Asymmetric Reactions of 8-Phenylmenthyl Pyruvate with Allyltrimethylsilane, Silyl Enol Ethers and Ketene Silyl Acetals

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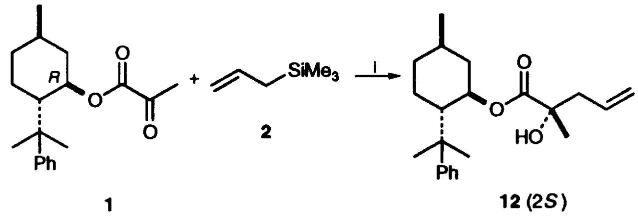
By mediation of $TiCl_4$, allylsilane, silyl enol ethers and ketene silyl acetals attacked (−)-phenylmenthyl pyruvate and (−)-phenylmenthyl phenylglyoxylate at their *si*-faces. The reactions are hypothesised to proceed with rigid cyclic transition states: *anti* aldol adducts **16a** and **17a** were favourably obtained from *E*-ketene silyl acetals **6** and **7** having *E*-configuration, whereas *syn* aldol adducts **18b–21b** were predominantly obtained from *Z*-ketene silyl acetal **18** and *Z*-silyl enol ethers **19–21**.

Formation of C–C bonds in a stereoselective controlled manner is an important synthetic method of current interest. Among many chiral auxiliaries,[1] (−)-8-phenylmenthol is a useful reagent utilized frequently to direct asymmetric reactions of its preformed carboxylates, such as alkylations,[2] Michael reactions,[3] Diels–Alder reactions,[4] Wittig rearrangements[5] and radical reactions.[6] Application of (−)-phenylmenthol to asymmetric reactions of α-oxocarboxylates has been reported, such as reductions,[7] additions with Grignard reagents,[8] additions with crotyltributylstannane or crotyltrimethylsilane mediated by BF_3,[9] the addition with methyl(triisopropoxy)-titanium,[10] additions with alkynyllithium reagents,[11] ene reactions promoted by $SnCl_4$,[12] Henry reactions with nitroalkanes[13] and photochemical [2 + 2] cycloadditions with oxazolines.[14] The degree of diastereoselectivity is found to be affected by the counterion of the nucleophile in addition to other controlling factors. In one report,[9b] stereochemical addition of crotyltrimethylsilane to (−)-phenylmenthyl pyruvate **1** has been successfully carried out by promotion with BF_3 but failed in the presence of $TiCl_4$. However, considering the high stereoselectivities in many examples of $TiCl_4$-mediated nucleophilic reactions toward α-oxycarbonyl compounds,[15] we investigated the reactions of (−)-8-phenylmenthyl pyruvate with allyltrimethylsilane, silyl enol ethers and ketene silyl acetals using the Mukaiyama procedure. These reactions proceeded smoothly and stereoselectively and provided a route to assemble chiral quaternary carbon centres.

Results and Discussion

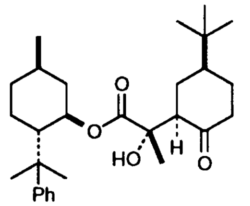
The addition of allysilane to (−)-8-phenylmenthyl pyruvate **1** was conducted by mediation of $TiCl_4$ at −78 °C in CH_2Cl_2 solution (Scheme 1). The reaction gave a single product, the tertiary alcohol **12** having the 2*S*-configuration. The absolute configuration of **12** was confirmed by saponification to (*S*)-(+)-2-hydroxy-2-methylpent-4-enoic acid.[16]



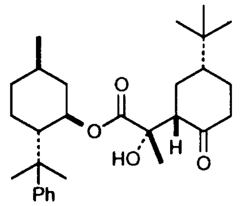
Scheme 1 *Reagents and conditions:* i, $TiCl_4$, CH_2Cl_2, −78 °C (96%)

The aldol reactions of **1** with a variety of silyl enol ethers (**3**, **4** and **9–11**) and ketene silyl acetals (**5–8**) were carried out by similar procedures. The results are listed in Table 1. The aldol reactions occurred exclusively at the *si*-face of the pyruvate to give the products **13–21** of 2*S*-configuration. Depending on the configuration of the silyl enol ether or ketene silyl acetal, the aldol reaction showed asymmetric induction to give either the 2,3-*syn* or 2,3-*anti* product as the major product. The ketene silyl acetals **6** and **7** of *Z*-configuration yielded predominantly the *anti* isomers of **16** and **17** in 2*S*,3*R* configuration, whereas the ketene silyl acetal **8** and silyl enol ethers **9–11** of *E*-configuration produced the aldol adducts **18–21** in predominantly 2*S*,3*S* configuration.

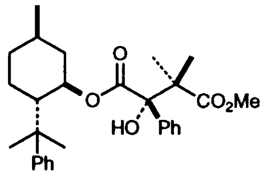
The additions using the 8-phenylmenthol auxiliary appeared to exert better stereocontrol than the corresponding reactions of **2–4** with (−)-menthyl pyruvate [44–55% diastereoisomeric excess (d.e.)].[17] The reaction of ketene silyl acetal **5** with (−)-8-phenylmenthyl phenylglyoxylate in the presence of $TiCl_4$ gave the aldol adduct **22** exclusively in the 2*R*-configuration. The reaction of **6** under similar conditions also afforded a single product **23** having the 2*R*,3*R* configuration.



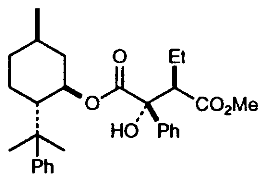
21a (2*S*,3*R*)



21b (2*S*,3*S*)



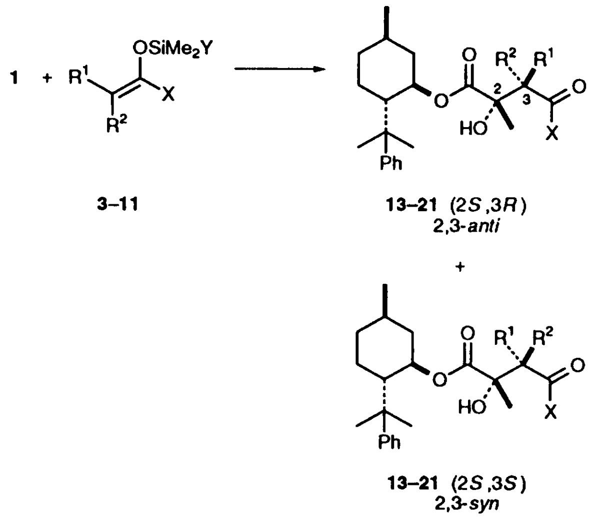
22 (2*R*)



23 (2*R*,3*R*)

The stereochemical outcome shown in Table 1 implies that the $TiCl_4$-mediated reactions proceeded *via* rigid transition states as depicted in Fig. 1.[17,18] The titanium enolate generated from **3–11** was chelated with both carbonyl groups of the pyruvate, the phenyl group of the auxiliary was preferably oriented to the *endo* face of the pyruvate, and the aldol reaction occurred at the less hindered face (*si*-face) of (−)-8-phenylmenthyl pyruvate *via* a [3.2.1]bicyclic transition state to give the observed major products. This model explains the consequence that the 2*S*,3*R*-adduct is obtained from the *Z*-enolate and the 2*S*,3*S*-adduct from the *E*-enolate. The products **21a** and **21b**

Table 1 Reactions of (−)-8-phenylmenthyl pyruvate with silyl enol ethers and ketene silyl acetals ($TiCl_4$, CH_2Cl_2, −78 °C, 10 min)



Nucleophile	R^1	R^2	X	Y	Product (yield %)	Ratio of 3*R*:3*S* isomers
3	H	H	Bu^t	Me	**13** (90)	
4	H	H	Ph	Me	**14** (72)	
5	Me	Me	OMe	Bu^t	**15** (85)	
6	Et	H	OMe	Bu^t	**16** (90)	71:29
7	Ph	H	OEt	Bu^t	**17** (93)	62:38
8	H	Me	OEt	Bu^t	**18** (94)	29:71
9	H	$-(CH_2)_3-$		Me	**19** (84)	20:80
10	H	$-(CH_2)_4-$		Me	**20** (87)	12:88
11	H	$-CH_2CH(Bu^t)CH_2CH_2-$		Me	**21** (83)	14:86

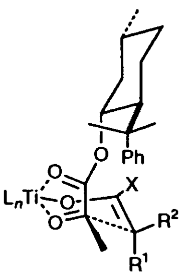


Fig. 1

were obtained presumably by approaching the silyl enol ether of 4-*tert*-butylcyclohexanone **11** at the equatorial position.

Experimental

General information concerning instrumentation and materials was described previously.[19] (−)-8-Phenylmenthyl pyruvate and (−)-8-phenylmenthyl phenylglyoxylate were prepared[20] by acid-catalysed condensation of (1*R*,2*S*,5*R*)-(−)-8-phenylmenthol[21] with pyruvic acid and benzoylformic acid, respectively. The silyl enol ethers and ketene silyl acetals **3**–**11** were prepared according to literature methods.[22] $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. *J* Values are given in Hz.

General Procedure for Reactions of (−)-*8-Phenylmenthyl Pyruvate with Allyltrimethylsilane, Silyl Enol Ethers and Ketene Silyl Acetals* **2**–**11**.—Under an atmosphere of N_2, $TiCl_4$ (0.07 cm^3, 0.6 mmol) was added dropwise to a cold (−78 °C) stirred solution of (−)-8-phenylmenthyl pyruvate (0.5 mmol) in anhydrous CH_2Cl_2. A solution of the appropriate nucleophile (allyltrimethylsilane, silyl enol ether or ketene silyl acetal, 0.6 mmol) was subsequently added dropwise. The reaction mixture was stirred for 20 min at −78 °C and poured into ice–water. After removal of CH_2Cl_2 by rotary evaporator, the residue was extracted three times with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4) and then concentrated under reduced pressure to give crude products **12**–**21**. Separation of products was accomplished by column chromatography (SiO_2) and/or HPLC with elution of the gradients of EtOAc in hexane indicated in each case. The reactions of (−)-phenylmenthyl phenylglyoxylate with ketene silyl acetals **5** and **6** were carried out by similar procedures to give **22** and **23**, respectively, in 80 and 78% yields.

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2-*methylpent*-4-*enoate* **12**.—2*S*-Isomer: oil; HPLC (3% EtOAc in hexane) t_R 14.3 min; $[\alpha]_D^{25}$ −8.6 ($CHCl_3$, *c* 7); ν_{max}(neat)/cm^{-1} 3516, 1714 and 1595; δ_H($CDCl_3$, 200 MHz) 0.72–1.14 (2 H, m), 0.88 (3 H, d, *J* 6.4, Me), 1.16 (3 H, s, Me), 1.17–1.29 (2 H, m), 1.22 (3 H, s, Me), 1.32 (3 H, s, Me), 1.36–1.64 (2 H, m), 1.94 (1 H, m), 2.09 (1 H, ddd, *J* 10.7, 10.7, 5.5), 2.30 (2 H, m), 2.65 (1 H, br s, OH), 4.88 (1 H, ddd, *J* 10.6, 10.6, 4.4), 5.04–5.14 (2 H, m), 5.64–5.84 (1 H, m), 7.11–7.24 (1 H, m, PhH) and 7.28–7.40 (4 H, m, PhH); δ_C($CDCl_3$, 50 MHz) 21.6 (q), 24.5 (q), 26.6 (q), 26.8 (q), 27.0 (t), 31.2 (d), 34.3 (t), 39.6 (s), 41.5 (t), 44.3 (d), 49.6 (d), 73.8 (s), 76.8 (d), 118.9 (t), 125.2 (d), 125.3 (d), 125.6 (d), 128.1 (d), 128.3 (d), 132.3 (d), 151.0 (s) and 175.5 (s, CO_2); *m*/*z* 344 (M^+, 13%) and 119 (100) (Found: M^+, 344.2344. Calc. for $C_{22}H_{32}O_3$, *M*, 344.2351). Saponification of **12** with aqueous KOH in MeOH gave (*S*)-2-hydroxy-2-methylpent-4-enoic acid, *viz*. citramalic acid, as an oil; $[\alpha]_D^{25}$ +10.6 ($CHCl_3$, *c* 9.2), lit.,[16] $[\alpha]_D^{25}$ +11.3 (EtOH *c* 1); δ_C($CDCl_3$) 25.3 (q), 44.3 (t), 74.5 (s), 119.9 (t), 131.7 (d) and 209.3 (s).

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2,5,5-*trimethyl*-4-*oxohexanoate* **13**.—2*S*-Isomer: oil; TLC (5% EtOAc in hexane) R_f 0.12; $[\alpha]_D^{25}$ +17.8 ($CHCl_3$, *c* 6.6); ν_{max}(neat)/cm^{-1} 3543, 1730 and 1600; δ_H($CDCl_3$) 0.73–1.05 (3 H, m), 0.87 (3 H, d, *J* 6.4), 1.14 (9 H, s), 1.20 (3 H, s), 1.25 (3 H, s), 1.31–1.56 (2 H, m), 1.90 (3 H, s), 2.00–2.06 (2 H, m), 2.64 (1 H, d, *J* 17.8), 2.93 (1 H, d, *J* 17.8), 4.79 (1 H, ddd, *J* 10.4, 10.4, 4.6), 7.10–7.17 (1 H, m) and 7.19–7.32 (4 H, m); $\delta_C(CDCl_3)$ 21.6 (q), 25.6 (q, 3 C), 26.2 (q), 26.6 (q), 26.9 (q), 30.1 (s), 31.1 (t), 34.4 (d), 39.7 (t), 40.9 (s), 43.7 (t), 45.7 (t), 49.7 (d), 72.3 (s), 76.7 (d), 125.1 (d), 125.5 (d, 2 C), 127.9 (d, 2 C), 151.0 (s), 174.9 (s, CO_2) and 214.8 (S, CO); *m/z* 402 (M^+, 6%) and 119 (100) (Found: M^+, 402.2761. Calc. for $C_{25}H_{38}O_4$, *M*, 402.2770).

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2-*methyl*-4-*oxo*-4-*phenylbutanoate* **14**.—2*S*-Isomer: oil; TLC (10% EtOAc in hexane) R_f 0.24; $[\alpha]_D^{25}$ +29.9 ($CHCl_3$, *c* 1.2); ν_{max}(neat)/cm^{-1} 3543 and 1728; $\delta_H(CDCl_3)$ 0.69–1.51 (3 H, m), 0.84 (3 H, d, *J* 6.4), 1.24 (3 H, s), 1.31 (3 H, s), 1.42 (3 H, s), 1.35–1.52 (3 H, m), 1.96–2.13 (2 H, m), 3.09 (1 H, d, *J* 18.0), 3.32 (1 H, d, *J* 18.0), 3.71 (1 H, br s, OH), 4.85 (1 H, ddd, *J* 10.6, 10.6, 4.5), 7.11–7.38 (5 H, m), 7.41–7.52 (3 H, m) and 7.87–7.93 (2 H, m); $\delta_C(CDCl_3)$ 21.7 (q), 25.9 (q), 26.8 (q), 27.0 (q), 29.8 (t), 31.2 (d), 34.5 (d), 39.9 (s), 40.8 (t), 47.3 (t), 49.7 (d), 72.7 (s), 77.0 (d), 125.2 (d, 2 C), 125.6 (d, 2 C), 128.0 (d, 2 C), 128.1 (d, 2 C), 128.6 (d, 2 C), 133.5 (s), 151.4 (s), 175.0 (s) and 198.7 (s); *m/z* 422 (M^+, 8%), 119 (100) (Found: M^+, 422.2433. Calc. for $C_{27}H_{34}O_4$, *M*, 422.2457).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl*] 4-*Methyl* 2-*Hydroxy*-2,3,3-*trimethylbutanedioate* **15**.—2*S*-Isomer: oil TLC (10% EtOAc in hexane) R_f 0.20; $[\alpha]_D^{25}$ −40.6 ($CHCl_3$, *c* 0.4); ν_{max}(neat)/cm^{-1} 3511 and 1727; $\delta_H(CDCl_3)$ 0.70–1.23 (3 H, m), 0.87 (3 H, d, *J* 6.4), 1.27 (12 H, br s), 1.30–1.62 (3 H, m), 1.37 (3 H, s), 1.95–2.10 (2 H, m), 3.72 (3 H, s), 4.94 (1 H, ddd, *J* 10.6, 10.6, 4.6), 7.11–7.22 (1 H, m) and 7.24–7.35 (4 H, m); $\delta_C(CDCl_3)$ 20.3 (q), 21.2 (q), 21.6 (q), 21.7 (q), 25.1 (q), 27.2 (t), 29.0 (q), 31.3 (d), 34.3 (t), 40.1 (s), 41.3 (t), 49.2 (s), 50.0 (d), 52.0 (t), 77.6 (d), 77.6 (s), 125.4 (d), 125.5 (d, 2 C), 128.1 (d, 2 C), 150.5 (s), 175.0 (s) and 176.6 (s); *m/z* 404 (M^+, 1%) and 119 (100) (Found: M^+, 404.2552. Calc. for $C_{24}H_{36}O_5$, *M*, 404.2563).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl*] 4-*Methyl* 3-*Ethyl*-2-*hydroxy*-2-*methylbutanedioate* **16**—2*S*,3*R*-Isomer: oil; TLC (3% EtOAc in hexane) R_f 0.08; $[\alpha]_D^{25}$ −5.7 ($CHCl_3$, *c* 1.2); ν_{max}(neat)/cm^{-1} 3526 and 1734; $\delta_H(CDCl_3)$ 0.84–1.12 (3 H, m), 0.87 (3 H, d, *J* 6.4 Hz), 0.88 (3 H, t, *J* 7.4), 1.18 (3 H, s), 1.24 (3 H), 1.34 (3 H, s), 1.35–1.77 (3 H, m), 1.93 (1 H, m), 2.07 (1 H, ddd, *J* 10.1, 10.1, 4.4), 2.52 (1 H, dd, *J* 6.4, 4.5), 3.68 (3 H, s), 4.86 (1 H, ddd, *J* 10.6, 10.6, 4.4), 7.15–7.20 (1 H, m) and 7.25–7.32 (4 H, m); $\delta_C(CDCl_3)$ 12.3 (q), 19.7 (q), 21.8 (q), 22.3 (q), 26.0 (q), 27.1 (t), 28.0 (t), 31.2 (d), 34.4 (t), 40.0 (s), 41.0 (t), 49.7 (d), 51.4 (d), 53.1 (d), 75.0 (s), 77.0 (d), 125.3 (d), 125.6 (d, 2 C), 128.1 (d, 2 C), 150.8 (s), 175.0 (s) and 175.1 (s); *m/z* 404 (M^+, 7%) and 119 (100) (Found: M^+, 404.2541. Calc. for $C_{24}H_{36}O_5$, *M*, 404.2563). 2*S*,3*S*-Isomer: oil; TLC (3% EtOAc in hexane) R_f 0.09; $[\alpha]_D^{25}$ +0.1 ($CHCl_3$, *c* 3.7); ν_{max}(neat)/cm^{-1} 3495 and 1733; $\delta_H(CDCl_3)$ 0.85–1.16 (3 H, m), 0.88 (3 H, d, *J* 6.4), 0.89 (3 H, t, *J* 7.4), 1.21 (3 H, s), 1.23 (3 H, s), 1.34 (3 H, s), 1.38–1.63 (3 H, m), 1.80 (1 H, m), 1.98 (1 H, m), 2.10 (1 H, ddd, *J* 10.0, 10.0, 3.9), 2.54 (1 H, dd, *J* 12.0, 3.1), 3.71 (3 H, s), 4.91 (1 H, ddd, *J* 10.6, 10.6, 4.4), 7.15–7.20 (1 H, m) and 7.25–7.31 (4 H, m); $\delta_C(CDCl_3)$ 12.3 (q), 20.8 (q), 21.7 (q), 23.5 (q), 26.2 (q), 27.0 (t), 27.5 (t), 31.2 (d), 34.3 (t), 39.9 (s), 41.1 (t), 49.7 (d), 51.5 (d), 55.6 (d), 75.0 (s), 77.5 (d), 125.4 (d, 3 C), 128.1 (d, 2 C), 150.8 (s) 173.5 (s) and 174.3 (s); *m/z* 405 (M^+ +1, 7%) 119 (100) (Found: M^+, 404.2566. Calc. for $C_{24}H_{36}O_5$, *M*, 404.2563).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl*] 4-*Ethyl* 2-*Hydroxy*-2-*methyl*-3-*phenylbutanedioate* **17**.—2*S*,3*R*-Isomer: solid, m.p. 109–110 °C; HPLC (15% EtOAc in hexane) t_R 4.8 min; $[\alpha]_D^{25}$ +14.5 ($CHCl_3$, *c* 8); ν_{max}(KBr)/cm^{-1} 3540 and 1736; $\delta_H(CDCl_3)$ 0.75–1.13 (3 H, m), 0.89 (3 H, d, *J* 6.4), 1.19 (3 H, d, *J* 7.4), 1.26 (3 H, s), 1.40 (3 H, s), 1.41–1.58 (3 H, m), 2.02 (1 H, m), 2.14 (1 H, d, *J* 10.5, 10.5, 4.6), 3.83 (1 H, br s, OH), 4.04 (1 H, s), 4.93 (1 H, ddd, *J* 10.6, 10.6, 4.5) and 7.14–7.40 (10 H, m); $\delta_C(CDCl_3)$ 14.0 (q), 21.7 (q), 23.3 (q), 26.3 (q), 27.0 (t), 27.7 (q), 31.2 (d), 34.5 (t), 40.0 (s), 41.1 (t), 49.7 (d), 56.7 (d), 61.1 (t), 75.1 (s), 77.0 (d), 125.4 (d), 125.6 (d, 2 C), 127.7 (d), 128.1 (d, 2 C), 128.2 (d, 2 C), 130.1 (d, 2 C), 133.7 (s), 150.9 (s), 173.2 (s) and 175.2 (s); *m/z* 405 (M^+ +1, 7%) and 119 (100) (Found: C, 74.3; H, 8.1. $C_{29}H_{38}O_5$ requires C, 74.28; H, 8.03%). 2*S*,3*S*-Isomer: oil; HPLC (15% EtOAc in hexane) t_R 6.6 min; $[\alpha]_D^{25}$ −21.8 ($CHCl_3$, *c* 5.5); ν_{max}(KBr)/cm^{-1} 3540 and 1735; $\delta_H(CDCl_3)$ 0.70–0.97 (3 H, m), 0.80 (3 H, d, *J* 6.4), 1.04 (3 H, s), 1.10 (3 H, s), 1.25 (3 H, t, *J* 7.4), 1.27–1.42 (3 H, m), 1.40 (3 H, s), 1.52 (1 H, m), 1.95 (1 H, d, *J* 10.6, 10.6, 5.2), 3.53 (1 H, br s, OH), 3.97 (1 H, s), 4.17 (2 H, m), 4.71 (1 H, ddd, *J* 10.6, 10.6, 4.6), 7.10–7.31 (8 H, m) and 7.36–7.47 (2 H, m); $\delta_C(CDCl_3)$ 14.0 (q), 21.6 (q), 25.1 (q), 25.5 (q), 27.1 (t), 28.2 (q), 31.2 (d), 34.4 (t), 39.8 (s), 40.9 (t), 49.7 (d), 57.5 (d), 61.1 (t), 76.0 (s), 77.6 (d), 125.3 (d), 125.5 (d, 2 C), 127.8 (d), 128.0 (d, 2 C), 128.1 (d, 2 C), 130.1 (d, 2 C), 134.2 (s), 150.8 (s), 171.7 (s) and 173.3 (s); *m/z* 405 (M^+ +1, 5%) and 119 (100) (Found: C, 74.3; H, 8.1%).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 4-*Ethyl* 2-*Hydroxy*-2,3-*dimethylbutanedioate* **18**.—2*S*,3*S*-Isomer: oil HPLC (15% EtOAC in hexane) t_R 6.6 min; $[\alpha]_D^{25}$ −5.7 ($CHCl_3$, *c* 3.6); ν_{max}(neat)/cm^{-1} 3512 and 1721; $\delta_H(CDCl_3)$ 0.76–1.05 (3 H, m), 0.86 (3 H, d, *J* 6.4), 1.18 (3 H, s), 1.20 (3 H, d, *J* 7.3), 1.23 (3 H, s), 1.27 (3 H, t, *J* 7.2), 1.35 (3 H, s), 1.44–1.60 (3 H, m), 1.95–2.10 (2 H, m), 2.68 (1 H, q, *J* 7.3), 3.54 (1 H, br s, OH), 4.16 (2 H, q, *J* 7.2), 4.86 (1 H, ddd, *J* 10.6, 10.6, 4.3), 7.13–7.19 (1 H, m) and 7.24–7.33 (4 H); $\delta_C(CDCl_3)$ 11.0 (q), 14.1 (q), 21.7 (q), 22.5 (q), 25.9 (q), 27.1 (q), 27.9 (t), 31.2 (d), 34.4 (t), 40.0 (s), 41.0 (t), 45.4 (t), 49.8 (d), 60.6 (d), 74.6 (s), 76.9 (d), 125.2 (d), 125.5 (d, 2 C), 128.0 (d, 2 C), 150.8 (s), 175.2 (s) and 175.3 (s), *m/z* 405 (M^+ +1, 7%) and 119 (100) (Found: M^+, 404.2563. Calc. for $C_{24}H_{36}O_5$, *M*, 404.2563). 2*S*,3R-Isomer: oil; HPLC (15% EtOAc in hexane) t_R 7.2 min; $[\alpha]_D^{25}$ −0.05 ($CHCl_3$, *c* 3) ν_{max}(neat)/cm^{-1} 3515 and 1724; $\delta_H(CDCl_3)$ 0.72–1.12 (3 H, m), 0.88 (3 H, d, *J* 6.4), 1.18 (3 H, d, *J* 7.3), 1.25 (6 H, s), 1.28 (3 H, t, *J* 7.2), 1.35 (3 H, s), 1.37–1.62 (3 H, m), 1.96–2.13 (2 H, m), 2.72 (1 H, q, *J* 7.3), 3.24 (1 H, br s, OH), 4.17 (2 H, q, *J* 7.2), 4.92 (1 H, ddd, *J* 10.6, 10.6, 4.3), 7.12–7.22 (1 H, m) and 7.26–7.35 (4 H, m); $\delta_C(CDCl_3)$ 12.6 (q), 14.1 (q), 21.7 (q), 23.6 (q), 25.9 (q), 27.1 (q), 28.0 (t), 31.3 (d), 34.4 (t), 40.0 (s), 41.3 (t), 47.6 (t), 49.8 (d), 60.6 (d), 75.1 (s), 77.4 (d), 125.4 (d), 125.5 (d, 2 C), 128.1 (d, 2 C), 150.8 (s), 173.7 (s) and 174.2 (s); 405 (M^+ +1, 7%) and 119 (100) (Found: M^+, 404.2560. Calc. for $C_{24}H_{36}O_5$, *M*, 404.2563).

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2-(2-*oxocyclopentyl*)*propanoate* **19**.—2*S*,3*R*-Isomer: oil; HPLC (15% EtOAc in hexane) t_R 9.0 min; $[\alpha]_D^{25}$ −40.6 ($CHCl_3$, *c* 0.4); ν_{max}(neat)/cm^{-1} 3513 and 1739; $\delta_H(CDCl_3)$ 0.85–1.08 (3 H, m), 1.11 (3 H, d, *J* 6.4), 1.27 (3 H, s), 1.28 (3 H, s), 1.35 (3 H, s), 1.40–1.84 (4 H, m), 1.85–2.19 (5 H, m), 2.20–2.37 (2 H, m), 2.47 (1 H, ddd, *J* 10.6, 10.6, 5.5), 2.76 (1 H, br s, OH), 4.85 (1 H, ddd, *J* 10.6, 10.6, 4.4), 7.07–7.16 (1 H, m) and 7.19–7.38 (4 H, m). $\delta_C(CDCl_3)$ 20.5 (q), 21.8 (q), 23.8 (q), 25.5 (q), 25.8 (t), 27.2 (t), 28.6 (t), 31.4 (d), 34.4 (t), 39.2 (t), 40.1 (s), 41.4 (t), 50.1 (d), 54.5 (d), 76.2 (s), 77.6 (d), 125.4 (d), 125.6 (d, 2 C), 128.1 (d, 2 C), 150.6 (s), 174.2 (s) and 219.8 (s); *m/z* 386 (M^+, 1%) and 119 (100) (Found: M^+, 386.2611. Calc. for $C_{24}H_{34}O_4$, *M*, 386.2613). 2*S*,3*S*-Isomer: solid, m.p. 112–114 °C; HPLC (15% EtOAc in hexane) t_R 9.6 min; $[\alpha]_D^{25}$ +16.2 ($CHCl_3$, *c* 1.5); ν_{max}(neat)/cm^{-1} 2960 and 1735; $\delta_H(CDCl_3)$ 0.85–1.06 (3 H, m), 0.90 (3 H, d, *J* 6.4), 1.13 (3 H, s), 1.23 (3 H, s), 1.36 (3 H, s), 1.40–1.87 (5 H, m), 1.90–2.16 (5 H, m), 2.17–2.30 (2 H, m), 2.46 (1 H, ddd, *J* 10.6, 10.6, 5.5), 2.88 (1 H, br s, OH), 4.90 (1 H, ddd, *J* 10.6, 10.6, 4.4), 7.15–7.19 (1 H, m) and 7.23–7.36 (4 H, m);

δ_C(CDCl$_3$) 20.3 (q), 21.8 (q), 24.3 (q), 24.8 (q), 26.8 (t), 26.9 (t), 27.1 (t), 31.4 (d), 34.6 (t), 38.7 (t), 39.9 (s), 40.7 (t), 49.8 (d), 55.8 (d), 73.6 (s), 77.9 (d), 125.2 (d), 125.6 (d, 2 C), 128.0 (d, 2 C), 151.4 (s), 167.0 (s) and 217.4 (s); *m*/*z* 386 (M$^+$, 1%), and 119 (100) (Found: M$^+$, 386.2610. Calc. for $C_{24}H_{34}O_4$, *M*, 386.2613).

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2-(2-*oxocyclohexyl*)*propanoate* **20**.—2*S*,3*S*-Isomer: oil; HPLC (15% EtOAc in hexane) t_R 10.2 min; $[\alpha]_D^{25}$ +30.8 (CHCl$_3$, *c* 5.7); ν_{max}(neat)/cm^{-1} 3542 and 1721; δ_H(CDCl$_3$) 0.79–1.10 (2 H, m), 0.86 (3 H, d, *J* 6.4), 1.08 (3 H, s), 1.21 (3 H, s), 1.30–1.78 (7 H, m), 1.30 (3 H, s), 1.79–2.18 (5 H, m), 2.19–2.47 (3 H, m), 3.05 (1 H, br s, OH), 4.75 (1 H, ddd, *J* 10.6, 10.6, 4.3), 7.17–7.21 (1 H, m) and 7.25–7.38 (4 H, m); δ_C(CDCl$_3$)21.7 (q), 22.9 (q), 24.7 (q), 26.4 (q), 26.8 (t), 27.0 (d, 2 C), 27.4 (t), 31.2 (d), 34.6 (t), 39.7 (s), 40.5 (t), 42.1 (t), 49.8 (d), 56.1 (d), 73.4 (s), 76.9 (d), 125.1 (d), 125.5 (d, 2 C), 127.9 (d, 2 C), 151.7 (s), 175.9 (s) and 212.4 (s); *m*/*z* 400 (M$^+$, 3%) and 119 (100) (Found: M$^+$, 400.2601. Calc. for $C_{25}H_{36}O_4$, *M*, 400.2613). 2*S*,3*S*-Isomer: solid, m.p. 113–115 °C; HPLC (15% EtOAc in hexane) t_R 11.0 min; $[\alpha]_D^{25}$ −25.4 (CHCl$_3$, *c* 1.5); ν_{max}(KBr)/cm^{-1} 3542 and 1725; δ_H(CDCl$_3$) 0.77–1.07 (2 H, m), 0.87 (3 H, d, *J* 6.4), 1.21 (3 H, s), 1.25 (3 H, s), 1.37–1.83 (7 H, m), 1.40 (3 H, s), 1.84–2.08 (5 H, m), 2.13–2.58 (2 H, m), 2.60 (1 H, m), 3.28 (1 H, br s, OH), 4.87 (1 H, ddd, *J* 10.6, 10.6, 4.3), 7.15–7.20 (1 H, m) and 7.25–7.37 (4 H, m); δ_C(CDCl$_3$) 21.7 (q), 22.9 (q), 24.7 (q), 26.4 (q), 26.9 (t), 27.4 (t), 27.7 (t), 31.2 (d), 34.5 (t), 34.6 (t), 39.7 (s), 40.5 (t), 42.1 (5), 49.8 (d), 56.1 (d), 73.4 (s), 76.8 (d), 125.1 (d), 125.2 (d, 2 C), 127.9 (d, 2 C), 151.6 (s). 175.9 (s) and 212.4 (s); *m*/*z* 400 (M$^+$, 1%) and 119 (100) (Found: M$^+$, 400.2611. Calc. for $C_{25}H_{36}O_4$, *M*, 400.2613).

5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl* 2-*Hydroxy*-2-(2-*oxo*-5-tert-*butylcyclohexyl*)*propanoate* **21**.—2*S*,3*S*-Isomer: oil; HPLC 15% EtOAc in hexane) t_R 4.8 min; $[\alpha]_D^{25}$ −22.3 (CHCl$_3$, *c* 1.3); ν_{max}(neat)/cm^{-1} 3544 and 1721; δ_H(CDCl$_3$) 0.77–1.10 (3 H, m), 0.87 (9 H, s), 0.88 (3 H, d, *J* 6.4), 1.15–1.73 (8 H, m), 1.26 (3 H, s), 1.37 (3 H, s), 1.48 (3 H, s), 1.74–2.05 (2 H, m), 2.06–2.25 (2 H, m), 2.47 (1 H, m), 2.57 (1 H, br s, OH), 4.90 (1 H, ddd, *J* 10.6, 10.6, 4.4) and 7.10–7.40 (5 H, m); δ_C(CDCl$_3$) 21.7 (q), 21.9 (q), 22.6 (q), 22.9 (q), 26.0 (q), 26.9 (q), 27.3 (q), 27.5 (t), 27.6 (t), 28.1 (s), 31.2 (d), 32.6 (d), 34.6 (t), 39.7 (s), 40.2 (t), 41.4 (t), 46.2 (t), 49.2 (d), 55.2 (d), 72.2 (s), 76.9 (d), 125.1 (d), 125.4 (d, 2 C), 128.0 (d, 2 C), 151.5 (s), 175.7 (s) and 212.5 (s); *m*/*z* 456 (M$^+$, 5%) and 119 (100). 2*S*,3*S*-Isomer: oil HPLC (15% EtOAc in hexane) t_R 6.0 min; $[\alpha]_D^{25}$ +28.5 (CHCl$_3$ *c* 5.5); ν_{max}(neat)/cm^{-1} 3540 and 1720; δ_H(CDCl$_3$) 0.76–1.10 (3 H, m), 0.88 (3 H, d, *J* 6.4), 0.97 (3 H, s), 1.10 (3 H, s), 1.24 (3 H, s), 1.27–1.52 (8 H, m), 1.92 (3 H, s), 1.99–2.21 (3 H, m), 2.22–2.51 (2 H, m), 3.04 (1 H, br s, OH), 4.72 (1 H, ddd, *J* 10.5, 10.5, 4.6), 7.11–7.23 (1 H, m) and 7.25–7.40 (4 H, m); δ_C(CDCl$_3$) 21.7 (q), 23.0 (q), 26.1 (q), 26.9 (q), 27.3 (q), 27.5 (q), 27.6 (q), 27.7 (t), 27.9 (t), 28.1 (s), 31.2 (d), 32.6 (d), 34.6 (t), 39.8 (s), 40.5 (t), 41.3 (t), 46.4 (t), 49.7 (d), 55.3 (d), 73.5 (s), 76.9 (d), 125.2 (d), 125.5 (d, 2 C), 127.9 (d, 2 C), 151.8 (s), 175.9 (s) and 212.6 (s); *m*/*z* 456 (M$^+$, 3%) and 119 (100) (Found: M$^+$, 456.3227. Calc. for $C_{29}H_{44}O_4$, *M*, 456.3240).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl*] 4-*Methyl* 2-*Hydroxy*-3,3-*dimethyl*-2-*phenylbutanedioate* **22**.—2*R*-Isomer: oil; TLC (5% EtOAc in hexane) R_f 0.20; ν_{max}(neat)/cm^{-1} 3553 and 1720 cm^{-1}; δ_H(CDCl$_3$) 0.66–0.98 (3 H, m), 0.78 (3 H, d, *J* 6.4), 1.14 (3 H, s), 1.18–1.34 (3 H, m), 1.30 (3 H, s), 1.31 (3 H, s), 1.40 (3 H, s), 1.59 (3 H, s), 1.81–1.94 (2 H, m), 3.77 (3 H, s), 4.51 (1 H, s, OH), 4.86 (1 H, ddd, *J* 10.5, 10.5, 4.3), 7.12–7.19 (3 H, m), 7.23–7.37 (5 H, m) and 7.45–7.50 (2 H, m); δ_C(CDCl$_3$) 14.0 (q), 21.7 (q), 22.0 (q), 22.6 (q), 22.7 (q), 23.5 (q), 27.4 (t), 30.0 (q), 31.3 (d), 31.5 (s), 34.3 (t), 40.4 (s), 40.5 (t), 50.1 (s), 76.9 (s), 82.6 (s), 125.3 (d), 125.8 (d, 2c), 127.3 (d, 2 C), 127.8 (d, 2 C), 128.0 (d, 2 C), 137.0 (s), 150.5 (s) and 179.4 (s); *m*/*z* 467 (M$^+$, 1%), 207 (100) and 119 (100) (Found: M$^+$, 466.2711. Calc. for $C_{29}H_{38}O_5$, *M*, 466.2719).

1-[5-*Methyl*-2-(1-*methyl*-1-*phenylethyl*)*cyclohexyl*] 4-*Methyl* 3-*Ethyl*-2-*hydroxy*-2-*phenylbutanedioate* **23**. 2*R*,3*R*-Isomer: oil; TLC (3% EtOAC in hexane) R_f 0.16; ν_{max}(neat)/cm^{-1} 3430 and 1730; δ_H(CDCl$_3$) 0.69–1.08 (3 H, m), 0.76 (3 H, d, *J* 6.4), 1.00 (3 H, t, *J* 7.4), 1.12 (3 H, s), 1.17 (3 H, s), 1.20–1.67 (5 H, m), 1.84–2.00 (2 H, m), 3.44 (3 H, s), 3.45 (1 H, dd, *J* 10.9, 4.1), 3.72 (1 H, s, OH), 4.85 (1 H, ddd, *J* 10.5, 10.5, 4.2), 7.16–7.35 (8 H, m) and 7.54–7.59 (2 H, m); δ_C(CDCl$_3$) 12.3 (q), 21.6 (q), 21.8 (t), 24.1 (q), 27.2 (t), 29.2 (q), 31.2 (d), 34.2 (t), 40.1 (s), 40.8 (t), 50.1 (d), 51.5 (q), 54.5 (d), 77.2 (d), 79.9 (s), 125.1 (d), 125.2 (d, 2 C), 125.6 (d, 3 C), 127.9 (d 2 C), 128.0 (d, 2 C), 140.0 (s), 150.3 (s), 171.0 (s) and 174.4 (s); *m*/*z* 466 (M$^+$, 30%) and (100).

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