Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8260

www.rsc.org/obc

PAPER

Organocatalytic dynamic kinetic resolution *via* conjugate addition: synthesis of chiral *trans*-2,5-dialkylcyclohexanones†

Ganesh Pandey,*[a] Priyanka A. Adate[a] and Vedavati G. Puranik[b]

Received 9th April 2012, Accepted 24th August 2012
DOI: 10.1039/c2ob26597d

A novel strategy of initiating an organocatalysed dynamic kinetic resolution (dr up to 99 : 1 and er up to 94 : 6) for the synthesis of chiral *trans*-2,5-dialkylcyclohexanones by an asymmetric conjugate addition of dimethyl malonate on to 6-substituted cyclohexenones is reported.

Introduction

In the last few years asymmetric conjugate addition has emerged as one of the most powerful C–C bond forming strategies and many ligands and catalysts are designed to affect this important reaction.[1] Transition metals in combination with chiral ligands have been successfully demonstrated to catalyze asymmetric conjugate addition of stabilized as well as non-stabilized carbanions.[2] The versatility of this reaction has been amply demonstrated utilizing wide spectrum of donor–acceptor combinations. Of all donor and acceptor pairs used, the conjugate adduct obtained between cyclohexenone and dimethylmalonate pair is known to have maximum synthetic utility as this has served as a starting material for building complex molecular entities.[3] Sibasaki *et al.* have employed a BINOL–heterobimetallic complex to catalyze this conjugate addition reaction even up to a kilogram scale[4] with excellent enantioselectivity. Recently, several organocatalysts have also been developed to catalyse this reaction with excellent yields and enantioselectivity[5] but it is limited to only those with simple non-substituted cyclohexenones. To the best of our knowledge conjugate addition on substituted cyclohexenones using organocatalysts has still remained unexplored.

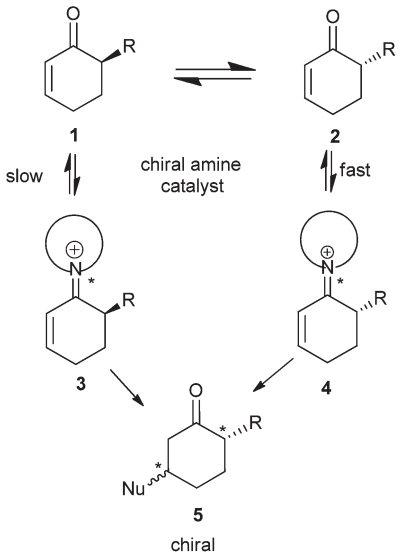
Considering the importance of 2,5-dialkylcyclohexanone moieties as versatile building blocks for the synthesis of many complex structures with pharmacological importance[6] and our requirement of a scalable synthesis of chiral *trans*-2,5-dialkylcyclohexanone for an ongoing project, we envisioned its synthesis *via* organocatalysed conjugate addition of malonate on 6-alkyl cyclohexenones. It may be appropriate to mention that most of the methodologies pertaining to the syntheses of the molecules displaying 2,5-disubstituted cyclohexanone core structure have relied either on chiral pool[6] approach utilizing menthone, dihydrocarvone, isopulegone or kinetic resolution of racemic substituted cyclohexenones. In this paper, we would like to disclose our success in initiating dynamic kinetic resolution processes during organocatalyzed conjugate addition of dialkyl malonate on racemic 6-alkyl cyclohexenone producing *trans*-2,5-dialkyl cyclohexanone with good to excellent enantioselectivity.

Results and discussion

Initially, as per our planning, we attempted the synthesis of chiral *trans*-2,5-dialkylcyclohexanones *via* asymmetric conjugate addition of dimethyl malonate on racemic 6-alkyl substituted cyclohexenone (**1**) in the presence of organocatalyst **IIa** (readily available in the group), but to our surprise, no reaction occurred. We also evaluated the same reaction using chiral 6-alkyl cyclohexenone using achiral secondary amine (pyrrolidine and piperidine); however, here too the complete starting material was recovered. Interestingly the recovered starting material (**1**) was found to be optically inactive (racemised). This unexpected observed racemisation was tentatively rationalized by implicating iminium/enamine tautomerization as shown in Scheme 1. This racemisation phenomenon led us to envision that in the presence of a chiral amine catalyst and a base, the rate of iminium ions (**3** and **4**) formation may vary[7] leading to either one of the enriched iminium ion diastereomer preferentially, which on conjugate addition with malonate would produce enantiomerically enriched **5** stereoselectively. Furthermore, fast equilibration of slower forming diastereomer **3** through tautomerization may set in a dynamic kinetic resolution (DKR) processes as shown in Scheme 1. To our knowledge dynamic kinetic resolution of 6-substituted cyclohexenone *via* organocatalytic conjugate addition is not studied so far.[8] Based on this hypothesis, we first scanned different catalysts (Fig. 1) under various reaction conditions to optimize the conjugate addition of dimethyl malonate on to enone **6**[9] (Table 1). Stirring a solution of **6** (1 mmol, 1.0 equiv.)

[a]*Division of Organic Chemistry, National Chemical Laboratory, Pune-411 008, India. E-mail: gp.pandey@ncl.res.in; Fax: +91 20 2590-2628; Tel: +91 20 2590-2281*
[b]*Centre for Material Characterization, National Chemical Laboratory, Pune-411 008, India. E-mail: vg.puraniknl.res.in*

†Electronic supplementary information (ESI) available: NMR and HPLC spectra of all new compounds. CCDC 861580. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26597d



Scheme 1 DKR Hypothesis.

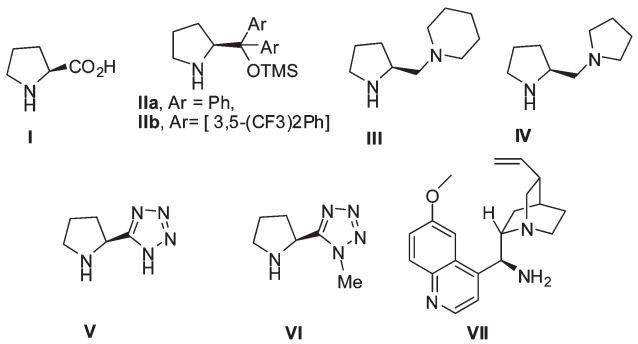


Fig. 1 Catalyst evaluated.

in dichloromethane with catalyst **V**[10] (10 mol%) and piperidine (1.0 equiv., as an additive) gave **6A** as an exclusive product with 50% conversion. Chiral stationary phase HPLC analysis of **6A** indicated it to be an enantiomerically enriched diastereomeric mixture (dr = 85 : 15, er = 93 : 7) (Table 1, entry 6). We were delighted to find recovered **6** to be racemic (analysed using Kromasil 5-Amycoat, mobile phase i-PrOH–petroleum ether 5 : 95, 1.0 mL min^{-1}, wavelength: 220 nm) thus, supporting our hypothesis. Furthermore, DKR using recovered **6** gave identical results indicating its probable reuse. The relative stereochemistry of 2,5-dialkyl substituent of major and minor diastereomers (isolated by preparative HPLC column: Kromasil RP-8, acetonitrile–H_2O = 35 : 65, wavelength: 220 nm) were confirmed as *trans*-**6A** and *cis*-**6A**, respectively, by extensive 2D NMR studies (Fig. 2). Relative and absolute stereochemistry of the major diastereomer of **6A** was further confirmed as *trans* (14*R*, 15*R*) using X-ray crystallographic analysis under Cu radiations (λ = 1.5418) (Fig. 3).[11] At this point, we do not exactly understand the origin of *trans* stereoselectivity[12] in this reaction but believe that addition is somehow directed by tetrazole moiety from only one face of the enone moiety possibly due to combined effects of electronic and steric factors.[13]

Table 1 Scanning of different catalyst for DKR studies[a]

Sr. no.	Catalyst	Solvent	Conversion[b] %	dr[c]	er[d]
1	**I**	CH_2Cl_2	NR	—	—
2	**IIa**	CH_2Cl_2	NR	—	—
3	**IIb**	CH_2Cl_2	NR	—	—
4	**III**	CH_2Cl_2	NR	—	—
5	**IV**	CH_2Cl_2	NR	—	—
6	**V**	CH_2Cl_2	50	85 : 15	93 : 7
7	**VI**	CH_2Cl_2	5	65 : 35	47 : 53
8	**V**	$CHCl_3$	70	87 : 13	94 : 6
9	**VII**	CH_2Cl_2	5	49 : 51	92 : 8

[a] Enone (1 mmol), catalyst (10 mol%), dimethyl malonate (1.5 mmol), piperidine (1 mmol), solvent 3 mL, 5 days, RT (25 °C). [b] Conversion monitored by GC. [c] Diastereomeric ratio determined either by HPLC or NMR. [d] Enantiomeric excess determined by chiral stationary phase HPLC. NR = no reaction.

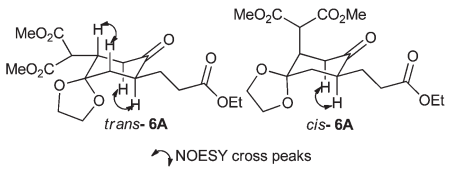


Fig. 2 Relative stereochemistry of **6A** confirmation using NMR.

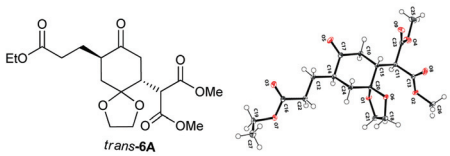
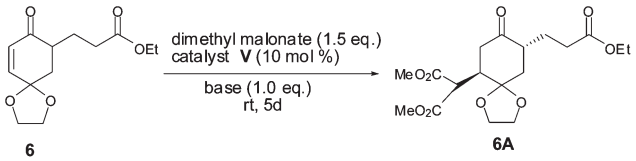


Fig. 3 ORTEP diagrams of *trans*-**6A**.

It may be worth mentioning that there are very few methods known in the literature for the synthesis of chiral 2,5-disubstituted cyclohexanone. For example, Tamioka *et al.* have demonstrated asymmetric conjugate addition of either arylboronic acid or dialkylzinc on racemic 6-alkyl cyclohexenone in the presence of chiral amidophosphane-$[RhCl(C_2H_4)]_2$ [14] and chiral amidophosphane-copper(I) complex[15] as catalysts, respectively, and corresponding conjugate addition products were obtained in 1 : 1 diastereomeric mixtures which were eventually epimerized to thermodynamically more stable *trans*-2,5-dialkyl cyclohexanones (ee up to 99%) using a strong base. Luo *et al.*[16] have synthesized chiral *cis*-2,5-disubstituted cyclohexanones (dr = 1 : 99) *via* kinetic resolution of 3-substituted cyclohexanone by α-alkylation using pyrrolidine derived functionalized chiral ionic liquids in low to moderate enantioselectivity (ee = 69–84%).

In order to improve the enantioselectivity and diastereoselectivity further, we evaluated primary amine based catalyst **VII**,[17] derived from cinchona alkaloid, but the results were not very exciting as **6A** was formed only with 5% conversion (no conjugate adduct was observed in the absence of a base) and without any diastereoselectivity, however, the enantioselectivity (er = 92 : 8) obtained was excellent. To improve the enantioselectivity and diastereoselectivity further, different solvent and base combinations were scanned (Table 2). From the results of solvent

Table 2 Base and solvent studies[a]



6 6A

Sr. no.	Solvent	Base	Conversion[b] %	dr[c]	er[d] (major diastereomer)
1	MeCN	Piperidine	4	2 : 1	ND
2	THF	Piperidine	NR	—	—
3	$PhCH_3$	Piperidine	NR	—	—
4	EtOH	Piperidine	NR	—	—
5	DMF	Piperidine	3	—	ND
6	DMSO	Piperidine	10	1 : 5	12 : 88
7	$CHCl_3$	Piperidine	70	85 : 15	94 : 6
8[e]	$CHCl_3$	Piperidine	NR	—	—
9	$CHCl_3$	—	NR	—	—
10	$CHCl_3$	NEt_3	NR	—	—
11	$CHCl_3$	DBU	20	3 : 1	60 : 40
12	$CHCl_3$	Pyrrolidine	60	87 : 13	72 : 28
13	$CHCl_3$	K_2CO_3	NR	—	—
14	$CHCl_3$	Pyridine	SM decompose	—	—

[a] Enone (1.0 mmol), catalyst **V** (10 mol%), dimethylmalonate (1.5 mmol), base (1.0 mmol), solvent (3 mL), 5 days, RT (25 °C). [b] Determined by GC analysis. [c] Diastereomeric ratio determined either by HPLC or NMR. [d] Enantiomeric excess determined by chiral stationary phase HPLC and mentioned only for major diastereomer. [e] No catalyst used. NR = no reaction, ND = not determined. THF = tetrahydrofuran, DMF = dimethylformamide, DMSO = dimethylsulfoxide.

scanning, it was observed that DKR works well in chlorinated hydrocarbon solvents. Use of chloroform as a solvent improved conversion to 70% compared to dichloromethane. This observation can be correlated with Guttmans acceptor number[18] (AN) (AN of acetonitrile 18.9, DMSO 19.3, CH_2Cl_2 20.4, $CHCl_3$ 23.1), as a solvent with higher AN is known to enhance the reactivity of the intermediate iminium cation. Among the different solvent and bases[19] tried, chloroform and piperidine combination was found to be the best giving better conversion and stereoselectivity. The bulk scale (up to 20.0 g of **6**) DKR gave **6A** with almost same enantioselectivity and diastereoselectivity (dr = 70 : 30, er = 94 : 6).

Without any catalyst or base additive, no background reaction was observed (Table 2, entry 8) (Table 2, entry 9). Other variants for reaction were also evaluated systematically to improve the yield and selectivity. For example, increasing the malonate concentration (3 equiv.) did not improve reaction conversion rather made purification of **6A** difficult. Surprisingly, reaction at lower temperature (10 °C) did not improve enantioselectivity (dr = 87 : 13, er = 94 : 6) rather just decreased the rate of reaction.

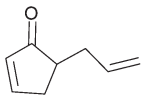
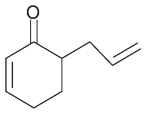
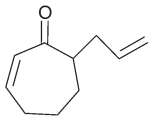
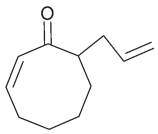
Having standardized the DKR reaction, we next studied the reaction with other enones of different ring sizes using dimethyl malonate as the donor (Table 3). For example, 5-allylcyclopentenone (**7**) underwent conjugate addition with good conversion (80%) but with low stereoselectivity (dr = 82 : 18, er = 66 : 34) as compared to its 6-membered congener (**8**). 2,5-*trans* Stereochemistry of **8A** was confirmed by extensive 2D NMR studies. Surprisingly, **9** did not undergo DKR under our standard reaction conditions.[20] In contrast, **10** underwent conjugate addition (60% conversion) with poor diastereoselectivity (60 : 40) but without any enantioselectivity (52.15 : 47.85) (Table 3, entry 3).

Next, we studied the substituent effect at the 6th position of the cyclohexenones.[21] It was observed that **11** having sterically bulky TBS group on the alkyl chain at the 6th position improved the conversion slightly but decreased diastereoselectivity (dr = 60 : 40) and enantioselectivity (er = 90 : 10) as compared to **6**. Excellent conversions (92–95%) were obtained with enones without any substitution at the 4th position (*e.g.* **8**, **12–14**). Generally better enantiomeric ratios were observed using diethyl malonate as a nucleophile in comparison to dimethyl malonate (Table 4, entries 2 and 3; 4 and 5; Table 3, entry 2 and Table 4, entry 7). A considerable decrease in diastereoselectivity was noticed with the reaction of 6-methyl cyclohexenone (**13**) and diethyl malonate in comparison to dimethyl malonate (Table 4, entries 4, 5). The stereochemistry of cycloadduct **13A** was confirmed as usual by 2D NMR studies. Conjugate addition of 2-nitropropane on to **13** gave corresponding conjugate adduct (**13C**) in excellent diastereoselectivity (dr = 94 : 6) and enantioselectivity (er = 88 : 12) (Table 4, entry 9). Surprisingly, no conjugate addition occurred with piperitone (**15**) while aliphatic enone **16** gave very low diastereoselectivity and enantioselectivity (Table 4, entries 11, 12).

Conclusions

In summary, we have developed a conceptually new strategy of initiating a DKR reaction for preparing chiral *trans*-2,5-dialkylcyclohexanones by organocatalyzed asymmetric conjugate addition of dimethyl malonate on to 6-substituted cyclohexenones. Application of this methodology for the synthesis of complex terpenes is in progress and will be disclosed in the near future.

Table 3 Studies on effect of ring size of enones on DKR[a]

Sr. no.	Starting enone	Michael donor[e]	Yields[b] %	Dr[c]	er[d] Major (Minor)
1	 **7**	A	80	82 : 18	66 : 34 (41 : 59)
2	 **8**	A	92	99 : 1	87 : 13
3	 **9**	A	NR	—	—
4	 **10**	A	70	60 : 40	50.4 : 49.6 (52.2 : 47.8)

[a] Enone (1 mmol), catalyst V (10 mol%), malonate (1.5 mmol), piperidine (1 mmol), $CHCl_3$ (3 mL), 5 days, RT (25 °C). [b] Isolated yields on purification. [c] Diastereomeric ratio determined either by HPLC or NMR. [d] Enantiomeric excess determined by chiral stationary phase HPLC. [e] A = dimethylmalonate, B = diethylmalonate.

Experimental

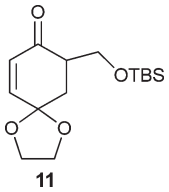
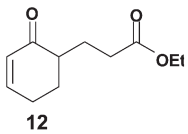
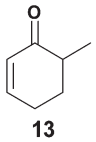
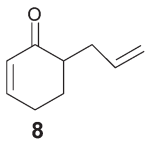
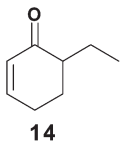
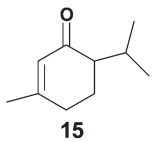
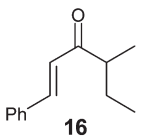
General

All moisture-sensitive reactions were performed under an atmosphere of argon and glasswares were dried in an oven at 125 °C prior to use. Dry tetrahydrofuran (THF) was obtained by passing commercially available pre-dried, oxygen-free formulations through activated neutral alumina columns and dried by distillation over sodium/benzophenone. All the solvents and bases used were distilled prior to use. Solvents used for chromatography were distilled at respective boiling points using known procedures. All commercial reagents were obtained from Sigma-Aldrich Chemical Co and S. D. Fine Chemical Co. India. Reactions were monitored by thin layer chromatography (TLC, 0.25 mm E. Merck silica gel plates, 60F254) and visualized by using UV light, ethanolic solution of phosphomolybdic acid and iodine. Column chromatography was performed on silica gel 60–120/100–200/230–400 mesh obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents. All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX500 instruments using deuteriated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (bs, broadened; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AV-400 and Bruker DRX 500 instruments operating at 100 MHz and 125 MHz respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). HPLC were performed on Shimadzu Class-VP V6.12 SP5 with UV detector. Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on a Finnigan Mat-1020 spectrometer. Elemental analyses were determined at Central Elemental Analysis Facility division at National Chemical Laboratory. Optical rotations were measured on a JASCO P-1020 polarimeter. High resolution mass (HR-ESI-MS) spectra was recorded on a Thermo scientific make Q-exactive model spectrometer using electrospray ionization. Racemic samples of Michael adduct were prepared using an equivalent amount of lithium perchlorate and catalytic amount of triethylamine in dry CH_2Cl_2 as solvent.

General procedure for DKR reaction

To a stirred suspension of 6-substituted enones (0.2 mmol) and catalyst (10 mol%) in $CHCl_3$ (2 mL) was added dialkylmalonate (0.3 mmol) and piperidine (0.2 mmol) at room temperature. The progress of the reaction was monitored by thin layer chromatography and gas chromatography. After 5 days of stirring when no further conversion was noticed, the reaction was quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated in vacuum, purified by flash column chromatography to obtain conjugate addition product.

Table 4 Generalization of substrate scope for DKR[a]

Sr. no.	Starting enone	Michael donor[e]	Conversion[b]%	dr[c]	er[d] Major (Minor)
1	 **11**	A	80	60 : 40	90 : 10 (81 : 19)
2	 **12**	A	95	85 : 15	84 : 16 (86 : 14)
3		B	95	96 : 4	90 : 10
4	 **13**	A	95	99 : 1	79 : 21
5		B	95	42 : 58	88 : 12 (87 : 13)
6	 **8**	C	75	94 : 6	88 : 12
7		B	90	91 : 9	91 : 9 (89 : 11)
8	 **14**	B	95	75 : 25	88 : 12 (87 : 13)
9	 **15**	A	NR	—	—
10		C	NR	—	—
11	 **16**	A	40	50.2 : 49.8	52 : 48 (51 : 49)
12		B	35	78 : 22	50.5 : 49.5 (92.1 : 7.9)

[a] Enone (1 mmol), catalyst V (10 mol%), malonate (1.5 mmol), piperidine (1 mmol), $CHCl_3$ (3 mL), 5 days, RT (25 °C). [b] Isolated yields on purification. [c] Diastereomeric ratio determined either by HPLC or NMR. [d] Enantiomeric excess determined by chiral stationary phase HPLC. NR = no reaction. [e] A = dimethylmalonate, B = diethylmalonate, C = 2-nitropropane.

Dimethyl-2-(9-(3-ethoxy-3-oxopropyl)-8-oxo-1,4-dioxaspiro-[4.5]decan-6-yl)malonate (6A). Pale yellow solid, M.P. = 81.9 °C; $[\alpha]_D^{25}$: +19.12 (c = 1.9, $CHCl_3$, 70% de, 88% ee); IR ν_{max} ($CHCl_3$): 2982, 2955, 2903, 1732, 1435, 1155; ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.23 (t, J = 5.0 Hz, 3 H), 1.47–1.60 (m, 2 H), 2.03 (dd, J = 14.8, 7.2 Hz, 1 H), 2.11 (dd, J = 13.4, 5.8 Hz, 1 H), 2.25–2.43 (m, 2 H), 2.50 (dd, J = 13.9, 4.7 Hz, 1 H), 2.63 (dd, J = 12.8, 7.0 Hz, 1 H), 2.69–2.78 (m, 1 H), 2.99 (ddd, J = 13.9, 7.0, 4.7 Hz, 1 H), 3.68 (d, J = 7.3 Hz, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 3.9–4.1 (m, 4 H), 4.1–4.1 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm (only for major diastereomer): 14.2, 23.9, 31.7, 39.0, 41.4, 44.4, 45.4, 50.6, 52.4, 52.6, 60.3, 64.7, 65.0, 107.8, 168.3, 168.4, 173.3, 208.5. m/z (%): 425.28 (M + K, 41), 409.29 (M + Na, 100), 237 (50), 221 (47). Elemental analysis calcd (%) for $C_{18}H_{26}O_9$: C 55.95, H 6.78; found: C 55.91, H 6.85; HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{27}O_9$, 387.1650; found, 387.1654. HPLC: major diastereomer: τ_R = 70.01 min (major enantiomer), τ_R = 64.2 min (minor enantiomer); minor diastereomer: τ_R = 53.15 min (major enantiomer); τ_R = 44.03 min (minor enantiomer); (Chromasil OJ-H, i-propanol–petroleum ether 20 : 80, 0.5 mL min^{-1}, 220 nm).

Data for *trans* 6A. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.24 (t, J = 7.02 Hz, 3 H), 1.49–1.60 (m, 2 H), 2.04 (dq, J = 14.27, 7.25 Hz, 1 H), 2.12 (dd, J = 13.43, 5.80 Hz, 1 H), 2.31 (dt, J = 15.87, 7.63 Hz, 1 H), 2.35–2.44 (m, 1 H), 2.51 (dd, J = 14.04, 4.58 Hz, 1 H), 2.64 (dd, J = 13.12, 6.71 Hz, 1 H), 2.75 (t, J = 13.89 Hz, 1 H), 2.96–3.03 (m, 1 H), 3.69 (d, J = 7.02 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.98–4.07 (m, 4 H), 4.11 (q, J = 7.22 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 14.2, 23.9,

31.9, 39.0, 41.4, 44.4, 45.1, 50.8, 52.4, 52.8, 60.3, 64.6, 65.0, 107.9, 166.3, 166.4, 173.3, 206.5.

Data for *cis* 6A. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 1.24–1.27 (t, 3 H), 1.61 (d, J = 6.71 Hz, 1 H), 1.90–1.98 (m, 1 H), 2.01–2.16 (m, 2 H), 2.30–2.37 (m, 2 H), 2.42 (dd, J = 15.26, 5.80 Hz, 1 H), 2.67 (dd, J = 10.83, 6.26 Hz, 1 H), 2.75–2.84 (m, 1 H), 2.98–3.10 (m, 1 H), 3.43 (d, J = 9.46 Hz, 1 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 3.92–4.09 (m, 4 H), 4.10–4.17 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 14.2, 24.7, 31.7, 37.7, 40.7, 43.2, 45.9, 51.9, 52.7, 60.4, 64.7, 64.8, 107.9, 168.1, 168.5, 173.2, 209.6.

Dimethyl-2-(4-allyl-3-oxocyclopentyl)malonate (7A). Colourless liquid, $[\alpha]_D^{25}$: +29.01 (c = 1.2, $CHCl_3$, 64% de, 32% ee); IR ν_{max} ($CHCl_3$): 2956, 1735, 1437, 1223, 1156; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.27–1.38 (m, 1 H), 1.96 (dd, J = 18.70, 11.67 Hz, 1 H), 2.03–2.19 (m, 1 H), 2.25–2.44 (m, 2 H), 2.44–2.63 (m, 2 H), 2.71–2.84 (m, 0.77 H), 2.9–2.96 (m, 0.19 H), 3.30–3.39 (d, J = 10.04, 1 H), 3.74 (s, 3 H), 3.77 (s, 3 H), 4.93–5.12 (m, 2 H), 5.63–5.78 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm (only for major diastereomer): 33.4, 33.6, 34.1, 42.8, 49.3, 52.6, 56.2, 116.81, 135.3, 168.4, 168.5, 216.8; m/z (%): 277 (M + Na, 100), 240 (12), 195 (8); Elemental analysis calcd (%) for $C_{13}H_{18}O_5$: C 61.40, H 7.14; found: C 61.68, H 6.95; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{13}H_{18}O_5Na$, 277.1046; found, 277.1054. HPLC: major diastereomer: τ_R = 57.392 min (major enantiomer), τ_R = 69.808 min (minor enantiomer); minor diastereomer: τ_R = 87.192 min (major enantiomer); τ_R = 65.525 min (minor enantiomer); (Chiralpak AS-H, petroleum ether–i-propanol 98.0 : 2.0, 0.5 mL min^{-1}, 230 nm).

Dimethyl 2-(4-allyl-3-oxocyclohexyl)malonate (8A). Colourless liquid, $[\alpha]_D^{25}$: +6.12 (c = 1.03, $CHCl_3$, 98% de, 74% ee); IR ν_{max} ($CHCl_3$): 2953, 1752, 1735, 1710, 1435, 1252, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.27–1.40 (m, 1 H), 1.49–1.62 (m, 1 H), 1.93–2.02 (m, 2 H), 2.12–2.20 (m, 1 H), 2.24–2.34 (m, 2 H), 2.40–2.60 (m, 3 H), 3.34 (d, J = 7.53 Hz, 1 H), 3.75 (s, 3 H), 3.75 (s, 3 H), 4.97–5.06 (m, 2 H), 5.70–5.83 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 29.29, 31.1, 33.2, 39.1, 45.4, 49.46, 52. 6, 56.8, 116.5, 136.1, 168.1, 168.2, 209.5; m/z (%): 307.31 (M + K, 20), 291.14 (M + Na, 100); Elemental analysis calcd (%) for $C_{14}H_{20}O_5$: C 62.67, H 7.51; found: C 62.89, H 7.88; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{14}H_{20}O_5Na$, 291.1203; found, 291.1210. HPLC: major diastereomer: τ_R = 19.308 min (major enantiomer), τ_R = 70.667 min (minor enantiomer); minor diastereomer: τ_R = 62.317 min (major enantiomer); τ_R = 58.517 min (minor enantiomer); (Chiralcel OJ-H, petroleum ether–i-propanol 95 : 05, 0.5 mL min^{-1}, 230 nm).

Diethyl 2-(4-allyl-3-oxocyclohexyl)malonate (8B). Colourless liquid, $[\alpha]_D^{25}$: +7.38 (c = 1.45, $CHCl_3$, 82% de, 82% ee); IR ν_{max} ($CHCl_3$): 2981, 2937, 1750, 1732, 1713, 1155; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.27 (td, J = 7.15, 1.00 Hz, 6 H), 1.30–1.40 (m, 1 H), 1.57 (qd, J = 12.72, 3.26 Hz, 1 H), 1.91–2.03 (m, 2 H), 2.09–2.21 (m, 1 H), 2.24–2.35 (m, 2 H), 2.42–2.59 (m, 3 H), 3.29 (d, J = 7.53 Hz, 1 H), 4.16–4.25 (m, 4 H), 4.96–5.08 (m, 2 H), 5.70–5.83 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 14.0, 29.3, 31.2, 33.2, 39.02, 45.4, 49.5, 57.0, 61.5, 116.4, 136.2, 167.7, 167.8, 209.7. m/z (%): 319.93 (M + Na, 25), 318.99 (100), 296.99 (M + H, 32), 161.83 (33), 160.5 (100), 136.56 (100), 132.82 (31). Elemental analysis calcd (%) for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 65.10, H 8.07; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{24}O_5Na$, 319.1516; found, 319.1524. HPLC: major diastereomer: τ_R = 38.183 min (major enantiomer), τ_R = 42.85 min (minor enantiomer); minor diastereomer: τ_R = 51.342 min (major enantiomer); τ_R = 47.617 min (minor enantiomer); (Chiralcel OJ-H, petroleum ether–i-propanol 99.5 : 0.5, 0.5 mL min^{-1}, 230 nm).

Dimethyl 2-(4-allyl-3-oxocyclooctyl) malonate (10A). Colourless liquid, IR ν_{max} ($CHCl_3$): 2932, 1751, 1735, 1701, 1437, 1195, 1157; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 1.34–1.46 (m, 2 H), 1.50–1.63 (m, 3 H), 1.64–1.83 (m, 4 H), 2.05–2.14 (m, 1 H), 2.24–2.48 (m, 3 H), 2.75–2.85 (m, 1 H), 2.90–3.02 (m, 1 H), 3.35 (d, J = 7.53 Hz, 0.62 H), 3.46 (d, J = 7.53 Hz, 0.27), 3.72–3.78 (m, 6 H), 4.91–5.09 (m, 2 H), 5.59–5.82 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm (only for major diastereomer): 23.6, 25.4, 31.9, 33.2, 35.1, 37.2, 45.9, 50.0, 52.5, 52.5, 57.1, 116.7, 135.5, 168.7, 168.8, 216.8; m/z (%): 319.66 (M + 23, 100), 297.72 (M + 1, 100), 265.92 (55), 264.58 (100), 246 (12), 232.91 (100). Elemental analysis calcd (%) for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 64.68, H 8.35; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{24}O_5Na$, 319.1516; found, 319.1524. HPLC: major diastereomer: τ_R = 22.517 min (major enantiomer), τ_R = 28.058 min (minor enantiomer); minor diastereomer: τ_R = 46.867 min (major enantiomer); τ_R = 83.650. min (minor enantiomer); (Kromasil 5-Amycoat, EtOH–*n*-Hexane 2.0 : 98.0, 0.5 mL min^{-1}, 230 nm).

Dimethyl 2-(9-((*tert*-butyldimethylsilyloxy)methyl)-8-oxo-1,4-dioxaspiro[4.5]decan-6-yl)malonate (11A). Colourless liquid, $[\alpha]_D^{25}$: +6.0 (c = 0.57, $CHCl_3$, 20% de, 80% ee); IR ν_{max} ($CHCl_3$): 2955, 2630, 1736, 1435, 1257, 1153, 837, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.04 (s, 6 H), 0.87 (s, 9 H), 1.64–1.70 (m, 0.7 H), 1.79 (s, 0.3 H), 2.30 (dd, J = 13.69, 5.87 Hz, 1 H), 2.51 (dd, J = 14.43, 4.65 Hz, 1 H), 2.66–2.81 (m, 2 H), 2.97–3.09 (m, 1 H), 3.64–3.72 (m, 2 H), 3.73 (s, 2 H), 3.72 (s, 4 H), 3.78 (d, J = 5.68 Hz, 0.3 H), 3.87 (dd, J = 10.51, 4.16 Hz, 1 H), 3.97–4.08 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: −5.5, 18.2, 25.8, 35.7, 41.6, 43.9, 48.7, 50.8, 52.5, 52.6, 61.13, 64.6, 64.7, 64.9, 108.1, 168.4, 168.5, 207.9; m/z (%): 469.15 (M + K, 70), 453.21 (M + Na, 100), 150.25 (10); Elemental analysis calcd (%) for $C_{20}H_{34}O_8Si$: C 55.79, H 7.96; found: C 55.60, H 8.01; HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{20}H_{34}O_8NaSi$, 453.1915; found, 453.1930. HPLC: major diastereomer: τ_R = 20.14 min (major enantiomer), τ_R = 21.78 min (minor enantiomer); minor diastereomer: τ_R = 18.91 min (major enantiomer); τ_R = 18.11 min (minor enantiomer); (Kromasil 5-Amycoat, i-propanol–petroleum ether 1.5 : 98.5, 0.5 mL min^{-1}, 220 nm).

Dimethyl-2-(4-(3-ethoxy-3-oxopropyl)-3-oxocyclohexyl)malonate (12A). Colourless liquid, $[\alpha]_D^{25}$: +6.42 (c = 2.93, $CHCl_3$, 70% de, 68% ee); IR ν_{max} ($CHCl_3$): 2955, 1755, 1738, 1732, 1714, 1435, 1250, 1179, 1155; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.24 (t, J = 7.09 Hz, 3 H), 1.31–1.44 (m, 1 H), 1.48–1.69 (m, 2 H), 1.91–2.17 (m, 3 H), 2.24–2.54 (m, 6 H), 3.29–3.36 (m, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 4.11 (q, J = 7.09 Hz, 2 H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ ppm 14.2, 24.3, 29.3, 31.7, 31.8, 39.2, 45.4, 48.9, 52.6, 56.7, 60.3, 168.09, 168.2, 173.5, 209.7; *m/z* (%) = 351.54 (M + Na, 100), 319.78 (10), 297 (25), 151.15 (5); Elemental analysis calcd (%) for $C_{16}H_{24}O_7$: C 58.52, H 7.37; found: C 58.3, H 7.25; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{16}H_{24}O_7Na$, 351.1414; found, 351.1422. HPLC: major diastereomer: τ_R = 90.38 min (major enantiomer), τ_R = 98.43 min (minor enantiomer); minor diastereomer: τ_R = 70.03 min (major enantiomer): τ_R = 66.67 min (minor enantiomer); (Chiralcel OD-H, *n*-hexane–EtOH 1.5 : 98.5, 0.5 mL min^{-1}, 230 nm).

Diethyl-2-(4-(3-ethoxy-3-oxopropyl)-3-oxocyclohexyl) malonate (12B). Colourless liquid, $[\alpha]_D^{25}$: +7.91 (*c* = 1.92, $CHCl_3$, 92% de, 80% ee); IR ν_{max} ($CHCl_3$): 2982, 2937, 1751, 1735, 1725, 1719, 1710, 1369, 1247, 1222, 1178, 1154; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.21–1.30 (m, 9 H), 1.31–1.44 (m, 1 H), 1.48–1.63 (m, 2 H), 1.94–2.17 (m, 3 H), 2.25–2.55 (m, 6 H), 3.27–3.31 (d, *J* = 7.53 Hz, 1 H), 4.11 (q, *J* = 7.28 Hz, 2 H), 4.20 (qd, *J* = 7.19, 3.26 Hz, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 14.0, 14.2, 24.3, 29.3, 31.7, 31.9, 39.1, 45.5, 48.9, 57.0, 60.3, 61.5, 167.7, 167.8, 173.5, 209.8; *m/z* (%): 379.14 (M + Na, 100), 368.5 (2), 151.44 (1); Elemental analysis calcd (%) for $C_{18}H_{28}O_7$: C 60.66, H 7.92; found: C 60.44, H 7.67; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{18}H_{28}O_7Na$, 379.1727; found, 379.1738. HPLC: major diastereomer: τ_R = 48.5 min (major enantiomer), τ_R = 57.14 min (minor enantiomer); minor diastereomer: τ_R = 40.5 min (major enantiomer), τ_R = 37.5 min (minor enantiomer); (Chiralcel OD-H, *n*-hexane–EtOH 98.5 : 1.5, 0.5 mL min^{-1}, 230 nm).

Dimethyl 2-(4-methyl-3-oxocyclohexyl)malonate (13A). Colourless liquid, $[\alpha]_D^{25}$: +3.98 (*c* = 1.08, $CHCl_3$, 98% de, 58% ee); IR ν_{max} ($CHCl_3$): 2935, 2956, 1735, 1713, 1436, 1251, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ ppm: 1.02 (d, *J* = 6.53 Hz, 3 H), 1.38 (qd, *J* = 13.09, 3.39 Hz, 1 H), 1.58 (qd, *J* = 12.72, 3.51 Hz, 1 H), 1.88–1.98 (m, 1 H), 2.09 (ddd, *J* = 13.24, 6.09, 3.26 Hz, 1 H), 2.25–2.54 (m, 4 H), 3.34 (d, *J* = 7.78 Hz, 1 H), 3.74 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 14.2, 29.4, 33.9, 39.1, 44.7, 45.1, 52.5, 56.8, 168.1, 168.2, 210.6; *m/z* (%): 281.15 (M + K, 100), 265.49 (M + Na, 42), 257.14 (10); Elemental analysis calcd (%) for $C_{12}H_{18}O_5$: C 59.94, H 7.35; found: C 60.06, H 7.13; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{12}H_{18}O_5Na$, 265.1046; found, 265.1054. HPLC: major diastereomer: τ_R = 74.26 min (major enantiomer), τ_R = 67.33 min (minor enantiomer); minor diastereomer: τ_R = 58.33 min (major enantiomer), τ_R = 54.95 min (minor enantiomer); (Chiralcel OD-H, *n*-hexane–EtOH 99.6 : 0.4, 0.5 mL min^{-1}, 230 nm).

Diethyl 2-(4-methyl-3-oxocyclohexyl)malonate (13B). Colourless liquid, $[\alpha]_D^{25}$: +5.26 (*c* = 5.25, $CHCl_3$, 16% de, 76% ee); IR ν_{max} ($CHCl_3$): 2964, 2937, 1715, 1733, 1713, 1243, 1156, 1032. ^1H NMR (diastereomeric mixture 3 : 2) M + K M + K (400 MHz, $CDCl_3$) δ ppm: 1.03 (d, *J* = 6.53 Hz, 2.26 H), 1.10 (d, *J* = 7.03 Hz, 0.75 H), 1.27 (td, *J* = 7.09, 1.63 Hz, 6 H), 1.38 (qd, *J* = 13.13, 3.26 Hz, 0.8 H), 1.53–1.71 (m, 1.3 H), 1.89–2.00 (m, 1.27 H), 2.05–2.14 (m, 0.75 H), 2.27–2.54 (m, 4 H), 3.24–3.32 (m, 1 H), 4.20 (qd, *J* = 7.11, 3.51 Hz, 4 H); ^{13}C NMR (diastereomeric mixture 3 : 2) (101 MHz, $CDCl_3$) δ ppm: 11.6, 11.7, 14.1, 21.8, 23.5, 25.0, 28.6, 29.4, 31.3, 37.8, 39.1, 42.8, 45.5, 51.2, 51.5, 56.0, 57.1, 61.5, 61.6, 61.7, 77.3, 167.8, 167.9, 167.9, 210.5, 212.5; *m/z* (%): 309.18 (M + K, 100), 293.43 (M + Na, 45), 154.46 (5); Elemental analysis calcd (%) for $C_{14}H_{22}O_5$: C 62.20, H 8.20; found: C 62.32, H 8.33; HRMS-ESI (*m/z*): $[M + Na]^+$ calcd for $C_{14}H_{22}O_5Na$, 293.1359; found, 293.1369. HPLC: major diastereomer: τ_R = 30.267 min (major enantiomer), τ_R = 26.45 min (minor enantiomer); minor diastereomer: τ_R = 25.008 min (major enantiomer), τ_R = 28.5 min (minor enantiomer); (Chiralcel OJ-H, *n*-hexane–EtOH 99.4 : 0.6, 0.7 mL min^{-1}, 230 nm).

2-Methyl-5-(2-nitropropan-2-yl)cyclohexanone (13C). Colourless solid; M.P.: Compound decomposes above 189 °C; $[\alpha]_D^{25}$: +9.67 (*c* = 0.34, $CHCl_3$, 88% de, 76% ee); IR ν_{max} ($CHCl_3$): 3019, 2400, 1540, 1475, 1215, 758, 66; ^1H NMR (500 MHz, $CDCl_3$) δ ppm: 0.97 (td, *J* = 7.32, 2.44 Hz, 0.6 H), 1.04 (d, *J* = 6.41 Hz, 3 H), 1.12–1.17 (m, 0.4 H), 1.30–1.39 (m, 1 H), 1.49–1.55 (m, 1 H), 1.58 (s, 3 H), 1.57 (s, 2 H), 1.76–1.82 (m, 1 H), 2.11–2.19 (m, 2 H), 2.30–2.44 (m, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 14.1, 22.5, 23.8, 26. 6, 33.7, 42.8, 44.7, 47.6, 90.6, 210.1; *m/z* (%): 254.06 (20), 222.05 (M + Na, 100), 102.31 (5); Elemental analysis calcd (%) for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found: C 60.32, H 8.77; N 7.15; HPLC: major diastereomer: τ_R = 19.008 min (major enantiomer), τ_R = 22.358 min (minor enantiomer); minor diastereomer: τ_R = 20.417 min (major enantiomer); τ_R = 21.283 min (minor enantiomer); (Chiralcel OD-H, petroleum ether–i-propanol 95 : 05, 0.5 mL min^{-1}, 230 nm).

Diethyl 2-(4-ethyl-3-oxocyclohexyl)malonate (14B). Colourless liquid, $[\alpha]_D^{25}$: +5.04 (*c* = 1.2, $CHCl_3$, 50% de, 76%); IR ν_{max} ($CHCl_3$): 2937, 2872, 1750, 1732, 1716, 1224, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ ppm (diastereomeric mixture 3 : 1): 0.89 (td, *J* = 7.34, 1.63 Hz, 3 H), 1.27 (t, *J* = 7.03 Hz, 6 H), 1.34–1.48 (m, 1 H), 1.56–1.6 (m, 0.4 H), 1.65–1.94 (m, 4 H), 2.08–2.20 (m, 1 H), 2.22–2.33 (m, 1 H), 2.36–2.56 (m, 2 H), 2.61–2.72 (m, 0.51 H), 3.26–3.32 (m, 0.88 H), 3.45–3.49 (m, 0.11 H), 4.17–4.26 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm (major diastereomer only): 14.0, 14.2, 29.4, 33.9, 39.0, 44.7, 45.2, 57.1, 61.5, 167.8, 167.9, 210.8; *m/z* (%): 323.3 (M + K, 15), 307.15 (M + Na, 100), 284.27 (M + 1, 10); Elemental analysis calcd (%) for $C_{15}H_{24}O_5$: C 63.36, H 8.51; found: C 62.98, H 8.65; HPLC: major diastereomer: τ_R = 35.717 min (major enantiomer), τ_R = 41.6 min (minor enantiomer); minor diastereomer: τ_R = 26.892 min (major enantiomer), τ_R = 33.792 min (minor enantiomer); (Kromasil 5-Amycoat, *n*-hexane–EtOH 98.0 : 02, 0.7 mL min^{-1}, 230 nm).

Dimethyl 2-(4-methyl-3-oxo-1-phenylhexyl) malonate (16A). Colourless liquid, IR ν_{max} ($CHCl_3$): 2963, 1752, 1735, 1710, 1434, 1253, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ ppm (diastereomeric mixture 1 : 1): 0.61–0.70 (m, 1 H), 0.74 (t, *J* = 7.40 Hz, 2 H), 0.87 (d, *J* = 7.03 Hz, 1 H), 0.94 (d, *J* = 6.78 Hz, 2 H), 1.17–1.33 (m, 1 H), 1.53 (ddt, *J* = 18.51, 14.05, 6.93, 6.93 Hz, 1 H), 2.31 (dq, *J* = 15.65, 6.83 Hz, 1 H), 2.86–3.07 (m, 2 H), 3.51 (s, 2 H), 3.56 (brs., 1 H), 3.71–3.84 (m, 4 H), 4.01 (ddt, *J* = 11.67, 9.10, 2.42, 2.42 Hz, 1 H), 7.14–7.35 (m, 5 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm (diastereomeric mixture 1 : 1): 11.2, 11.5, 15.2, 15.4, 25.5, 25.5, 40.3, 44.6, 44.7, 47.9, 48.1, 52.3, 52.6, 57.0, 127.1, 128.1, 128.4, 140.6, 168.1, 168.6, 211.7; *m/z* (%): 359 (M + K, 10), 343 (M + Na, 100), 321 (M + H, 30),

274 (37), 239 (34); Elemental analysis calcd (%) for $C_{18}H_{24}O_5$: C 67.48, H 7.55; found: C 67.78, H 7.37; HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{18}H_{24}O_5Na$, 343.1516; found, 343.1522. HPLC: major diastereomer: τ_R = 20.500 min (major enantiomer), τ_R = 24.033 min (minor enantiomer); minor diastereomer: τ_R = 32.325 min (major enantiomer); τ_R = 42.231 min (minor enantiomer); (Kromasil 5-Amycoat, EtOH–*n*-Hexane 7.0 : 93.0, 0.5 mL min^{-1}, 230 nm).

Diethyl 2-(4-methyl-3-oxo-1-phenylhexyl)malonate (16B). Colourless liquid, IR ν_{max} ($CHCl_3$): 2966, 1788, 1734, 1722, 1369, 1299, 1250; ^1H NMR (500 MHz, $CDCl_3$) δ ppm (diastereomeric mixture 4 : 1): 0.64 (t, *J* = 7.48 Hz, 1.5 H), 0.73 (t, *J* = 7.48 Hz, 1.5 H), 0.86 (d, *J* = 7.02 Hz, 1.5 H), 0.93 (d, *J* = 7.02 Hz, 1.5 H), 1.01 (t, *J* = 7.17 Hz, 3 H), 1.16–1.31 (m, 4 H), 1.45–1.58 (m, 1 H), 2.30 (dq, *J* = 18.92, 6.82 Hz, 1 H), 2.85–3.04 (m, 2 H), 3.73 (dd, *J* = 9.92, 1.68 Hz, 1 H), 3.95 (q, *J* = 7, 2 H), 3.98–4.03 (m, 1 H), 4.20 (qdd, *J* = 7.12, 7.12, 7.12, 2.29, 1.07 Hz, 2 H), 7.15–7.20 (m, 1 H), 7.23–7.26 (m, 4 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm (diastereomeric mixture 4 : 1): 11.2, 11.5, 13.7, 14.0, 15.2, 15.4, 40.3, 44.9, 44.9, 47.9, 48.1, 57.3, 61.3, 61.5, 127.0, 128.3, 167.7, 168.3 211.7, 211.8; *m*/*z* (%): 256.92 (100), 387.01 (M + K, 8), 371.94 (M + Na, 31), 370.94 (98), 349.07 (M + 1, 95), 302.92 (81); Elemental analysis calcd (%) for $C_{20}H_{28}O_5$: C 68.94, H 8.10; found: C 68.78, H 8.34; HRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{20}H_{28}O_5Na$, 371.1829; found, 371.1841. HPLC: major diastereomer: τ_R = 35.342 min (major enantiomer), τ_R = 39.825 min (minor enantiomer); minor diastereomer: τ_R = 68.767 min (major enantiomer); τ_R = 78.158 min (minor enantiomer); (Kromasil 5-Amycoat, i-PrOH–*n*-Hexane 2.5 : 97.5, 0.5 mL min^{-1}, 230 nm).

Acknowledgements

We gratefully acknowledge Mrs Sunita Kunte, Dr Rahul Banerjee and Mr Tamas Panda, Dr Rajmohanan and his group for helping with HPLC analysis, X-ray crystallography and NMR studies, respectively. The authors would like to thank DST-India for funding. P. A. thanks CSIR, New-Delhi, for the Research Fellowship.

Notes and references

1 (*a*) B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, 1992, **92**, 771–808; (*b*) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, 1992.

2 (*a*) B. E. Rossiter and N. Swingle, *Chem. Rev.*, 1992, **92**, 771; (*b*) M. P. Sibi and S. Manyem, *Tetrahedron*, 2000, **56**, 8033; (*c*) N. Krause and A. Hoffmann-Röder, *Synthesis*, 2001, 171; (*d*) S. C. Jha and N. N. Joshi, *Arkivoc*, 2002, **vii**, 167; (*e*) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829; (*f*) J. Comelles, M. Moreno-Mañas and A. Vallribera, *Arkivoc*, 2005, **ix**, 207.

3 Selected references for the synthetic utility of dimethyl 2-(3-oxocyclohexyl)malonate: (*a*) T. Ohshima, Y. Xu, R. Takita and M. Shibasaki, *Tetrahedron*, 2004, **60**, 9569; (*b*) Y. Haruta, K. Onizuka, K. Watanabe, K. Kono, A. Nohara, K. Kubota, S. Imoto and S. Sasaki, *Tetrahedron*, 2008, **64**, 7211; (*c*) J. Jiricek and S. Blechert, *J. Am. Chem. Soc.*, 2004, **126**, 3534.

4 (*a*) K. Majima, R. Takita, A. Okada, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 15837; (*b*) K. Majima, S. Y. Tosaki, T. Ohshima and M. Shibasaki, *Tetrahedron Lett.*, 2005, **46**, 5377; (*c*) Y. Xu, K. Ohori, T. Ohshima and M. Shibasaki, *Tetrahedron*, 2002, **58**, 2585.

5 (*a*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Symmetry*, 2011, **3**, 84; (*b*) D. Almaşi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*c*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*d*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Eur. J. Org. Chem.*, 2002, 1877; (*e*) O. M. Berner, L. Tedeschi and D. Ender, *Eur. J. Org. Chem.*, 2002, 1877.

6 Selected references for the total synthesis using dihydrocarvone, menthone, isopulegone(*a*) H. M. Cheng, W. Tian, P. A. Peixoto, B. Dhudshia and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2011, **50**, 4165; (*b*) D. M. Hodgson, S. Salik and D. J. Fox, *J. Org. Chem.*, 2010, **75**, 2157; (*c*) M. E. Flanagan, T. A. Blumenkopf, W. H. Brissette, M. F. Brown, J. M. Casavant, C. Shang-Poa, J. L. Doty, E. A. Elliott, M. B. Fisher, M. Hines, C. Kent, E. M. Kudlacz, B. M. Lillie, K. S. Magnuson, S. P. McCurdy, M. J. Munchhof, B. D. Perry, P. S. Sawyer, T. J. Strelevitz, C. Subramanyam, J. Sun, D. A. Whipple and P. S. Changelian, *J. Med. Chem.*, 2010, **53**, 8468; (*d*) M. Friedel, G. Golz, P. Mayer and T. Lindel, *Tetrahedron Lett.*, 2005, **46**, 1623; (*e*) A. Hartikka and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2004, **15**, 1831; (*f*) B. A. Sÿolaja, N. Terzic, G. Pocsfalvi, L. Gerena, B. Tinant, D. Opsenica and W. K. Milhous, *J. Med. Chem.*, 2002, **45**, 3331.

7 (*a*) J. Yang, T. Wang, Z. Ding, Z. Shen and Y. Zhang, *Org. Biomol. Chem.*, 2009, **7**, 2208; (*b*) Y. Wang, Z. Shen, B. Li, Y. Zhang and Y. Zhang, *Chem. Commun.*, 2007, 1284.

8 H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 659.

9 K. R. Knudsen, C. E. T. Mitchell and S. V. Ley, *Chem. Commun.*, 2006, 66.

10 Enone 6 was selected for optimization of the reaction conditions as masked ketone functionality at the 4th position was visualized as an additional handle for the synthesis of highly substituted cyclohexanone moiety.

11 CCDC-861580 contains the supplementary crystallographic data for this paper.†

12 Computational studies for better understanding of the transition state to justify the observed relative *trans* stereochemical outcome is planned in future.

13 A. J. A. Cobb, D. M. Shaw and S. V. Ley, *Synlett*, 2004, 558.

14 Q. Chen, T. Soeta, M. Kuriyama, K. Yamada and K. Tomioka, *Adv. Synth. Catal.*, 2006, **348**, 2604.

15 K. Selim, T. Soeta, K. Yamada and K. Tomioka, *Chem.–Asian J.*, 2008, **3**, 342.

16 L. Zhang, L. Cui, X. Li, J. Li, S. Luo and J.-P. Cheng, *Eur. J. Org. Chem.*, 2010, 4876.

17 P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang and J. Ye, *Org. Lett.*, 2009, **11**, 753.

18 V. Gutmann, *Coord. Chem. Rev.*, 1976, **18**, 225.

19 At this moment, we are not very sure on the exact role of the base in DKR, however, from the studies mentioned above it is clear that changing base affects diastereoselectivity as well as enantioselectivity. It may be possible that malonate and base forms contact ion pair which participates in the addition reaction affecting diastereoselectivity and enantioselectivity (see: A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2004, 1808).

20 It might be due to the conformation of 7-substituted cycloheptenone but at present we are unable to reason this observation.

21 We limited our studies to the use of dimethyl and diethyl malonate only, owing to the utility of the Michael addition product.(*a*) A. P. Krapcho, *Synthesis*, 1982, 805; (*b*) A. P. Krapcho, *Synthesis*, 1982, 893.