 (2*R*,3*S*)
8	$ZnMe_2$	CH_2Cl_2	−30	2	78/22	73 (2*R*,3*S*)
9	$AlMe_3$	Et_2O	−50	2	81:19	77 (2*R*,3*S*)
10	$AlMe_3$	CH_2Cl_2	−50	2	91:9	12 (2*R*,3*S*)
11	$AlMe_3$	Toluene	−50	2	54:46	62 (2*R*,3*S*)

[a] Ratio of MR/**1a**/Cu(TC)/LA = 0.75/0.5/0.01/0.02 mmol; 2 ml solvent.
[b] Diastereoselectivity **1a** determined by ^1H NMR on freshly quenched sample; ee by HPLC (Daicel Chiralpak OJ-H column).
[c] No conversion.

2.3. Studies using 3-acylcoumarins 2

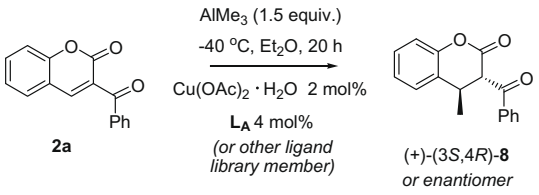
Compound **2a** was selected as a parent substrate for system optimisation. Since $AlMe_3$ had provided the highest level of stereoselectivity in the studies with **1a**, the use of organoalanes over organozinc reagents was also selected in the initial trials. However, in case of unexpected advantages for organozincs over organoalanes, we also tested $ZnEt_2$ on substrate **2a**, but no reaction occurred. Therefore, in the ACA study of coumarin derivatives we selected organoalanes as the nucleophile. In addition to commercial $\mathbf{L_A}$, 11 other phosphoramidites $\mathbf{L_B}$–$\mathbf{L_I}$ (Scheme 3) were selected as these represent modulations of the 'ligand space' around the ligated phosphorus atom.



Scheme 3. Phosphamidites $\mathbf{L_A}$–$\mathbf{L_I}$ used in comparison of ligand effects for $AlMe_3$ additions to **2a**.

Initial tests confirmed that Et_2O was the optimal solvent with respect to the enantioselectivity but revealed that Cu(TC) could be replaced with air-stable, low cost $Cu(OAc)_2$ monohydrate in line with the findings of Alexakis.[10a] Additionally, Alexakis demonstrated that sometimes in ACA processes, there is a radical side-reaction which can lower the enantioselectivity of the reaction, and that by adding styrene such by-reaction can be suspended.[10b] In the optimisation, we trialled the use of 10 equiv of styrene in the reaction, however, no obvious change was noted. The modularity of phosphoramidite ligands allows excellent opportunities for rational optimisation of 'ligand space' effects for these additives (Table 2). Comparison of commercial $\mathbf{L_A}$ with its diastereomer $\mathbf{L_B}$ confirmed that the (*R,S,S*)-configuration is the stereochemically matched case (Runs 1–2). The induced atropisomeric ligands $\mathbf{L_D}$–$\mathbf{L_F}$ confirmed that increasing the bulk of the 'diol portion' of the ligand was of small benefit (Run 1 vs Run 4), while increasing the size of the amine had at best a neutral effect (Run 1 vs Run 3 and Runs 4–6). These trends were confirmed by the use of the unsubstituted biphenyls $\mathbf{L_G}$ and $\mathbf{L_I}$ (Runs 7 and 9) while the inclusion of a potentially coordinating OMe had a catastrophic effect on the reaction's selectivity ($\mathbf{L_H}$, Run 8). In conclusion, commercial $\mathbf{L_A}$ and easily prepared[11] $\mathbf{L_D}$ were identified as optimal phosphoramidites. Conveniently this pair of ligands allows access to both enantiomeric series of **8**. The 'selective modification of ligand space' approach proved much the most efficient optimisation procedure in this study. Speculative screening of other ligand classes (e.g., Duphos, Ferrophites,[12] Josiphos and chiral carbenes) revealed only very poorly performing systems.

Table 2
Ligand effects in 1,4-addition of $AlMe_3$ to coumarin **2a**[a]



Run	L	Yield (%)	*trans*:*cis*	ee[b] (%)
1	L_A	64	88:12	86 (3*S*,4*R*)
2	L_B	49	91:9	23 (3*S*,4*R*)
3	L_C	56	88:12	71 (3*S*,4*R*)
4	L_D	89	91:9	88 (3*R*,4*S*)
5	L_E	89	86:14	88 (3*R*,4*S*)
6	L_F	64	85:15	77 (3*R*,4*S*)
7	L_G	62	86:14	66 (3*S*,4*R*)
8	L_H	80	85:15	33 (3*S*,4*R*)
9	L_I	30	90:10	12 (3*S*,4*R*)

[a] Ratio of $AlMe_3$/**2a**/$Cu(OAc)_2{\cdot}H_2O$/ligand = 1.5/1/0.02/0.04 mmol; 2 ml solvent.
[b] Diastereoselectivity determined by ^1H NMR on purified sample after flash chromatography; ee by HPLC (Daicel Chiralpak OD-H column); absolute configuration based on X-ray determination of a derivative from a run using (*R,R*)-$\mathbf{L_D}$ (see later).

The generality of the alane ACA reaction was now tested against the 3-acyl coumarin family **2** of Scheme 2 (Table 3).

Initially, the absolute stereochemical selectivity induced by ligand (*R,R*)-$\mathbf{L_D}$ was confirmed by a crystallographic study on the 8-bromo methyl addition product **10** attained from this ligand (Fig. 1a). Flack analysis confirmed the ACA reaction results in a 4*S* stereocentre in the derived (−)-methyl product and that a *trans* relationship was present between the 3,4-related substituents. An advantage of the crystallinity of **10** (and many of the other coumarin products) is that it enables essentially enantiomerically and diastereomerically pure materials to be attained easily. We assume that additions to other members of the substrate family **2** proceed with equivalent facial selectivity using (*R,R*)-$\mathbf{L_D}$. The *trans* diaxially related 3,4-CH groups in **10** provide a $^3J_{3,4}$ coupling of only 5.6 Hz in its ^1H NMR spectrum. Support for the retention of solid state conformations of these dihydrocoumarins in solution comes from the crystal structure of closely related **13**. Here it is the ethyl and benzoyl groups that are placed axially (Fig. 1b, the absolute and relative stereochemistries are equivalent to **10**). In **13** the equivalent $^3J_{3,4}$ coupling is only 2.2 Hz indicating that an equatorially placed CHCH pair is retained in solution. Compound **18** (not shown) is present in the same conformer as **10** in the solid state and similarly shows a $^3J_{3,4}$ coupling of 5.6 Hz in its solution ^1H NMR spectrum.

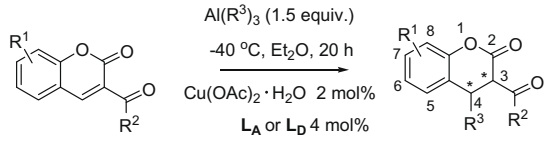
The specific rotations of the methyl (−) and ethyl (+) series ACA products are reversed compared to one another but their HPLC elution order remains identical. Reversal of the enantiofacial selectivity between methyl and ethyl nucleophiles when using the same phosphoramidite ligand is not reported in the entirety of the ACA alane literature.[1] We believe that observed reversal of the sign of the optical specific rotation between the methyl and ethyl cases is associated with the conformation effects seen in Figure 1. A less extreme case of $[\alpha]_D$ reversal between methyl and ethyl adducts is known in acyclic ACA products.[13] A similar situation exists in products **6** and **7**, but here we could not attain supporting X-ray structures.

Allowing for the differences in ligand topicity ($\mathbf{L_D}$ provides the opposite enantiomeric series to $\mathbf{L_A}$), the facial selectivity observed in the 3-acylcoumarins **2** is identical to the 2-acylcyclohex-2-enone **1** supporting our idea that the phosphoramidite ligand $\mathbf{L_A}$ struggles to differentiate between the steric profiles presented by the cyclohexenyl and the aryl rings in Michael acceptor **1**. In general, the enantioselectivity attained in ACA reactions of the 3-acylcoumarins **2** using $\mathbf{L_D}$ is dominated by steric rather than electronic or coordination effects. Substitution at the 7- and 8-position is well tolerated (Runs 3–6). However, the catalyst copes more poorly with substitution at the 5- and 6-position, especially in the cases where a methyl nucleophile is used (Runs 7–13). Steric discrimination, rather than electronic effects, seems best to account for these outcomes as the closely electronically related 6- and 8-methoxy compounds (Runs 3 and 7) give radically different ee values. In accord with this picture, reducing the steric crowding at the 6-position to a methyl group leads to a recovery in the enantioselectivity (Runs 9–10). In the case of the methyl addition product **18** synthetically useful levels of enantioselectivity can be attained through simple recrystallisation. Values of 88% ee with 99:1 *trans*:*cis* ratio are attained after crystallisation from dichloromethane–pentane. In these demanding 6-substituted coumarins reducing the steric profile of the ligand from $\mathbf{L_D}$ to $\mathbf{L_A}$ can sometimes be helpful. Such an approach is successful in ethylation of the 5,6-phenylene derivative **2g** where use of $\mathbf{L_A}$ results in synthetically useful enantioselectivities (Run 11). However, in the case of the methyl addition, the use of both $\mathbf{L_A}$ and $\mathbf{L_D}$ led to catalysts of low activity. Similar improvement could be achieved with the use of $\mathbf{L_A}$ for $AlMe_3$ additions to the 3-ester derivative **2i** (Run 13 vs <10% ee with $\mathbf{L_D}$). Overall, optimal enantioselectivities are attained for the addition of $AlEt_3$ compared to both small and larger nucleophiles (Runs 3–5). It is worthy to note however that in the case of $Ali\mathrm{Bu}_3$ no competing β-elimination-derived reduction products are formed. The use of β,β-disubstituted **2h** with both $\mathbf{L_A}$ and $\mathbf{L_D}$ was not tolerated; presumably due to adverse steric congestion. Finally, the benzyl derivative **2j** underwent facile conjugate addition but analyses of the product enantioselectivities were highly complicated by the presence of an enol tautomer and studies in this area were not continued.

In addition, we tested the readily available vinylalane, prepared by hydroalumination,[14] on the coumarin substrate **2** (Scheme 4).

The products were obtained in good to excellent yields (Scheme 4), however, no enantioselectivity was observed. We then checked the background reaction, and the results showed that the

Table 3
Substituent effects in 1,4-addition of AlR_3 (R = Me, Et, *i*Bu) to coumarins **2**



Addition products...

	R^1	R^2	R^3
8	H	Ph	Me
9	H	Ph	Et
10	8-Br	Ph	Me
11	8-Br	Ph	Et
12	8-OMe	Ph	Me
13	8-OMe	Ph	Et
14	8-OMe	Ph	*i*Bu
15	7-OMe	Ph	Et

	R^1	R^2	R^3
16	6-OMe	Ph	Me
17	6-OMe	Ph	Et
18	6-Me	Ph	Me
19	6-Me	Ph	Et
20	$-(CH)_4-$	Ph	Et
21	H	CO_2Et	Me
22	H	CO_2Et	Et

Run	Coumarin	R^1 aryl substituent	L	Alane	Yield (%) (product)	*trans*:*cis*	ee[a] (%)
1	**2a**	H	L_D	$AlMe_3$	89 (**8**)	91:9	88 (3*R*,4*S*)
2	**2a**	H	L_D	$AlEt_3$	86 (**9**)	93:7	96 (3*R*,4*S*)
3	**2b**	8-Br	L_D	$AlMe_3$	62 (**10**)	85:15	88 (3*R*,4*S*)
4	**2b**	8-Br	L_D	$AlEt_3$	72 (**11**)	82:8	96 (3*R*,4*S*)
3	**2c**	8-OMe	L_D	$AlMe_3$	64 (**12**)	90:10	87 (3*R*,4*S*)
4	**2c**	8-OMe	L_D	$AlEt_3$	78 (**13**)	95:5	96 (3*R*,4*S*)
5	**2c**	8-OMe	L_D	$Ali Bu_3$	71 (**14**)	75:25	75 (3*R*,4*S*)
6	**2d**	7-OMe	L_D	$AlEt_3$	74 (**15**)	>99:1	98 (3*R*,4*S*)
7	**2e**	6-OMe	L_D	$AlMe_3$	40 (**16**)	88:12	37 (3*R*,4*S*)
8	**2e**	6-OMe	L_D	$AlEt_3$	55 (**17**)	90:10	48 (3*R*,4*S*)
9	**2f**	6-Me	L_D	$AlMe_3$	78 (**18**)	90:10	67 (3*R*,4*S*)
10	**2f**	6-Me	L_D	$AlEt_3$	94 (**19**)	97:3	85 (3*R*,4*S*)
11	**2g**	5,6-Phenylene	L_A	$AlEt_3$	79 (**20**)	97:3	90 (1*R*,2*S*)[b]
12	**2h**	H	L_D	$AlEt_3$	—	—	—
13	**2i**	H	L_A	$AlMe_3$	67 (**21**)	89:11	53 (3*S*,4*R*)
14	**2i**	H	L_D	$AlEt_3$	68 (**22**)	93:7	90 (3*R*,4*S*)

[a] Diastereoselectivity determined by ^1H NMR on purified sample after flash chromatography; ee by HPLC (Daicel Chiralpak OD-H column).
[b] The nomenclature of the 2-benzoyl-1-ethyl-1,2-dihydro-benzo[*f*]chromen-3-one product is unique; the 2 and 1 positions correspond to the equivalent 3 and 4 positions in the other coumarin products.

vinylalane could be added to the substrate in the absence of copper-catalyst, supporting the earlier findings. Because of the reactivity these sp^2 carbon nucleophiles towards these combinations were not further investigated.

This is of considerable interest in small heterocyclic species, potentially derived from coumarins, as potential medicinal chemical leads. For example, 3-hydroxypyrazoles demonstrate a wide range of biological activity including antihyperglycaemic, angiotensin II antagonist and phytotoxicity.[15] Recently, closely related edaravone (Scheme 4) has recently been introduced as a therapeutic agent for post-stroke trauma.[16] Simple reflux of 3-substituted 4,5-dihydrocoumarin **12** with ethanolic H_2NNHMe

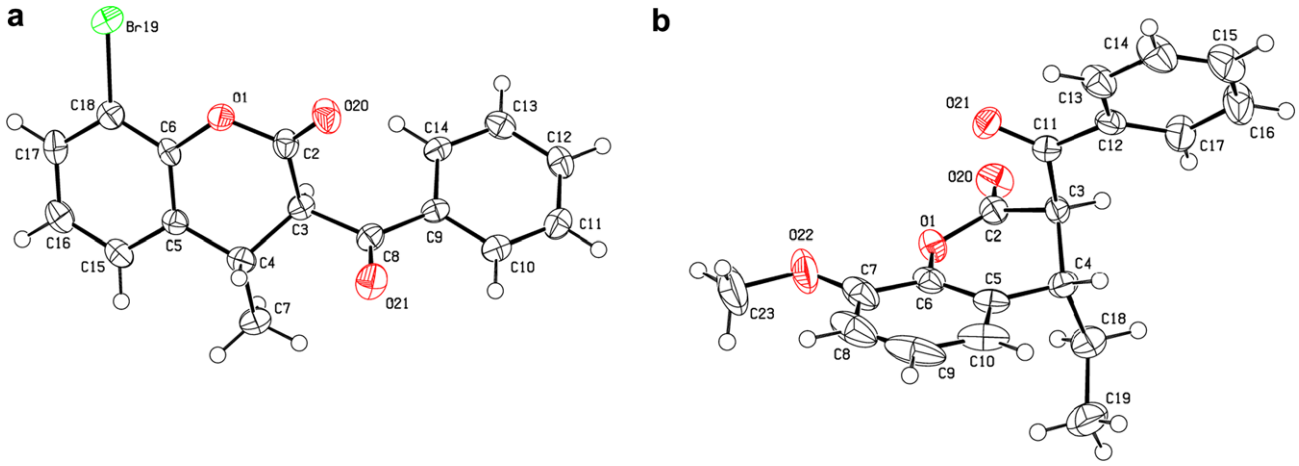
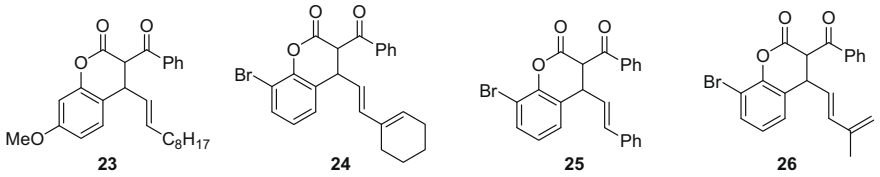
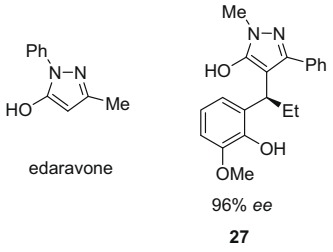


Figure 1. Conformational biasing in the solid-state structures of (a) (−)-(3*R*,4*S*)-**10** (methyl adduct) and (b), (+)-(3*R*,4*S*)-**13** (ethyl adduct).



Scheme 4. Vinylalane addition to coumarin 2.



Scheme 5. 3-Hydroxyprazoles.

resulted in the formation of 3-hydroxypyrazoles in high enantiopurity (Scheme 5).

3. Conclusion

The use of the readily available phosphoramidites $\mathbf{L_A}$ (commercial) and $\mathbf{L_D}$ (one-pot preparation) allows highly selective ACA reactions of AlR_3 to 3-acylcoumarins affording products with up to 98% ee. Steric encumbrance at the 5- or 6-position can lead to a reduction in selectivity but in many cases the products can be enriched to enantiopurity through simple recrystallisation. Overall, a generalised procedure providing these useful chiral building blocks has been realised. Attempted extension of the process to ACA reactions of 2-acylcyclohex-2-enone is not possible due to the reduced steric profile of such substrates present to the present ligand set.

4. Experimental

The general instrumentation used has been described previously.[12] All reactions involving air sensitive materials were carried out under argon using standard Schlenk techniques. THF and diethyl ether were distilled under argon from Na-benzophenone. Light petroleum refers to the fraction bp 40–60 °C. Solutions of AlR_3 and ZnR_2 were commercial products (Aldrich). Infrared spectra were recorded using Perkin–Elmer 983 G infrared and Perkin–Elmer 882 infrared spectrophotometers. ^1H and ^{13}C NMR spectra were recorded on either Jeol (JNM-GX270) or Bruker (AM400, AV400 or DRX500) spectrometers using $CHCl_3$ (7.27 ppm) or tetramethylsilane (0.00 ppm) as standard; *J* values are given in hertz; the term 'app.' indicates signals with significant 2nd order NMR distortions, typically associated with the phenyl groups. All spectra were recorded at ambient temperature. Mass spectra were obtained on Finnigan-MAT 1020 or Autospec VG (electron impact ionisation, EI), Finnigan-QMS (electrospray ionisation, ESI), VG-ZAB, or Autospec VG (fast atom bombardment, FAB). Elemental Analyses were performed using a Fisons Instruments EA 1108 CHN elemental analyser. Optical rotations were measured on a APD440 polarimeter in units of $10^{-1}{}^{\circ}cm^2\,g^{-1}$ (*c* in g/100 cm^3). HPLC analyses were carried out on an Agilent Technologies system.

4.1. General procedure A—preparation of 3-acylcoumarins 2

To a mixture of α-hydroxyl benzylaldehyde (1 equiv typically 10 mmol) and ethyl benzoylacetate or an equivalent 1,3-dicarbonyl species (1 equiv, 10 mmol), was added a few drops of piperidine or pyrrolidine. The neat mixture was kept stirring at room temperature, until a solid was formed. The solid was then dissolved in CH_2Cl_2 and neutralised with HCl (1 M). After extracting with CH_2Cl_2, the organic phase was dried over $MgSO_4$ and concentrated. The crude product was then recrystallised from CH_2Cl_2–pentane to give a pure product.

4.2. General procedure B—ACA reactions with $AlMe_3$ or $AlEt_3$

In a dry argon-flashed Schlenk tube, $Cu(OAc)_2{\cdot}H_2O$ (2 mol %, 0.01 mmol) and ligand (4 mol %, 0.02 mmol; ligand (*R,R*)-$\mathbf{L_D}$ is preferred unless stated otherwise) were dissolved in Et_2O (2 ml). After stirring at room temperature for 30 min, the mixture was cooled to −40 °C; $AlMe_3$ (or $AlEt_3$) (1.5 equiv, 0.75 mmol) was then added dropwise, after 5 min, starting material (1 equiv, 0.5 mmol) was added, and the mixture was stirred at −40 °C for 20 h. The reaction was then quenched with HCl (1 M) and the reaction mixture was extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (light petroleum/Et_2O) over silica gel to give pure product. The pure product was then recrystallised from CH_2Cl_2/pentane to effect stereoenrichment if desired. Reactions with ZnR_2 (R = Me, Et) were conducted in an equivalent manner.

4.3. General procedure—preparation of $i\mathbf{Bu_2Al(CH{=}CH_2R)}$

In a dry argon-flashed Schlenk tube, terminal alkynes (1 equiv, 0.75 mmol) were dissolved in hexane (1.5 ml). The mixture was cooled with a water bath, and DIBAL-H (0.14 ml, 0.75 mmol) was added dropwise. The mixture was then heated to 60 °C for 6 h, and used immediately.

4.4. General procedure C—1,4-addition with $i\mathbf{Bu_2Al(CH{=}CH_2R)}$

In a dry argon-flashed Schlenk tube, $Cu(OAc)_2{\cdot}H_2O$ (2 mol %, 0.01 mmol) and ligand (4 mol %, 0.02 mmol) were dissolved in Et_2O (2 ml). After stirring at room temperature for 30 min, the mixture was cooled to −40 °C, freshly prepared $^iBu_2Al(CH{=}CH_2R)$ (1.5 equiv, 0.75 mmol) was added dropwise. After 5 min, starting material (1 equiv, 0.5 mmol) was added, and the mixture was stirred at −40 °C for 20 h. The reaction was then quenched with HCl (1 M) and the reaction mixture was extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, the crude product was then purified by flash column chromatography (light petroleum/Et_2O) over silica gel to give pure product.

4.5. Preparation of the ACA Michael acceptors

The substrates for this study were prepared by the procedures outlined in Scheme 2 and in general procedure A (for coumarins **2**). Substrate **1a** was prepared from cyclohex-2-enone via **5**–**6**. Spectroscopic data for these compounds are given below.

4.5.1. 2-Benzoylcyclohex-2-enone 1a

Compound **5** (1.67 g, 8.3 mmol) was dissolved in CH_2Cl_2 (30 ml), Dess–Martin Periodinane (4.2 g, 9.9 mmol) was added, and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (light petroleum/Et_2O: 4/6) over silica gel to give pure product **1a** (1.5 g, 91%) as a low melting point solid (mp ~44 °C). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.81 (app. d, J = 8.8 Hz, 2H, Ph-*o*), 7.57 (app. t, J = 7.8 Hz, 1H, Ph-*p*), 7.46 (app. t, J = 7.8 Hz, 2H, Ph-*m*), 7.29 (t, J = 4.1 Hz, 1H, =CH), 2.64–2.59 (m, 4H, 2 × ring-CH_2), 2.22–2.19 (m, 2H, ring-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 196.5 (C=O), 194.9 (C=O), 152.1 (=CH), 141.1, 136.7, 133.5, 129.5, 128.5, 38.4, 25.9, 22.5. IR ($CHCl_3$ solution) ν = 3011, 2956, 2872, 1684 (C=O), 1667 (C=O), 1598, 1449, 1424, 1359, 1273, 1164, 939, 913, 835 cm^{-1}. HRMS: [M−H$^+$] $C_{13}H_{11}O_2$, theoretical mass 199.0762, found 199.0765. Compound **1a** has appeared briefly in the literature but no spectroscopic data were presented.[17]

4.5.2. 3-Benzoyl-2*H*-chromen-2-one 2a

Salicylaldehyde (1.05 ml, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2a** was obtained as colourless microcrystals (1.70 g, 68% yield). Mp: 130–132 °C (CH_2Cl_2/light petroleum) [Lit. 134–136 °C (EtOH)[18]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.11 (s, 1H, H-4), 7.92 (app. dd, J = 8.4 Hz and 1.3 Hz, 2H, Ph-*o*), 7.68–7.62 (m, 3H, Ph-*p* and H-5,7), 7.52 (app. t, J = 7.7 Hz, 2H, Ph-*m*), 7.45 (d, J = 8.4 Hz + unresolved ^4J coupling, 1H, H-8), 7.39 (dd, J = 6.6 and 7.7 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 191.7 (C=O), 158.4 (C=O), 154.8, 145.4, 136.2, 133.8, 133.7, 129.6, 129.2, 128.6, 127.0, 124.9, 118.2, 116.9. IR ($CHCl_3$ solution) ν = 3011, 1747 (C=O), 1718 (C=O), 1665, 1610, 1567, 1455, 1367, 1318, 1165, 1145, 1121, 942, 889 cm^{-1}. HRMS: [M]$^+$ $C_{16}H_{10}O_3$, theoretical mass 250.0630, found 250.0631. These data were consistent with the published values.[18]

4.5.3. 3-Benzoyl-8-bromo-2*H*-chromen-2-one 2b

3-Bromo-2-hydroxybenzaldehyde (1.00 g, 5 mmol) and ethyl benzoylacetate (0.86 ml, 5 mmol) were treated according to the general procedure A; the pure product **2b** was obtained as yellow microcrystals (1.40 g, 87% yield). Mp: 173–174 °C (CH_2Cl_2–light petroleum). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.07 (s, 1H, H-4), 7.93–7.89 (m, 3H, Ph-*o* and H-7), 7.66 (tt, J = 7.4 and 1.4 Hz, 1H, Ph-*p*), 7.59 (dd, J = 7.7 and 1.4 Hz, 1H, H-5), 7.52 (app. t, J = 7.7 Hz, 2H, Ph-*m*), 7.27 (t, J = 7.7 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 191.1 (C=O), 157.4 (C=O), 151.5, 144.9, 136.9, 135.9, 134.1, 129.7, 128.7, 128.4, 127.8, 125.7, 119.5, 110.5. IR ($CHCl_3$ solution) ν = 3011, 1736 (C=O), 1667 (C=O), 1613, 1557, 1445, 1364, 1318, 1290, 1244, 1161, 958, 924, 839 cm^{-1}. HRMS: [M+Na$^+$] $C_{16}H_9BrNaO_3$, theoretical mass 350.9609, found 350.9627.

4.5.4. 3-Benzoyl-8-methoxy-2*H*-chromen-2-one 2c

2-Hydroxy-3-methoxybenzaldehyde (1.52 g, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2c** was obtained as yellow microcrystals (1.71 g, 61% yield). Mp: 140–142 °C (CH_2Cl_2–light petroleum) [Lit. 145–146 °C (EtOAc/petroleum)[19]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.09 (s, 1H, H-4), 7.91 (app. d, J = 7.8 Hz, 2H, Ph-*o*), 7.64 (app. t, J = 7.4 Hz, 1H, Ph-*p*), 7.51 (app. t, J = 7.5 Hz, 2H, Ph-*m*), 7.31 (app. t, J = 7.8 Hz, 1H, H5, 6, or 7), 7.21 (app. t, J = 7.8 Hz, 2H, H5, 6, or 7), 4.03 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 191.7 (C=O), 157.9 (C=O), 147.2, 145.6, 144.5, 136.2, 133.8, 129.6, 128.5, 127.4, 124.8, 120.4, 118.8, 115.3, 56.4. IR ($CHCl_3$ solution) ν = 3011, 1735sh, 1731 (2 × C=O), 1666, 1611, 1577, 1476, 1439, 1366, 1318, 1275, 1240, 1178, 1105, 925, 863 cm^{-1}. HRMS: [M+Na$^+$] $C_{17}H_{12}NaO_3$, found 303.0613, theoretical mass 303.0628. This compound has appeared in the literature but no spectroscopic data have been reported.[19]

4.5.5. 3-Benzoyl-7-methoxy-2*H*-chromen-2-one 2d

2-Hydroxy-4-methoxybenzaldehyde (1.52 g, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2d** was obtained as yellow microcrystals (2.08 g, 74% yield). Mp: 147–148 °C (CH_2Cl_2–light petroleum) [Lit. 152–153 °C (EtOH)[20]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.12 (s, 1H, H-4), 7.89 (app. dd, J = 8.3 and 1.2 Hz, 2H, Ph-*o*), 7.63 (app. t, J = 7.4 Hz, 1H, Ph-*p*), 7.53–7.48 (m, 3H, Ph-*m* and H-5), 6.94 (dd, J = 8.6 and 2.4 Hz, 1H, H-6), 6.90 (d, J = 2.4 Hz, 1H, H-8), 3.95 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.0 (C=O), 164.7 (C=O), 158.8, 157.1, 146.4, 136.8, 133.4, 130.5, 129.5, 128.5, 122.9, 113.6, 111.8, 100.7, 56.0. IR ($CHCl_3$ solution) ν = 3011, 1724 (2 × C=O), 1660, 1609, 1559, 1507, 1372, 1293, 1147, 1026, 841 cm^{-1}. HRMS: [M−H$^+$] $C_{17}H_{11}O_4$, found 279.0652, theoretical mass 279.0663. The spectroscopic data were consistent with the published values.[20]

4.5.6. 3-Benzoyl-6-methoxy-2*H*-chromen-2-one 2e

2-Hydroxy-5-methoxybenzaldehyde (1.52 g, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2e** was obtained as yellow microcrystals (1.90 g, 68% yield). Mp: 158–160 °C (CH_2Cl_2–light petroleum) [Lit. 160–162 °C (CH_2Cl_2–hexane)[18]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.05 (s, 1H, H-4), 7.91 (app. dd, J = 8.4 and 1.3 Hz, 2H, Ph-*o*), 7.64 (tt, J = 7.7 and 1.4 Hz, 1H, Ph-*p*), 7.51 (app. t, J = 7.7 Hz, 2H, Ph-*m*), 7.36 (d, J = 9.1 Hz, 1H, H-8), 7.25 (dd, J = 9.1 and 2.9 Hz, 1H, H-7), 7.03 (d, J = 2.9 Hz, 1H, H-5), 3.89 (s, 3H, OMe). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 191.8 (C=O), 158.6 (C=O), 156.4, 149.3, 145.2, 136.3, 133.8, 129.6, 128.6, 127.3, 121.7, 118.5, 118.0, 110.6, 55.9. IR ($CHCl_3$ solution) ν = 3011, 1729 (2 × C=O), 1665, 1573, 1492, 1465, 1368, 1253, 1178, 1156, 1034, 929, 868, 844, 826 cm^{-1}. HRMS: [M+H$^+$] $C_{17}H_{13}O_4$, theoretical mass 281.0808, found 281.0810. The data were consistent with the published values.[20]

4.5.7. 3-Benzoyl-6-methyl-2*H*-chromen-2-one 2f

2-Hydroxy-5-methylbenzaldehyde (1.36 g, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2f** was obtained as colourless microcrystals (1.82 g, 69% yield). Mp: 172–174 °C (CH_2Cl_2–light petroleum) [Lit. 174 °C (CH_2Cl_2–hexane)[18]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.06 (s, 1H, H-4), 7.91 (app. dd, J = 8.4 and 1.3 Hz, 2H, Ph-*o*), 7.64 (tt, J = 7.4 and 1.4 Hz, 1H, Ph-*p*), 7.53–7.47 (m, 3H, Ph-*m* overlapped by H-7), 7.41 (br s, 1H, H-5), 7.33 (d, J = 8.4 Hz, 1H, H-8), 2.47 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 191.8 (C=O), 158.7 (C=O), 152.9, 145.6, 136.3, 134.8, 134.8, 133.8, 129.6, 128.9, 128.6, 126.8, 117.9, 116.7, 20.8. IR ($CHCl_3$ solution) ν = 3011, 1736 (C=O), 1731 (C=O), 1665, 1623, 1574, 1490, 1449, 1363, 1292, 1250, 1155, 929, 860, 820 cm^{-1}. HRMS: [M] $C_{17}H_{12}O_3$, theoretical mass 264.0786, found 264.0773. The data were consistent with the published values.[18]

4.5.8. 2-Benzoyl-3*H*-benzo[*f*]chromen-3-one 2g

2-Hydroxy-1-naphthaldehyde (1.72 g, 10 mmol) and ethyl benzoylacetate (1.73 ml, 10 mmol) were treated according to the general procedure A; the pure product **2g** was obtained as yellow microcrystals (1.59 g, 53% yield). Mp: 220–222 °C (CH_2Cl_2–light petroleum). [Lit. >200 °C (EtOH)[18]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.96 (s, 1H, H-4), 8.31 (d, J = 8.4 Hz, 1H, H-5 or 8), 8.15 (d, J = 9.0 Hz, 1H, H-5 or 8), 8.00–7.95 (m, 3H, Ph-*o* overlapped

by phenylene-H), 7.77 (tt, J = 7.0 Hz and 1.2 Hz, 1H, Ph-*p*), 7.70–7.64 (m, 2H, Ph-*m*), 7.59–7.52 (m, 3H, phenylene-H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.1 (C=O), 158.6 (C=O), 155.4, 141.9, 136.5, 135.4, 133.7, 130.3, 129.6, 129.4, 129.3, 129.0, 128.6, 126.6, 125.4, 121.5, 116.8, 112.7. IR ($CHCl_3$ solution) ν = 3011, 1734 (2 × C=O), 1662, 1600, 1565, 1518, 1464, 1449, 1394, 1344, 1262, 1179, 1097, 993, 946, 922, 820 cm^{-1}. HRMS: [M+Na$^+$] $C_{20}H_{12}NaO_3$, found 323.0677, theoretical mass 323.0679. The data were consistent with the published values.[18]

4.5.9. 3-Benzoyl-4-methyl-2*H*-chromen-2-one 2h

2′-Hydroxyacetophenone (1.2 ml, 10 mmol), ethyl benzoylacetate (1.73 ml, 10 mmol) and NaOH (200 mg, 5 ml) were mixed neat and heated to 90 °C for two days. The mixture was diluted by CH_2Cl_2 and washed with HCl (1 M), H_2O and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, the crude product was then purified by flash column chromatography (light petroleum/Et_2O) over silica gel to give pure product **2h** as pale tan solid (270 mg, 10% yield). Mp: 136–138 °C (CH_2Cl_2–light petroleum) [Lit. 138–139 °C (petroleum)[21]]. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.97 (app. d, J = 7.1 Hz, 2H, Ph-*o*), 7.75 (dd, J = 7.9 and 1.4 Hz, 1H, Ar), 7.65 (t, J = 7.6 Hz, 2H, Ar), 7.52 (app. t, J = 7.7 Hz, 2H, Ph-*m*), 7.45–7.39 (m, 2H, Ar), 2.39 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.2 (C=O), 158.7 (C=O), 153.2, 149.9, 136.1, 134.3, 132.6, 129.4, 128.9, 126.0, 125.2, 124.8, 119.6, 117.3, 15.9. IR ($CHCl_3$ solution) ν = 3413, 3011, 1714 (2 × C=O), 1243, 1081, 909 cm^{-1}. HRMS: [M+H$^+$] $C_{17}H_{13}O_3$, found 265.0857, theoretical mass 265.0859. Compound **2h** has appeared in the literature but only limited data were presented.[21]

4.5.10. Coumarin 2i

Coumarin **2i** is commercially available from Aldrich.

4.5.11. 3-(2-Phenylacetyl)-2*H*-chromen-2-one 2j

2-Hydroxybenzaldehyde (0.29 ml, 2.73 mmol) and ethyl 3-oxo-4-phenylbutanoate (500 mg, 2.73 mmol) were treated according to the general procedure A; the pure product **2j** was obtained as yellow microcrystals (540 mg, 75% yield). Mp: 154–155 °C (CH_2Cl_2–light petroleum). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 8.50 (s, 1H, H-4), 7.69–7.64 (m, 2H, Ph-*o*), 7.40–7.27 (m, 7H, Ar), 4.51 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 195.6 (C=O), 159.1 (C=O), 155.3, 148.2, 134.4, 133.9, 130.2, 129.9, 128.5, 127.0, 125.0, 124.4, 118.3, 116.7, 48.6. IR ($CHCl_3$ solution) ν = 2960, 1728 (2 × C=O), 1609, 1561, 1454, 1172, 977 cm^{-1}. HRMS: [M+H$^+$] $C_{17}H_{13}O_3$, found 265.0864, theoretical mass 265.0859. Compound **2j** has appeared in the literature but only limited spectroscopic data were presented.[22]

4.5.12. 2-(Hydroxy(phenyl)methyl)cyclohex-2-enone 5

Cyclohexenone (2.0 ml, 20 mmol), benzylaldehyde (1.0 ml, 10 mmol) and *N,N,N′,N′*-tetramethyl-1,3-propanediamine (1.7 ml, 10 mmol) were dissolved in THF/H_2O (8 ml, 1:1). The mixture was then stirred at room temperature for three days. A saturated solution of $NH_4Cl_{(aq)}$ was added, and the mixture was extracted with Et_2O. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and the crude product was then purified by flash column chromatography (light petroleum/Et_2O: 4:6) over silica gel to give pure product **5** (1.7 g, 84%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.36–7.26 (m, 5H, Ph), 6.79–6.77 (t, J = 4.0 Hz, 1H, =CH), 5.55 (d, J = 4.4 Hz, 1H, *CH*OH), 3.70 (br s, 1H, OH), 2.44–2.36 (m, 4H, 2 × ring CH_2), 2.00–1.96 (m, 2H, ring-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 200.3 (C=O), 147.4, 141.9, 141.1, 128.3, 127.4, 126.5, 72.1 (CH), 38.5, 25.8, 22.5. IR ($CHCl_3$ solution) ν = 3603 (OH), 3011, 2954, 2890, 1664 (C=O), 1493, 1454, 1407, 1383, 1239, 1171, 1019, 975, 916, 895 cm^{-1}. HRMS: [M−H$^+$] $C_{13}H_{13}O_2$, theoretical mass 201.0921, found 201.0910. The compound had the expected spectroscopic properties.[23]

4.6. Preparation of the ACA products

The 1,4-addition products were all attained by general procedure B or minor variations thereof.

4.6.1. (−)-(2*R*,3*S*)-2-Benzoyl-3-ethylcyclohexanone 6

To a dry argon-flashed Schlenk tube, CuTC (1.9 mg, 0.01 mmol) and (*R,S,S*)-**L$_A$** (11.0 mg, 0.02 mmol) were dissolved in Et_2O (2 ml). After stirring at room temperature for 30 min, the mixture was cooled to −30 °C, Et_2Zn (0.36 ml, 2.0 M solution in hexanes, 0.75 mmol) was then added dropwise, after 5 min, compound **1a** (100 mg, 0.5 mmol) was added, and the mixture was stirred at −30 °C for 2 h. The reaction was then quenched with HCl (1 M) and the reaction mixture was extracted with Et_2O, the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude product was then purified by flash column chromatography (light petroleum/Et_2O) over silica gel to give the pure product as a colourless solid **6** (179 mg, 78%). Mp: 68–70 °C. $[\alpha]_D^{24} = -1.6$ (*c* 2.4, $CHCl_3$, 18% ee, *trans*:*cis* 78:22). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.92–7.89 (m, 2H, Ph-*o*), 7.59–7.55 (m, 1H, Ph-*p*), 7.49–7.45 (m, 2H, Ph-*m*), 4.20 (d, J = 8.0 Hz, 1H, H-2), 2.62–2.56 (m, 1H, $CH_{2\alpha}CO$), 2.48–2.40 (m, 2H, $CH_{2\beta}CO$ and H-3), 2.16–2.05 (m, 2H, *CH*$_2$Me), 1.86–1.80 (m, 1H, ring-$CH_{2\alpha}$), 1.57–1.42 (m, 2H, ring-CH_2), 1.33–1.26 (m, 1H, ring-$CH_{2\beta}$), 0.94–0.90 (t, J = 7.2 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 208.4 (C=O), 197.8 (C=O), 137.2, 132.8, 128.3, 127.9, 63.6, 42.0, 41.5, 27.6, 27.0, 23.9, 10.8. IR ($CHCl_3$ solution) ν = 2936, 2876, 1710 (C=O), 1677 (C=O), 1597, 1448, 1342, 1126, 1001 cm^{-1}. HRMS: [M+Na$^+$] $C_{15}H_{18}O_2Na$, theoretical mass 253.1202, found 253.1199. HPLC: Daicel Chiralpak OJ-H, hexane/*i*PrOH = 97/3, flow rate: 1.0 ml min^{-1}. $T_{2S,3R}$ = 25.5 min, $T_{2R,3S}$ = 35.5 min.

The isolated compound had properties equivalent to those of known (2*R*,3*S*)-**6** prepared by a different route.[24]

4.6.2. (+)-(2*S*,3*R*)-2-Benzoyl-3-methylcyclohexanone 7

To a dry argon-flashed Schlenk tube, CuTC (1.9 mg, 0.01 mmol) and (*R,S,S*)-**L$_A$** (11 mg, 0.02 mmol) were dissolved in Et_2O (2 ml). After stirring at room temperature for 30 min, the mixture was cooled to −30 °C, after which Me_2Zn (0.75 ml, 1.0 M solution in toluene, 0.75 mmol) was added dropwise. After 5 min, compound **1a** (100 mg, 0.5 mmol) was added, and the mixture was stirred at −30 °C for 2 h. The reaction was then quenched with HCl (1 M) and the reaction mixture was extracted with Et_2O, the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude product was then purified by flash column chromatography (light petroleum/Et_2O) over silica gel to give pure product **7** as a pale yellow solid (174 mg, 81%). Mp: 60–62 °C. $[\alpha]_D^{24} = +10.5$ (*c* 1.2, $CHCl_3$, 62% ee, *trans*:*cis* 86:14). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.90 (app. d, J = 7.4 Hz, 2H, Ph-*o*), 7.59 (app. t, J = 7.4 Hz, 1H, Ph-*p*), 7.49 (app. t, J = 7.4 Hz, 2H, Ph-*m*), 4.10 (d, J = 9.9 Hz, 1H, H-2), 2.65–2.54 (m, 2H, $CH_{2\alpha}CO$ and H-3), 2.43 (dd, J = 13.9 and 5.6 Hz, 1H, $CH_{2\beta}CO$), 2.14–2.04 (m, 2H, ring-CH_2), 1.88–1.83 (m, 1H, ring-$CH_{2\alpha}$), 1.63–1.53 (m, 1H, ring-$CH_{2\beta}$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 208.5 (C=O), 198.1 (C=O), 137.7, 133.2, 128.7, 128.3, 65.6, 41.7, 36.5, 32.2, 24.8, 20.9. IR ($CHCl_3$ solution) ν = 3011, 2960, 1712 (C=O), 1681 (C=O), 1448, 1348, 1240, 1179, 1125, 1075 cm^{-1}. HRMS: [M+Na$^+$] $C_{14}H_{16}O_2Na$, theoretical mass 239.1042, found 239.1043. HPLC: Daicel Chiralpak OJ-H, hexane/*i*PrOH = 97/3, flow rate: 1.0 ml min^{-1}. $T_{2S,3R}$ = 26.0 min, $T_{2R,3S}$ = 36.0 min. The isolated compound had properties equivalent to those of known *ent*-**7** prepared by a different route.[24]

4.6.3. (−)-(3*R*,4*S*)-3-Benzoyl-4-methylchroman-2-one 8

Compound **2a** (125 mg, 0.5 mmol) was treated according to the general procedure B; the pure product **8** was obtained as colourless low melting solid (118 mg, 89% yield). $[\alpha]_D^{25} = -35.7$ (*c* 1.00, $CHCl_3$, 88% ee, *trans*:*cis* 91:9). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.95 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.4 Hz, 1H, Ph-*o*), 7.53 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.32 (dt, *J* = 1.6 and 7.6 Hz, 1H, H-6), 7.19–7.14 (m, 3H, H-5,7,8), 4.60 (d, *J* = 5.9 Hz, 1H, H-3), 3.63 (dq, *J* = 5.9 and 7.0 Hz, 1H, H-4), 1.46 (d, *J* = 7.0 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.9 (C=O), 165.7 (C=O), 150.6, 135.4, 134.1, 128.9, 128.8, 128.7, 127.0, 125.4, 125.0, 116.9, 55.1, 33.7, 20.1. IR ($CHCl_3$ solution) ν = 2975, 1760 (C=O), 1687 (C=O), 1489, 1448, 1240, 1174, 1085, 1001, 906 cm^{-1}. HRMS: [M−H$^+$] $C_{17}H_{13}O_3$, found 265.0862, theoretical mass 265.0870. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 18.6 min, $T_{3R,4S}$ = 28.4 min.

4.6.4. (+)-(3*R*,4*S*)-3-Benzoyl-4-ethylchroman-2-one 9

Compound **2a** (125 mg, 0.5 mmol) was treated according to the general procedure B; pure product **9** was obtained as colourless oil (120 mg, 86% yield). $[\alpha]_D^{25} = +83.8$ (*c* 1.00, $CHCl_3$, 96% ee, *trans*:*cis* 93:7). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.90 (app. d, *J* = 7.3 Hz, 2H, Ph-*o*), 7.64 (app. t, *J* = 7.3 Hz, 1H, Ph-*p*), 7.51 (app. t, *J* = 7.3 Hz, 2H, Ph-*m*), 7.33–7.28 (m, 1H, H-6), 7.14–7.03 (m, 3H, H-5,7,8), 4.83 (d, *J* = 2.1 Hz, 1H, H-3), 3.26 (dt, *J* = 2.1 and 6.8 Hz, 1H), 1.90–1.73 (m, 2H, *CH*$_2$Me), 1.07 (t, *J* = 7.3 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.6 (C=O), 165.7 (C=O), 150.9, 134.3, 134.0, 129.0, 128.8, 128.7, 128.5, 124.6, 123.1, 117.1, 54.6, 41.7, 28.7, 11.2. IR ($CHCl_3$ solution) ν = 2965, 1763 (C=O), 1683 (C=O), 1626, 1603, 1458, 1308, 1239, 835 cm^{-1}. HRMS: [M−H$^+$] $C_{18}H_{15}O_3$, found 279.1021, theoretical mass 279.1027. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 1.0 ml/min. $T_{3S,4R}$ = 14.8 min, $T_{3R,4S}$ = 20.9 min.

4.6.5. (−)-(3*R*,4*S*)-3-Benzoyl-8-bromo-4-methylchroman-2-one 10

Compound **2b** (164 mg, 0.5 mmol) was treated according to the general procedure B; pure product **10** was obtained as low melting yellow solid (107 mg, 62% yield). Mp: <50 °C. $[\alpha]_D^{25} = -9.3$ (*c* 1.00, $CHCl_3$, 88% ee, *trans*:*cis* 85:15). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.97 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.66 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.56–7.52 (m, 3H, Ph-*m* and H-7), 7.15 (d, *J* = 7.7 Hz, 1H, H-5), 7.04 (t, *J* = 7.7 Hz, 1H, H-6), 4.62 (d, *J* = 5.6 Hz, 1H, H-3), 3.68–3.61 (dq, *J* = 5.6 and 7.1 Hz, 1H, H-4), 1.46 (d, *J* = 7.1 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.2 (C=O), 164.4 (C=O), 147.5, 135.2, 134.2, 132.6, 129.0, 128.8, 127.5, 126.1, 125.7, 110.8, 54.8, 34.2, 20.0. IR ($CHCl_3$ solution) ν = 2969, 1772 (C=O), 1686 (C=O), 1624, 1598, 1446, 1239, 1139 cm^{-1}. HRMS: [M−H$^+$] $C_{17}H_{12}BrO_3$, found 342.9958, theoretical mass 342.9975. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/05, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 25.0 min, $T_{3R,4S}$ = 27.8 min.

4.6.6. (+)-(3*R*,4*S*)-3-Benzoyl-8-bromo-4-ethylchroman-2-one 11

Compound **2b** (164 mg, 0.5 mmol) was treated according to the general procedure B; pure product **11** was obtained as colourless oil (128 mg, 72% yield). $[\alpha]_D^{25} = +90.7$ (*c* 0.50, $CHCl_3$, 96% ee, *trans*:*cis* 82:8). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.92 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.66 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.55–7.53 (m, 3H, Ar), 7.01–6.98 (m, 2H, Ar), 4.84 (d, *J* = 2.1 Hz, 1H, H-3), 3.26 (dt, *J* = 2.1 and 6.3 Hz, 1H, H-4), 1.89–1.73 (m, 2H, *CH*$_2$Me), 1.07 (t, *J* = 7.4 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.9 (C=O), 164.4 (C=O), 147.8, 134.2, 132.6, 129.1, 128.8, 128.7, 128.1, 127.6, 125.3, 110.8, 54.3, 42.1, 28.4, 11.2. IR ($CHCl_3$ solution) ν = 2969, 1773 (C=O), 1685 (C=O), 1624, 1597, 1449, 1304, 1239, 1140 cm^{-1}. HRMS: [M−H$^+$] $C_{18}H_{14}BrO_3$, found 357.0119, theoretical mass 357.0132. Elemental Anal. Calcd for $C_{18}H_{15}BrO_3$: C, 60.18; H, 4.21. Found: C, 60.21; H, 4.24. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 0.5 ml min^{-1}. $T_{3S,4R}$ = 35.4 min, $T_{3R,4S}$ = 38.8 min.

4.6.7. (−)-(3*R*,4*R*)-3-Benzoyl-8-methoxy-4-methylchroman-2-one 12

Compound **2c** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **12** was obtained as waxy white solid (95 mg, 64% yield). Mp: <50 °C. $[\alpha]_D^{25} = -27.0$ (*c* 1.00, $CHCl_3$, 87% ee, *trans*:*cis* 90:10) ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.95 (app. d, *J* = 7.5 Hz, 2H, Ph-*o*), 7.63 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.50 (app. t, *J* = 7.5 Hz, 2H, Ph-*m*), 7.09 (t, *J* = 7.8 Hz, 1H, H-6), 6.91 (dd, *J* = 7.8 and 1.1 Hz, 1H, H-5 or 7), 6.77 (d, *J* = 7.8 Hz + unresolved ^4J coupling, 1H, H-5 or 7), 4.57 (d, *J* = 5.9 Hz, 1H, H-3), 3.92 (s, 3H, OMe), 3.62 (dq, *J* = 5.9 and 7.0 Hz, 1H, H-4), 1.43 (d, *J* = 7.0 Hz, 3H, CH*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.7 (C=O), 165.0 (C=O), 147.6, 139.8, 135.4, 133.9, 128.9, 128.8, 126.7, 124.9, 118.3, 111.5, 56.2, 54.9, 33.8, 19.9. IR ($CHCl_3$ solution) ν = 2968, 1765 (C=O), 1687 (C=O), 1486, 1277, 1181, 1115, 1068, 1002, 910 cm^{-1}. HRMS: [M−H$^+$] $C_{18}H_{15}O_4$, found 295.0959, theoretical mass 295.0976. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 90/10, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 22.4 min, $T_{3R,4S}$ = 46.1 min.

4.6.8. (+)-(3*R*,4*S*)-3-Benzoyl-4-ethyl-8-methoxychroman-2-one 13

Compound **2c** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **13** was obtained as white solid (121 mg, 78% yield). Mp: 139–140 °C (CH_2Cl_2–light petroleum). $[\alpha]_D^{25} = +32.2$ (*c* 1.00, $CHCl_3$, 96% ee, *trans*:*cis* 95:5). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.92 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.64 (tt, *J* = 7.4 and 1.1 Hz, 1H, Ph-*p*), 7.52 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.04 (t, *J* = 8.3 Hz, 1H, H-6), 6.90 (dd, *J* = 8.3 and 1.3 Hz, 1H, H-5 or 7), 6.64 (dd, *J* = 8.3 and 1.3 Hz, 1H, H-5 or 7), 4.80 (d, *J* = 2.2 Hz 1H, H-3), 3.94 (s, 3H, OMe), 3.26 (dt, *J* = 2.2 and 7.3 Hz, 1H, H-4), 1.87–1.76 (m, 2H, *CH*$_2$Me), 1.07 (t, *J* = 7.3 Hz, 3H, CH$_2$*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.3 (C=O), 164.9 (C=O), 147.6, 140.1, 134.4, 133.9, 128.9, 128.7, 124.5, 124.4, 119.9, 111.6, 56.1, 54.3, 41.7, 28.4, 11.2. IR ($CHCl_3$ solution) ν = 2968, 1767 (C=O), 1685 (C=O), 1486, 1278, 1240, 1176, 1115, 1075, 1003 cm^{-1}. HRMS: [M−H$^+$] $C_{19}H_{17}O_4$, found 309.1121, theoretical mass 309.1132. Elemental Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.56; H, 5.89. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 90/10, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 17.7 min, $T_{3R,4S}$ = 39.0 min.

4.6.9. (+)-(3*R*,4*S*)-3-Benzoyl-4-isobutyl-8-methoxychroman-2-one 14

Compound **2c** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **14** was obtained as colourless powder (120 mg, 71% yield). Mp: 128–129 °C (CH_2Cl_2–light petroleum). $[\alpha]_D^{25} = +7.3$ (*c* 1.00, $CHCl_3$, 75% ee, *trans*:*cis* 75:25). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.90 (app. d, *J* = 7.2 Hz, 2H, Ph-*o*), 7.63 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.51 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.02 (dd, 1H, *J* = 8.3 and 7.7 Hz, 1H, H-6), 6.89 (dd, *J* = 8.3 and 1.4 Hz, 1H, H-5 or 7), 6.62 (dd, *J* = 7.6 and 1.3 Hz, 1H, H-5 or 7), 4.74 (d, *J* = 1.7 Hz, 1H, H-3), 3.93 (s, 3H, OMe), 3.38 (dt, *J* = 1.7 and 7.6 Hz, 1H, H-4), 1.75–1.70 (m, 1H, *CH*Me$_2$), 1.60 (t, *J* = 7.6 Hz, 2H, *CH*$_2$*i*Pr), 1.03 (d, *J* = 6.5 Hz, 3H, CH$_2$*Me*$_\alpha$), 0.95 (d, *J* = 6.5 Hz, 3H, CH$_2$*Me*$_\beta$). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.2 (C=O), 164.9 (C=O), 147.7, 139.9, 133.9, 128.9, 128.7, 128.6, 128.3, 124.6, 119.7, 111.6, 56.2, 55.2, 44.8, 38.2, 24.9, 22.7, 22.3. IR ($CHCl_3$ solution) ν = 2961, 1766 (C=O), 1686 (C=O), 1486, 1280, 1240, 1175, 1089, 1004 cm^{-1}. HRMS: [M−H$^+$] $C_{21}H_{21}$-

O_4, found 337.1443, theoretical mass 337.1445. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 90/10, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 12.0 min, $T_{3R,4S}$ = 26.6 min.

4.6.10. (+)-(3*R*,4*S*)-3-Benzoyl-4-ethyl-7-methoxychroman-2-one 15

Compound **2d** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **15** was obtained as colourless oil (115 mg, 74% yield). $[\alpha]_D^{25} = +56.8$ (*c* 1.00, $CHCl_3$, 97% ee, *trans*:*cis* >99:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.89 (app. dd, *J* = 8.3 and 1.2 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.52 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 6.92 (d, *J* = 8.4 Hz, 1H, H-5), 6.71 (d, *J* = 2.5 Hz, 1H, H-8), 6.64 (dd, *J* = 8.4 and 2.5 Hz, 1H, H-6), 4.79 (d, *J* = 2.1 Hz, 1H, H-3), 3.82 (s, 3H, OMe), 3.19 (dt, *J* = 2.1 and 7.2 Hz, 1H, H-4), 1.87–1.69 (m, 2H, CH_2Me), 1.05 (t, *J* = 7.4 Hz, 3H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.8 (C=O), 165.8 (C=O), 160.0, 151.7, 134.3, 134.0, 129.0, 128.7, 128.1, 114.8, 110.8, 102.5, 55.5, 54.8, 41.2, 28.9, 11.2. IR ($CHCl_3$ solution) ν = 2967, 1764 (C=O), 1683 (C=O), 1627, 1508, 1155 cm^{-1}. HRMS: [M−H$^+$] $C_{19}H_{17}O_4$, found 309.1117, theoretical mass 309.1132. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 90/10, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 13.8 min, $T_{3R,4S}$ = 26.8 min.

4.6.11. (−)-(3*R*,4*R*)-3-Benzoyl-6-methoxy-4-methylchroman-2-one 16

Compound **2e** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **16** was obtained as colourless oil (60 mg, 40% yield). $[\alpha]_D^{25} = -13.1$ (*c* 1.00, $CHCl_3$, 37% ee, *trans*:*cis* 88:12). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.95 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.65 (tt, *J* = 7.4 Hz, 1H, Ph-*p*), 7.52 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.07 (d, *J* = 8.9 Hz, 1H, H-8), 6.83 (dd, *J* = 8.9 and 2.9 Hz, 1H, H-7), 6.71 (d, *J* = 2.7 Hz, 1H, H-5), 4.57 (d, *J* = 5.8 Hz, 1H, H-3), 3.80 (s, 3H, OMe), 3.63–3.54 (m, 1H, H-4), 1.44 (d, *J* = 7.0 Hz, 3H, CH*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.9 (C=O), 165.8 (C=O), 156.6, 144.4, 135.4, 134.0, 128.9, 128.7, 126.5, 117.7, 113.3, 112.5, 55.7, 55.0, 33.9, 19.9. IR ($CHCl_3$ solution) ν = 2967, 1759 (C=O), 1686 (C=O), 1598, 1497, 1267, 1179, 1038 cm^{-1}. HRMS: [M−H$^+$] $C_{18}H_{15}O_4$, found 295.0966, theoretical mass 295.0976. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 80/20, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 11.3 min, $T_{3R,4S}$ = 20.8 min.

4.6.12. (+)-(3*R*,4*S*)-3-Benzoyl-4-ethyl-6-methoxychroman-2-one 17

Compound **2e** (140 mg, 0.5 mmol) was treated according to the general procedure B; pure product **17** was obtained as colourless oil (85 mg, 55% yield). $[\alpha]_D^{25} = +1.0$ (*c* 1.00, $CHCl_3$, 48% ee, *trans*:*cis* 90:10). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.90 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.63 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.51 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.07 (d, *J* = 8.9 Hz, 1H, H-8), 6.81 (dd, *J* = 8.9 and 2.9 Hz, 1H, H-7), 6.56 (d, *J* = 2.9 Hz, 1H, H-5), 4.78 (d, *J* = 2.1 Hz, 1H, H-3), 3.76 (s, 3H, OMe), 3.20 (dt, *J* = 2.0 and 7.2 Hz, 1H, H-4), 1.88–1.72 (m, 2H, CH_2Me), 1.07 (t, *J* = 7.4 Hz, 3H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.6 (C=O), 165.8 (C=O), 156.2, 144.7, 134.3, 134.0, 129.0, 128.7, 124.1, 117.7, 113.8, 113.5, 55.5, 54.4, 41.9, 28.6, 11.2. IR ($CHCl_3$ solution) ν = 2967, 1761 (C=O), 1684 (C=O), 1597, 1497, 1178, 1037 cm^{-1}. HRMS: [M−H$^+$] $C_{19}H_{17}O_4$, found 309.1121, theoretical mass 309.1132. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 80/20, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 9.0 min, $T_{3R,4S}$ = 13.0 min.

4.6.13. (−)-(3*R*,4*R*)-3-Benzoyl-4,6-dimethylchroman-2-one 18

Compound **2f** (132 mg, 0.5 mmol) was treated according to the general procedure B; pure product **18** was obtained as white solid (110 mg, 78% yield). Mp: 103–104 °C (CH_2Cl_2–pentane). $[\alpha]_D^{25} = -43.9$ (*c* 1.00, $CHCl_3$, 67% ee, *trans*:*cis* 90:10). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.96 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.53 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.11 (dd, *J* = 8.3 and 1.8 Hz, 1H, H-7), 7.03 (d, *J* = 8.2 Hz, 1H, H-8), 6.98 (d, *J* = 1.8 Hz, 1H, H-5), 4.58 (d, *J* = 5.6 Hz, 1H, H-3), 3.61–3.54 (m, 1H, H-4), 2.34 (s, 3H, Me-6), 1.44 (d, *J* = 7.0 Hz, 3H, CH*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.9 (C=O), 165.9 (C=O), 148.5, 135.4, 134.6, 134.0, 129.2, 128.9, 128.8, 127.4, 125.0, 116.7, 55.2, 33.8, 20.9, 20.2. IR ($CHCl_3$ solution) ν = 2961, 1731 (C=O), 1600 (C=O), 1498, 1374, 1250, 1045 cm^{-1}. HRMS: [M−H$^+$] $C_{18}H_{15}O_3$, found 279.1021, theoretical mass 279.1027. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/05, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 16.5 min, $T_{3R,4S}$ = 29.6 min.

4.6.14. (+)-(3*R*,4*S*)-3-Benzoyl-4-ethyl-6-methylchroman-2-one 19

Compound **2f** (132 mg, 0.5 mmol) was treated according to the general procedure B; pure product **19** was obtained as colourless oil (140 mg, 94% yield). $[\alpha]_D^{25} = +46$ (*c* 1.00, $CHCl_3$, 85% ee, *trans*:*cis* 97:3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.92 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.52 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.09 (dd, *J* = 8.3 and 1.5 Hz, 1H, H-7) 7.03 (d, *J* = 8.3 Hz, 1H, H-8), 6.84 (d, *J* = 1.5 Hz, 1H, H-5), 4.80 (d, *J* = 2.1 Hz, 1H, H-3), 3.20 (dt, *J* = 2.0 and 7.3 Hz, 1H, H-4), 2.30 (s, 3H, Me-6), 1.90–1.71 (m, 2H, CH_2Me), 1.08 (t, *J* = 7.4 Hz, 3H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.6 (C=O), 165.9 (C=O), 148.7, 134.4, 134.1, 134.0, 129.3, 129.0, 128.9, 128.8, 122.8, 116.7, 54.6, 41.7, 28.8, 20.8, 11.2. IR ($CHCl_3$ solution) ν = 2967, 1763 (C=O), 1685 (C=O), 1602, 1498, 1458, 1304, 1257, 1194 cm^{-1}. HRMS: [M−H$^+$] $C_{19}H_{17}O_3$, found 293.1176, theoretical mass 293.1183. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 12.8 min, $T_{3R,4S}$ = 20.7 min.

4.6.15. (−)-(1*R*,2*S*)-2-Benzoyl-1-ethyl-1,2-dihydrobenzo[*f*]chromen-3-one 20

Compound **2g** (150 mg, 0.5 mmol) was treated according to the general procedure B, but by using ligand (*R*,*S*,*S*)-$\mathbf{L_A}$, pure product **20** was obtained as a colourless oil (130 mg, 79% yield). $[\alpha]_D^{25} = -38.1$ (*c* 1.00, $CHCl_3$, 90% ee, *trans*:*cis* 97:3). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.91 (app. dd, *J* = 8.4 and 1.2 Hz, 2H, Ph-*o*), 7.87–7.81 (m, 2H, Ar), 7.73 (d, *J* = 8.3 Hz, 1H, Ar), 7.63 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.52–7.45 (m, 4H, Ar), 7.34 (d, *J* = 8.9 Hz, 1H, H-6), 5.02 (d, *J* = 1.4 Hz, 1H, H-2), 4.01 (dt, *J* = 1.4 and 7.3 Hz, 1H, H-1), 2.06–1.84 (m, 2H, CH_2Me), 1.20 (t, *J* = 7.4 Hz, 1H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.4 (C=O), 165.6 (C=O), 148.6, 134.0, 131.3, 130.8, 129.6, 129.0, 128.7, 128.3, 127.2, 125.0, 122.3, 117.4, 116.8, 53.6, 37.6, 28.1, 11.4. IR ($CHCl_3$ solution) ν = 2969, 1765 (C=O), 1685 (C=O), 1239, 1174, 1070, 1002, 909 cm^{-1}. HRMS: [M−H$^+$] $C_{22}H_{17}O_3$, found 329.1178, theoretical mass 329.1183. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 1.0 ml min^{-1}. $T_{1S,2R}$ = 19.7 min, $T_{1R,2S}$ = 22.1 min.

4.6.16. (+)-(3*S*,4*R*)-Ethyl-4-methyl-2-oxochroman-3-carboxylate 21

Compound **2i** (109 mg, 0.5 mmol) was treated according to the general procedure B, but by using ligand (*R*,*S*,*S*)-$\mathbf{L_A}$, pure product **21** was obtained as a colourless oil (78 mg, 67% yield). $[\alpha]_D^{25} = +13.8$ (*c* 0.50, $CHCl_3$, 54% ee, *trans*:*cis* 89:11). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.33–7.24 (m, 2H, H-5,7), 7.17 (ddd, *J* = 8.1, 7.5 and 1.1 Hz, 1H, H-6), 7.10 (dd, *J* = 8.1 and 1.1 Hz, 1H, H-8), 4.23–4.13 (m, 2H, OCH_2), 3.62–3.55 (m, 2H, H-3,4), 1.39 (d, *J* = 6.9 Hz, 3H, CH_2*Me*), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 167.3 (C=O), 164.7 (C=O), 150.6, 128.7, 127.1, 125.6, 125.0, 116.9, 62.1, 53.6, 33.6, 19.3, 13.9. IR ($CHCl_3$ solution) ν = 2939, 1772 (C=O), 1736 (C=O), 1488, 1462, 1345, 1265, 1239, 1170, 1115, 1083, 1028 cm^{-1}. HRMS: [M−H$^+$] $C_{13}H_{13}O_4$, found

233.0815, theoretical mass 233.0819. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/5, flow rate: 0.5 ml min^{-1}. $T_{3S,4R}$ = 34.2 min, $T_{3R,4S}$ = 46.5 min. The racemic compound has been briefly reported.[25]

4.6.17. (+)-(3*R*,4*S*)-Ethyl-4-ethyl-2-oxochroman-3-carboxylate 22

Compound **2i** (109 mg, 0.5 mmol) was treated according to the general procedure B; pure product **22** was obtained as colourless oil (85 mg, 68% yield). $[\alpha]_D^{25} = +19.4$ (*c* 1.00, $CHCl_3$, 90% ee, *trans*:*cis* 93:7). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.29 (ddd, *J* = 8.1, 7.5 and 1.8 Hz, 1H, H-7), 7.18 (dd, *J* = 7.5 and 1.8 Hz, 1H, H-5), 7.13 (dd, *J* = 7.5 and 1.2 Hz, 1H, H-6), 7.09 (dd, *J* = 8.1 and 1.2 Hz, 1H, H-8), 4.13–4.01 (m, 2H, OCH_2), 3.80 (d, *J* = 2.6 Hz, 1H, H-3), 3.30 (dt, *J* = 2.6 and 7.5 Hz, 1H, H-4), 1.72–1.60 (m, 2H, CH_2Me), 1.04 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 167.2 (C=O), 164.6 (C=O), 150.8, 128.7, 124.6, 124.0, 117.0, 62.1, 51.8, 41.4, 27.4, 13.8, 11.1. IR ($CHCl_3$ solution) ν = 2936, 1771 (C=O), 1736 (C=O), 1487, 1460, 1259, 1168, 1098, 1030, 913 cm^{-1}. HRMS: [M−H^+] $C_{14}H_{15}O_4$, found 247.0971, theoretical mass 247.0976. HPLC: Daicel Chiralpak OD-H, hexane/*i*PrOH = 95/05, flow rate: 1.0 ml min^{-1}. $T_{3S,4R}$ = 8.3 min, $T_{3R,4S}$ = 9.7 min. The racemic compound has been briefly reported.[25]

4.6.18. (*E*)-3-Benzoyl-4-(dec-1-enyl)-7-methoxychroman-2-one 23

Compound **2d** (140 mg, 0.5 mmol) was treated according to the general procedure C; pure product **23** was obtained as yellow oil (145 mg, 69% yield). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.92 (app. d, *J* = 7.2 Hz, 2H, Ph-*o*), 7.63 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.51 (app. t, *J* = 7.7 Hz, 2H, Ph-*m*), 7.04 (d, *J* = 9.4 Hz, 1H, Ar), 6.71–6.69 (m, 2H, Ar), 5.61–5.53 (m, 1H, HC=CH), 5.44–5.38 (m, 1H, HC=CH), 4.66 (d, *J* = 6.8 Hz, 1H, H-3), 4.09 (t, *J* = 7.0 Hz, 1H, H-4), 3.83 (s, 3H, OMe), 2.04–1.94 (m, 2H), 1.35–1.16 (m, 12H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 193.8 (C=O), 165.5 (C=O), 160.1, 151.5, 135.8, 135.6, 133.9, 128.9, 128.7, 127.3, 115.1, 111.1, 102.4, 55.5, 53.7, 41.6, 32.3, 31.9, 29.4, 29.2, 29.0, 28.9, 22.7, 14.1. IR ($CHCl_3$ solution) ν = 2928, 1764 (C=O), 1686 (C=O), 1625, 1508, 1448, 1156. HRMS: [M−H^+] $C_{27}H_{31}O_4$, found 419.2221, theoretical mass 419.2228.

4.6.19. (*E*)-3-Benzoyl-8-bromo-4-(2-cyclohexenylvinyl)chroman-2-one 24

Compound **2b** (123 mg, 0.375 mmol) was treated according to the general procedure C, the pure product **24** was obtained as yellow oil (137 mg, 84% yield). ^1H NMR: (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.95 (app. d, *J* = 7.3 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.3 Hz, 1H, Ph-*p*), 7.55–7.51 (m, 3H, Ph-*m*, H-7), 7.14–7.11 (m, 1H, H-5), 7.02 (t, *J* = 7.8 Hz, 1H, H-6), 6.15 (d, *J* = 15.4 Hz, 1H, H C=CH), 5.81–5.76 (m, 1H, H C=CH), 5.46 (dd, *J* = 15.4 and 7.9 Hz, 1H, H C=CH), 4.76 (d, *J* = 6.1 Hz, 1H, H-3), 4.23 (t, *J* = 6.9 Hz, 1H, H-4), 2.17–1.99 (m, 4H), 1.69–1.60 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.8 (C=O), 164.1 (C=O), 147.7, 137.9, 135.3, 134.5, 134.1, 132.8, 131.7, 128.9, 128.8, 127.4, 125.6, 125.4, 121.6, 110.7, 53.6, 42.8, 25.9, 24.4, 22.3, 22.2. IR ($CHCl_3$ solution) ν = 2930, 1772 (C=O), 1686 (C=O), 1448, 1239, 1157. HRMS: [M−H^+] $C_{24}H_{20}BrO_3$, found 435.0588, theoretical mass 435.0601.

4.6.20. (*E*)-3-Benzoyl-8-bromo-4-styrylchroman-2-one 25

Compound **2b** (123 mg, 0.375 mmol) was treated according to the general procedure C; pure product **25** was obtained as a yellow oil (138 mg, 86% yield). ^1H NMR: (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.97 (app. d, *J* = 7.2 Hz, 2H, Ph-*o*), 7.65 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.59 (app. d, *J* = 7.4 Hz, 2H, Ph-*m*), 7.54–7.50 (m, 3H, Ph), 7.33–7.32 (m, 2H, Ph), 7.27–7.25 (m, 1H, Ar), 7.20 (d, *J* = 7.1 Hz, 1H, Ar), 7.06 (d, *J* = 7.1 Hz, 1H, Ar), 6.56 (d, *J* = 15.7 Hz, 1H, H C=CH), 6.13 (dd, *J* = 15.7 and 8.0 Hz, 1H, H C=CH), 4.83 (d, *J* = 6.9 Hz, 1H, H-3), 4.42 (t, *J* = 7.4 Hz, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.6 (C=O), 163.9 (C=O), 147.7, 135.7, 135.4, 134.7, 134.2, 133.0, 129.0, 128.8, 128.6, 128.3, 127.9, 127.3, 126.6, 125.7, 125.0, 110.9, 52.9, 42.6. IR ($CHCl_3$ solution) ν = 3011, 1772 (C=O), 1687 (C=O), 1448, 1239, 1156, 1135. HRMS: [M−H^+] $C_{24}H_{16}BrO_3$, found 431.0268, theoretical mass 431.0288.

4.6.21. (*E*)-3-Benzoyl-8-bromo-4-(3-methylbuta-1,3-dienyl)chroman-2-one 26

Compound **2b** (123 mg, 0.375 mmol) was treated according to the general procedure C; the pure product **26** was obtained as a yellow oil (120 mg, 81% yield). ^1H NMR: (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.96 (app. d, *J* = 7.2 Hz, 2H, Ph-*o*), 7.66 (app. t, *J* = 7.4 Hz, 1H, Ph-*p*), 7.58 (d, *J* = 7.9 Hz, 1H, H-7), 7.53 (app. t, *J* = 7.5 Hz, 2H, Ph-*m*), 7.13 (d, *J* = 7.6 Hz, 1H, H-5), 7.04 (t, *J* = 7.8 Hz, 1H, H-6), 6.27 (d, *J* = 15.5 Hz, 1H, H C=CH), 5.59 (dd, *J* = 15.5 and 7.8 Hz, 1H, H C=CH), 5.03 (d, *J* = 12.1 Hz, 2H, CH2=), 4.78 (d, *J* = 6.3 Hz, 1H, H-3), 4.35–4.23 (t, *J* = 7.0 Hz, 1H, H-4), 1.80 (s, 1H, CH3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 192.7 (C=O), 163.9 (C=O), 147.7, 140.5, 137.3, 135.3, 134.2, 132.9, 129.0, 128.8, 127.3, 125.8, 125.7, 125.0, 118.5, 110.8, 53.3, 42.5, 18.5. IR ($CHCl_3$ solution) ν = 2975, 1772 (C=O), 1687 (C=O), 1448, 1240, 1156, 1136. HRMS: [M−H^+] $C_{21}H_{16}BrO_3$, found 395.0275, theoretical mass 396.0288.

4.6.22. (*S*)-4-(1-(2-Hydroxy-3-methoxyphenyl)propyl)-1-methyl-3-phenyl-1H-pyrazol-5-ol 27

Compound (+)-**13** (240 mg, 0.77 mmol) and methylhydrazine (0.41 ml, 7.7 mmol) were dissolved in EtOH (15 ml). The mixture was then heated at reflux for 4 h. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, washed with HCl (1 M), $NaHCO_3$ (satd) and H_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the crude product was then purified by flash column chromatography (Et_2O) over silica gel to give pure product as a colourless powder (105 mg, 40% yield). Mp: 172–173 °C (CH_2Cl_2–light petroleum). $[\alpha]_D^{23} = -3.5$ (*c* 1.00, $CHCl_3$, 96% ee). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ = 7.47–7.45 (m, 3H, Ar), 7.27–7.24 (m, 2H, Ar), 7.00 (dd, *J* = 7.8 and 1.5 Hz, 1H, Ar), 6.80 (t, *J* = 7.9 Hz, 1H, Ar), 6.74–6.72 (m, 1H, Ar), 3.90 (s, 3H, OMe), 3.90–3.87 (m, 1H, *CH*Et), 3.55 (s, 3H, NMe), 2.17–2.09 (m, 1H, $CH_{2\alpha}$), 2.00–1.93 (m, 1H, $CH_{2\beta}$), 0.87 (t, *J* = 7.3 Hz, 3H, CH_2*Me*). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS) δ = 159.3, 146.5, 142.9, 142.6, 131.6, 130.4, 130.2, 128.7, 128.3, 121.5, 119.5, 108.4, 105.4, 56.0, 36.7, 36.1, 26.0, 13.0. IR ($CHCl_3$ solution) ν = 2966, 1712, 1520, 1477, 1276, 1074 cm^{-1}. HRMS: [M+H] $C_{20}H_{23}N_2O_3$, found 339.1706, theoretical mass 339.1703.

4.7. X-ray crystallography

Diffraction data for (−)-(3*R*,4*S*)-**10** and (+)-(3*R*,4*S*)-**13** were recorded at 150(2) K on Bruker SMART CCD area detector diffractometers. The Flack parameter for (−)-(3*R*,4*S*)-**10** refined to 0.022(12), confirming the absolute structure shown. Crystal data for (−)-(3*R*,4*S*)-**10** and (+)-(3*R*,4*S*)-**13** have been deposited with the Cambridge Crystallographic Data Centre (CCDC reference numbers 722200 and 722201, respectively).[26]

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26. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.