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Conjugate reduction of α,β-unsaturated esters and amides with tributyltin hydride in the presence of magnesium bromide diethyl etherate

Satomi Hirasawa, Yoshie Tajima, Yoko Kameda and Hajime Nagano*

Department of Chemistry, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

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Abstract—We report herein that the conjugate reduction of α,β-unsaturated esters and amides, such as aryl acrylates, pantolactone esters of acrylic acids, diethyl itaconate and *N*-crotonylcamphorsultam, with tributyltin hydride proceeded in moderate to high yields in the presence of magnesium bromide diethyl etherate. The effect of metal halide enhancing the yields is also described.
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1. Introduction

A number of metal hydrides have been prepared as reducing agents for organic molecules, but few are studied on the conjugate reduction of α,β-unsaturated carboxylic acid esters. Organotin hydrides are effective for the conjugate reduction of α,β-unsaturated aldehydes and ketones.[1] However, the reagents are not suitable for the conjugate reduction of α,β-unsaturated carboxylic acid alkyl esters, and the radical addition reactions to α,β-unsaturated carboxylic acid alkyl esters proceed preferably.[1d,2] Therefore, tandem benzenethiol addition–tributyltin hydride reduction has been used for the reduction of pyranose-derived α,β-unsaturated lactones and esters.[3] Recently, Wu and co-workers reported the radical-mediated conjugate reduction of *N*-(α-arylacryloyl)oxazolidinones with tributyltin hydride.[4] Furthermore, Baba and co-workers reported the conjugate reduction of unsaturated esters using iodotin hydride ate complex.[5] During the investigation on the chelation-controlled diastereoselective radical addition to α-methylene-γ-oxycarboxylic acid esters,[6] we found the conjugate reduction of phenyl acrylate **1a**[7] and pantolactone ester **4a** with tributyltin hydride in the presence of Lewis acid (Scheme 1). We now report our investigation results of the conjugate reduction of aryl esters **1a**–**1l**,[8] pantolactone esters **5a**–**5f**, diethyl itaconate (**8**) and amides **9**–**12** with tributyltin hydride proceeding in the presence of magnesium bromide diethyl etherate (Tables 1–4).[9]

The conjugate reduction with the mild and neutral organotin reagents is of interest from the point of view that the reduction of α,β-unsaturated esters and amides would proceed chemoselectively without affecting the unsaturated bond such as isolated double bond C=C and alkyl acrylate moieties.[10,11] Furthermore, the chelation-controlled diastereoselective reduction would be an alternative to catalytic hydrogenation being used commonly for the diastereoselective reduction of acrylic acid esters.[12]

2. Results and discussion

2.1. Preparation of the requisite substrates 1a, 1f, 1g, 4c, 4e and 12 for the reductions

The requisite substrates **1a**, **1f**, **1g**, **4c**, **4e** and **12** for the reductions were prepared as follows (Scheme 2). The condensation reaction of carboxylic acids **20** and **21**, obtained by hydrolyzing the corresponding ethyl esters **18** and **19**,[6d] with phenol using *N*,*N*′-dicyclohexylcarbodiimide gave phenyl esters **1a** and **1g** in 63 and 77% yields, respectively. Phenyl ester **1f** was prepared from alcohol **1e** using chloromethyl methyl ether and *N*,*N*-diisopropylethylamine in 68% yield. The condensation reaction of carboxylic acids **22** and **23**[6g] with pantolactone (**24**) was performed using *N*,*N*′-dicyclohexylcarbodiimide to give pantolactone esters **4c** and **4e** in 58 and 77% yields, respectively. Following the procedure reported,[13] 3-methylene-5-phenylpyrrolidin-2-one (**25**)[14] was treated with *n*-BuLi and then with benzoyl chloride to give *N*-benzoyl-γ-lactam **12** in 85% yield.

Keywords: Conjugate reduction; α,β-Unsaturated esters and amides; Tributyltin hydride; Lewis acid.
* Corresponding author. Fax: +81 359785715; e-mail: nagano.hajime@ocha.ac.jp

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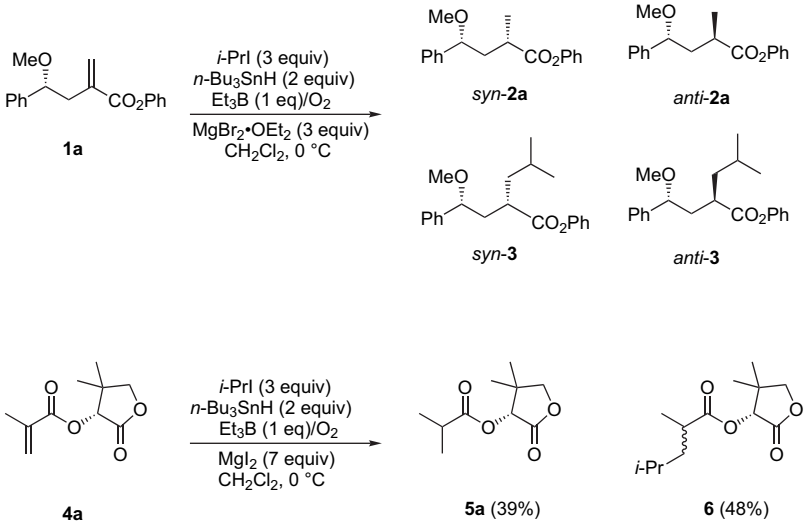


Scheme 1. Radical reaction of phenyl ester **1a** and pantolactone ester **4a** with isopropyl iodide.

Table 1. Reduction of **1a** with *n*-Bu_3SnH in the presence of Lewis acid

Entry	*n*-Bu_3SnH (equiv)	Lewis acid (3 equiv)	Et_3B (equiv)	Yield of **2a**[a] (%)
1[b]	2	$MgBr_2 \cdot OEt_2$	1	21
2	2	$MgBr_2 \cdot OEt_2$	1	51
3	1.2	$MgBr_2 \cdot OEt_2$	1	45
4	2	$MgBr_2 \cdot OEt_2$	0	65
5	2	$MgBr_2$	0	42
6	2	MgI_2	0	39

[a] Diastereomer ratio of **2a**: *syn*/*anti*=1.5:1.
[b] The reaction was performed with *i*-PrI to give **3a** (40% yield; *syn*/*anti*=2.8:1).

2.2. Conjugate reduction of aryl esters 1a–1l

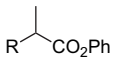
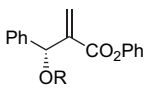
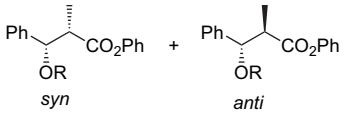
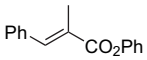
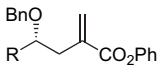
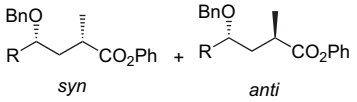
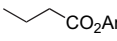
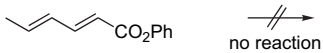
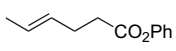
During the investigation on the diastereoselectivity in the alkyl radical addition to α-methylene-γ-oxycarboxylic acid esters,[6] we found, as mentioned above, that the reaction of phenyl ester **1a** with isopropyl iodide gave the conjugate reduction products **2a** (21%, *syn*/*anti*=1:1) together with radical adducts **3a** (40%, *syn*/*anti*=2.8:1) (Scheme 1 and Table 1, entry 1). The reaction of **1a** performed without isopropyl iodide gave **2a** in 51% yield with a diastereomer ratio *syn*/*anti*=1.5:1 (entry 2). Entry 3 shows that 2 equiv of *n*-Bu_3SnH are required to attain high yield. The reaction proceeded without Et_3B, a radical initiator, and gave **2a** in 65% yield (entry 4): this indicates that the conjugate reduction should proceed through an ionic mechanism. The Lewis acid $MgBr_2 \cdot OEt_2$ was indispensable for the reduction of **1a** and in fact, a complex mixture was yielded in the absence of the Lewis acid. The use of $MgBr_2$ or MgI_2 as Lewis acid gave **2a** in lower yield (entries 5 and 6). $Mg(ClO_4)_2$, $ZnCl_2$, $Yb(OTf)_3$, and $LiClO_4$ were ineffective. The reduction of **1a** using Ph_3SnH instead of *n*-Bu_3SnH did not proceed.

Under the optimized reaction conditions (Table 1, entry 4), we next carried out the reduction using various aryl acrylates **1b–1l** (Table 2). The reduction of phenyl acrylate (**1b**) gave **2b** in poor yield due to the dimerization of **1b** (entry 1). The yields in the reduction of α-substituted acrylates **1c**[15] and **1d**[6g] were 66 and 87%, respectively (entries 2 and 3), but β-hydroxy-α-methylenecarboxylic acid ester (Baylis–Hillman adduct) **1e**[8] afforded **2e** (*syn*/*anti*=2.2:1)[12] and the reductive dehydroxylation product **7**[16] in 25 and 21% yields, respectively (entry 4). In the case of the corresponding methoxymethyl (MOM) ether **1f**, α,β-unsaturated ester **7** was yielded exclusively in 96% yield (entry 5). The reduction of benzyl ethers **1g** and **1h**[6d] proceeded in good yields with high *syn*-selectivities (entries 6 and 7). In contrast to the methyl ether **1a** (Table 1), the benzyl ethers showed higher diastereoselectivity.

Although the reduction of α-substituted acrylates proceeded in moderate to high yields as mentioned above, the reduction of phenyl crotonate (**1i**)[15] was sluggish and gave **2i** in only 14% yield (entry 8). A longer reaction time (27 h) was required to increase the yield of **2i** (49%). *p*-Nitrophenyl crotonate (**1j**)[15] gave **2j** in 32% yield, but in this case only a slight increase of yield was observed even after 27 h of the reaction (entry 9). Further improvements were observed for the reduction of 2-naphthyl crotonate (**1k**),[15] although the reaction was not completed even after 27 h (entry 10). The reductions of aryl crotonates **1i–1k** (=non-terminal olefins) are very slow because the access to β-reaction center is hindered. The reduction of phenyl methacrylate (**1c**) with *n*-Bu_3SnD yielding β-deuterated product **2c** [$=CH_2D(CH_3)$-$CHCO_2Ph$] showed the β-attack of *n*-Bu_3SnD. With phenyl sorbate (**1l**), no reaction occurred (entry 11).

The semiempirical AM1 calculations of phenyl crotonate (**1i**) and ethyl crotonate showed that the lowest unoccupied molecular orbital (LUMO) energy of **1i** (−0.167 eV) is lower than that of ethyl crotonate (−0.008 eV).[10,17] Furthermore, the coordination of the carbonyl oxygen atom of phenyl acrylates to the Lewis acid lowers their LUMO energy. The synergistic effects lowering the LUMO energy of phenyl acrylates may accelerate the conjugate reduction. The higher reactivity of *p*-nitrophenyl crotonate (**1j**) and 2-naphthyl crotonate (**1k**) compared to phenyl crotonate (**1i**) is due to

Table 2. Conjugate reduction of aryl acrylates **1b–1l** with *n*-Bu_3SnH in the presence of $MgBr_2 \cdot OEt_2$

Entry	Substrate **1**	Product **2** (yield/%)	Other product (yield/%)
			
1	**1b** R=H	**2b** (25)	
2	**1c** R=Me	**2c** (66)	
3	**1d** R=$PhCH_2CH_2$	**2d** (87)	
			
4	**1e** R=H	**2e** (25; *syn*/*anti*=2.2:1)	**7** (21)
5	**1f** R=MOM	**2f** (0)	**7** (96)
			
6	**1g** R=*n*-C_7H_{15}	**2g** (87; *syn*/*anti*=18.0:1)	
7	**1h** R=Ph	**2h** (56; *syn*/*anti*=8.2:1)	
			
8	**1i** Ar=Ph	**2i** (14; conversion yield 37) (49)[a]	
9	**1j** Ar=*p*-$O_2NC_6H_4$	**2j** (32; conversion yield 38) (40)[a]	
10	**1k** Ar=1-naphthyl	**2k** (41; conversion yield 58) (74; conversion yield 84)[a]	
			
11	**1l**	**2l**	

[a] Reaction time: 27 h.

the next lowest unoccupied molecular orbital (next LUMO) energies of **1j** (−0.530 eV) and **1k** (−0.188 eV) being lower than the LUMO energy of phenyl crotonate (**1i**). The next LUMO's coefficients of **1j** and **1k** are localized in the crotonyl moiety, whereas their LUMO's coefficients are localized in the aryl moiety.

Table 3. Reduction of **4a** with *n*-Bu_3SnH in the presence of Lewis acid

Entry	Lewis acid (3 equiv)	Additive (equiv)	Yield of **5a** (%)
1	MgI_2[a]	—	76
2	MgI_2[b]	—	25
3	MgI_2[b]	LiI (0.1)	57
4	$MgBr_2 \cdot OEt_2$	—	44
5	$MgBr_2 \cdot OEt_2$	LiI (0.1)	72
6	$MgBr_2 \cdot OEt_2$	NaI (0.1)	71
7	$MgBr_2 \cdot OEt_2$	CuI (0.1)	38
8	$MgBr_2 \cdot OEt_2$	NaCl (0.03)	56
9	$MgBr_2 \cdot OEt_2$	NH_4Cl (0.5)	52
10	$MgBr_2 \cdot OEt_2$	KF (0.3)	25

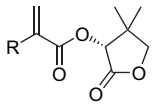
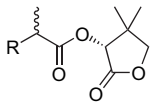
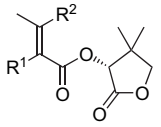
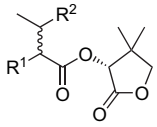
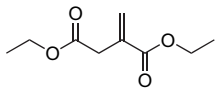
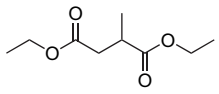
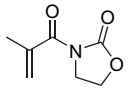
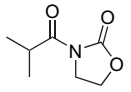
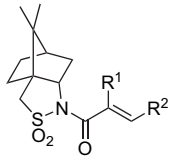
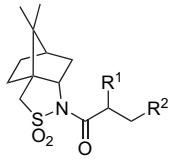
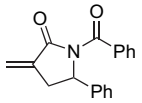
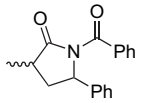
[a] Reserved in the laboratory for a long time.
[b] Newly purchased.

2.3. Conjugate reduction of pantolactone esters 4a–4f, diethyl itaconate (8) and amides 9–12

Furthermore, we recently found that the radical reaction of ester **4a** with isopropyl iodide gave the conjugate reduction product **5a** (39% yield) together with the adduct **6** (48% yield) (Scheme 1). This indicates that the conjugate reduction with tributyltin hydride would proceed even in the case of alkyl ester.

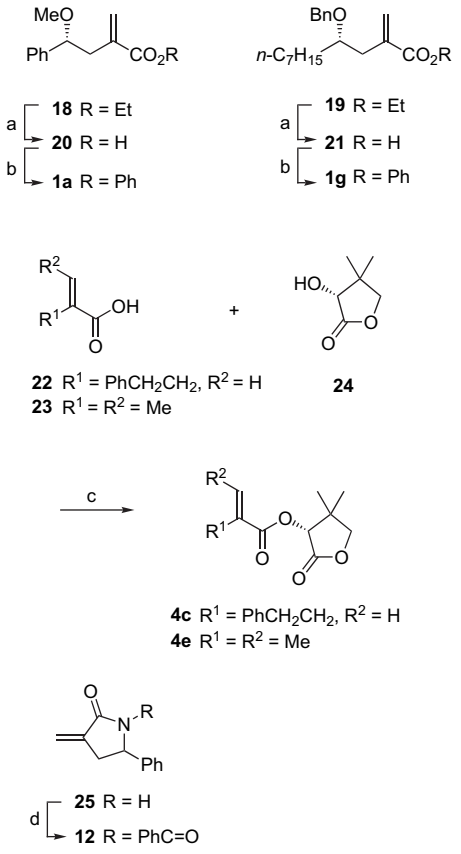
Although the reduction of **5a** with *n*-Bu_3SnH without Lewis acid did not proceed, the addition of 3 equiv of MgI_2 as Lewis acid gave the reduced product **5a** (Table 3, entries 1 and 2). However, the yields were not reproducible, i.e., the reaction of **4a** using MgI_2 reserved in the laboratory for a long time gave **5a** in 76% yield (entry 1), but the yield using newly purchased MgI_2 was only 25% (entry 2). We also found that the addition of LiI (0.1 equiv) enhanced the yield of **5a** to 57%. (entry 3) The yield using $MgBr_2 \cdot OEt_2$ (3 equiv) as Lewis acid instead of MgI_2 was reproducible, but the yield (44%) was not satisfactory (entry 4). As in the case of entry 3, the additional presence of LiI (0.1 equiv) enhanced the yield of **5a** to 72% yield (entry 5). NaI was also

Table 4. Conjugate reduction of **4a–4f** and **8–12** with *n*-Bu_3SnH in the presence of $MgBr_2 \cdot OEt_2$

Entry	Substrate	Additive (0.1 equiv)	Product (yield/%)
		⟶	
1	**4a** R=Me	—	**5a** (44)
2	**4a**	LiI	**5a** (72)
3	**4b** R=H	—	**5b** (4)
4	**4b**	LiI	**5b** (16)
5	**4c** R=$PhCH_2CH_2$	—	**5c** (43; dr=1:1)
6	**4c**	LiI	**5c** (53; dr=1:1)
		⟶	
7	**4d** R^1=R^2=H	—	**5d** (23)
8	**4d**	LiI	**5d** (49)
9	**4e** R^1=Me, R^2=H		**5e** (no reaction)
10	**4f** R^1=H, R^2=Me		**5f** (no reaction)
		⟶	
11	**8**	—	**13** (46)
12	**8**	LiI	**13** (89)
		⟶	
13	**9**	—	**14** (44)
14	**9**	LiI	**14** (38)
		⟶	
15	**10** R^1=H, R^2=Me	—	**15** (98)
16	**10**	LiI	**15** (78)
17	**11** R^1=Me, R^2=H	—	**16** (84)
18	**11**	LiI	**16** (72)
		⟶	
19	**12**	—	**17** (76; dr=6:1)
20	**12**	LiI	**17** (62; dr=6:1)

effective to increase the yield to 71% (entry 6). However, the additives such as CuI, NaCl, NH_4Cl, and KF were less effective (entries 7–10). The reaction proceeded even in the presence of radical scavenger TEMPO; this indicates that the reaction proceeded through ionic mechanisms.

Under the optimized reaction conditions (Table 3, entry 5), we next carried out the reduction using various α,β-unsaturated esters **4b–4f** and **8** and amides **9–12** (Table 4). The use of LiI as additive increased the yields of **5b–5d** (entries 1–8), although the yield of **5b** was poor (entry 3). Esters **4e** and **4f**



Scheme 2. Preparation of substrates **1a**, **1g**, **4c**, **4e**, and **12**. Reagents: (a) aqueous NaOH and then H^+; (b) *N*,*N*′-dicyclohexylcarbodiimide; (c) *N*,*N*′-dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine; (d) *n*-BuLi and then benzoyl chloride.

were not suitable for the reaction and the starting materials were recovered (entries 9 and 10) as in the case of the reduction of **1i**–**1k** (Table 2, entries 8–10). The reduction of diethyl itaconate (**8**) gave compound **13** in high yield in the presence of $MgBr_2 \cdot OEt_2$ and LiI (entries 11 and 12).

The yield of the reduction of amide **9** was moderate (entry 13). However, entries 15, 17, and 19 show that the reduction of camphorsultams **10**[18,19] and **11**[19,20] and lactam **12**[21] gave the corresponding saturated compounds **15**–**17**[18] in high yields, respectively. In contrast to the conjugate reductions of α,β-unsaturated esters, the addition of LiI lowered the yields of the amide reduction (entries 14, 16, 18, and 20). In the reduction of phenyl methacrylate **1c**, the addition of LiI also lowered the yield to 57% (cf. Table 2, entry 2).

Finally, we confirmed the seven-membered chelate ring formation of **4a** by the complexation experiment with $MgBr_2 \cdot OEt_2$ in $CDCl_3$.[6d] The large difference of chemical shift increments $\Delta\delta_1$ values [δ_H (substrate+$MgBr_2 \cdot OEt_2$)−δ_H (substrate)] suggests the formation of bidentate complexation as shown in Figure 1. Furthermore, the additive of LiI (0.1 equiv) lowered the chemical shift of the methine proton α to lactone carbonyl, see: $\Delta\delta_2$ value [δ_H (substrate+$MgBr_2 \cdot OEt_2$+LiI)−δ_H (substrate)] shown in parenthesis of Figure 1. The chelate ring formation lowered the LUMO energy of **4a** and consequently accelerated the conjugate reduction. In the case of diethyl itaconate (**8**),

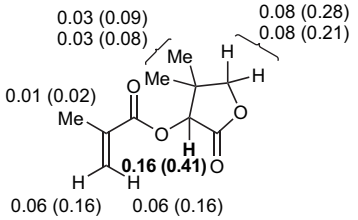


Figure 1. $\Delta\delta_1$ and $\Delta\delta_2$ (in parenthesis) for substrate **4a**: $\Delta\delta_1$ (ppm)=δ_H (substrate **4a**+3 equiv of $MgBr_2 \cdot OEt_2$)−δ_H (substrate **4a**) and $\Delta\delta_2$ (ppm)=δ_H (substrate **4a**+3 equiv of $MgBr_2 \cdot OEt_2$+0.1 equiv of LiI)−δ_H (substrate **4a**). The $\Delta\delta_1$ and $\Delta\delta_2$ values were obtained after sonication of **4a** with $MgBr_2 \cdot OEt_2$ (and LiI) in $CDCl_3$.

however, the addition of LiI did not affect the chemical shift values, i.e., $\Delta\delta_1$ and $\Delta\delta_2$ values were identical, although the yield of **5a** was increased by addition of LiI (Table 4, entries 11 and 12).

3. Conclusion

In conclusion, the phenyl esters of α-substituted acrylic acids were reduced with tributyltin hydride in the presence of magnesium bromide diethyl etherate to give the corresponding saturated esters in moderate to high yields. The LUMO energies of phenyl acrylates are lower than those of the corresponding alkyl acrylates. Furthermore, the coordination of the carbonyl oxygen atom of phenyl acrylates to the Lewis acid lowers their LUMO energies. In the reduction of pantolactone esters of acrylic acids and diethyl itaconate, the chelate ring formation of the ester carbonyl oxygens with Mg may lower their LUMO energies. In this case, the addition of LiI increased the yields. Although aryl esters of β-substituted acrylic acids were less reactive, the reduction of *N*-crotonylcamphorsultam proceeded in excellent yield.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a JEOL GSX-270 (270 MHz) or GSX-400 (400 MHz) spectrometer with $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on the instruments operating at 67.8 or 100 MHz with $CDCl_3$ as a solvent and internal standard (δ 77.0). Mass spectra (EI, 70 eV) were obtained on a JEOL JMS-700 mass spectrometer. IR spectra were taken on a SHIMADZU FTIR-8700 spectrometer. Melting points were determined with a Yanaco micro melting point apparatus. For thin layer chromatography (TLC) analysis, Merck precoated plates (silica gel 60 F_{254}) were used. Visualization was accomplished by UV light and cerium(IV) sulfate, potassium permanganate or molybdophosphoric acid. Products were purified by flash column chromatography using Kanto silica gel 60 (spherical neutral).

4.2. Preparation of substrates for conjugate reduction

4.2.1. 2-(2-Methoxy-2-phenylethyl)propenoic acid (20). To a stirred solution of ethyl ester **18** (449 mg, 1.92 mmol) in ethanol (19 cm^3) was added 1 mol dm^{-3} NaOH (4 cm^3).

The solution was heated under reflux for 3 h and then cooled to room temperature. Water (19 cm^3) was added and then 1 mol dm^{-3} hydrochloric acid was added until the aqueous solution remained acidic (pH 4). The product was extracted with ethyl acetate and the combined organic layers were washed with water and brine. The organic solution was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography [eluant: hexane–ethyl acetate (3:1)] to afford carboxylic acid **20** (385 mg, 97%) as a colorless solid. Mp 74.5–77.6 °C (from Et_2O–hexane); IR (neat) 1696, 1467, 1378, 1111, 1008, 952, 911, 845, 763, 704 cm^{-1}; ^1H NMR (270 MHz) δ 7.36–7.29 (5H, m, Ph), 6.33 (1H, d, J=1 Hz, =C*H*H), 5.61 (1H, d, J=1 Hz, =CH*H*), 4.39 (1H, dd, J=8.2, 5.3 Hz, C*H*OCH_3), 3.23 (3H, s, OCH_3), 2.79 (1H, dd, J=14.2, 8.2 Hz, C*H*H), 2.63 (1H, dd, J=14.2, 5.3 Hz, CH*H*); ^{13}C NMR (67.8 MHz) δ 172.1, 141.1, 136.2, 130.0, 128.3, 127.6, 126.6, 82.3, 56.8, 40.6; MS m/z 191 (M^+−Me, 10%), 135 (78), 121 (100), 105 (27), 91 (46), 77 (53); HRMS calcd for $C_{11}H_{11}O_3$ (M^+−Me) 191.0708, found 191.0702.

4.2.2. Phenyl 2-(2-methoxy-2-phenylethyl)propenoate (1a). To a stirred solution of *N*,*N*′-dicyclodihexylcarbodiimide (365 mg, 1.77 mmol) in dichloromethane (15 cm^3) were added successively carboxylic acid **19** (302 mg, 1.47 mmol) and phenol (420 mg, 4.46 mmol). The reaction mixture was stirred at room temperature for 3 days. The resulting precipitate of *N*,*N*′-dicyclohexylurea was filtered and the filtrate was evaporated in vacuo. Ether was added to the residue. The insoluble *N*,*N*′-dicyclohexylurea was further eliminated by filtration and the filtrate was washed successively with 0.5 mol dm^{-3} hydrochloric acid, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel [eluant: hexane–ethyl acetate (40:1)] to afford phenyl ester **1a** (260 mg, 63%) as an oil. IR (neat) 2918, 2829, 1737, 1637, 1592, 1488, 1455, 1334, 1308, 1200, 1123, 1096, 956, 807, 748, 696 cm^{-1}; ^1H NMR (270 MHz) δ 7.38–7.07 (10H, m, Ph×2), 6.41 (1H, d, J=1 Hz, =C*H*H), 5.71 (1H, d, 1 Hz, =CH*H*), 4.44 (1H, dd, J=8.1, 4.9 Hz, C*H*OCH_3), 3.23 (3H, s, OCH_3), 2.87 (1H, dd, J=14, 8 Hz, C*H*H), 2.62 (1H, dd, J=14, 4 Hz, CH*H*); ^{13}C NMR (67.8 MHz) δ 165.41, 150.7, 141.3, 136.4, 129.2, 129.1, 128.3, 127.6, 126.6, 125.6, 121.5, 82.2, 56.8, 41.0; MS m/z 251 (M^+−OMe, 1%), 189 (100), 157 (39), 129 (58), 121 (92); HRMS calcd for $C_{17}H_{15}O_2$ (M^+−OMe) 251.1072, found 251.1078.

4.2.3. Phenyl 2-(methoxymethoxyphenylmethyl)propenoate (1f). ^1H NMR (400 MHz) δ 7.43–6.96 (10H, m, Ph×2), 6.60 (1H, d, J=1.2 Hz, =C*H*H), 6.16 (1H, d, J=1.2 Hz, =CH*H*), 5.67 (1H, s, CH), 4.69 (1H, d, J=6.3 Hz, C*H*H), 4.65 (1H, d, J=6.3 Hz, CH*H*), 3.37 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 164.1, 150.4, 140.8, 139.0, 129.3, 128.3, 128.0, 127.8, 126.7, 125.7, 121.4, 94.3, 75.2, 55.8; MS m/z 237 (M^+−CH_2OCH_3, 10%), 205 (23), 175 (100), 116 (30), 115 (93); HRMS calcd for $C_{16}H_{13}O_2$ (M−CH_2OCH_3) 237.0916, found 237.0944.

4.2.4. Ethyl 2-(2-benzyloxynonyl)propenoate (19). To a solution of ethyl 2-(2-hydroxynonyl)propenoate (2.49 g, 10.3 mmol), prepared from octanal and ethyl 2-bromomethylpropenoate following the procedures reported (Ref. 6d), in cyclohexane–dichloromethane (2:1; 111 cm^3) cooled to 0 °C were added successively benzyl 2,2,2-trichloroacetimidate (3.85 cm^3, 20.7 mmol) and trifluoromethanesulfonic acid (0.73 cm^3, 8.25 mmol) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 0.5 h. After dilution with diethyl ether, the solution was washed successively with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography [eluant: hexane–ethyl acetate (30:1) and then hexane–diethyl ether (30:1)] to afford **19** (2.43 g, 73% yield) as an oil. IR (neat) 1715, 1185, 1096, 1022, 941, 811, 732, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.36–7.24 (5H, m, Ph), 6.21 (1H, d, J=1.6 Hz, =CIH), 5.62 (1H, d, J=1.6 Hz, =CH*H*), 4.53 (1H, d, J=11.6 Hz, OC*H*HPh), 4.49 (1H, d, J=11.6 Hz, OCH*H*Ph), 4.18 (2H, q, J=7.2 Hz, CO_2CH_2), 3.57 (1H, m, C*H*OBn), 2.61 (1H, ddd, J=14.0, 6.8, 0.8 Hz, C*H*HCHOBn), 2.43 (1H, dd, J=14.0, 8.4, 1.2 Hz, CH*H*CHOBn), 1.47 (2H, m, CH_2), 1.28 (3H, t, J=7.2 Hz, CH_3), 1.25 (10H, m, $(CH_2)_5$), 0.88 (3H, d, J=6.8 Hz, C*H*$_3$); ^{13}C NMR (100 MHz) δ 167.1, 138.8, 137.7, 128.2, 127.7, 127.3, 127.1, 77.7, 71.2, 60.7, 37.3, 34.1, 31.9, 29.7, 29.3, 25.4, 22.7, 14.3, 14.2; MS m/z 332 (M^+, 4%), 226 (24), 220 (8), 219 (47), 158 (31), 130 (36), 127 (18), 115 (11), 92 (41), 91 (100); HRMS calcd for $C_{21}H_{32}O_3$ (M^+) 332.2351, found 332.2363.

4.2.5. 2-(2-Benzyloxynonyl)propenoic acid (21). To a stirred solution of the ethyl ester **19** (2.30 g, 6.92 mmol) in ethanol (70 cm^3) was added aqueous NaOH (1 mol dm^{-3}; 15 cm^3). The solution was heated under refluxed for 4 h and then water (35 cm^3) was added. Dilute hydrochloric acid (1 mol dm^{-3}) was added until the aqueous solution remained acidic (pH 4). This solution was extracted with ethyl acetate and the extract was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography [eluant: hexane–ethyl acetate (15:1)] to afford carboxylic acid **21** (1.89 g, 90% yield) as an oil. IR (neat) 1696, 1630, 1455, 1303, 1226, 1092, 1066, 952, 822, 730, 696 cm^{-1}; ^1H NMR (400 MHz) δ 7.33–7.24 (5H, m, Ph), 6.36 (1H, s, =C*H*H), 5.74 (1H, s, =CH*H*), 4.53 (2H, s, OCH_2Ph), 3.60 (1H, m, C*H*OBn), 2.59 (1H, dd, J=14.0, 6.8 Hz, C*H*HCHOBn), 2.50 (1H, dd, J=14.0, 5.6 Hz, CH*H*CHOBn), 1.60–1.26 (12H, m, $(CH_2)_6$), 0.88 (3H, t, J=6.8 Hz, CH_3); ^{13}C NMR (100 MHz) δ 171.8, 138.3, 137.0, 129.7, 128.2, 127.8, 127.5, 77.8, 71.3, 36.9, 34.0, 31.9, 29.7, 29.3, 25.3, 22.7, 14.2; MS m/z 304 (M^+, 2%), 286 (10), 219 (40), 130 (27), 127 (18), 107 (46), 105 (10), 92 (67), 91 (100); HRMS calcd for $C_{19}H_{28}O_3$ (M^+) 304.2038, found 304.2054.

4.2.6. Phenyl 2-(2-benzyloxynonyl)propenoate (1g). To a stirred solution of **21** (217 mg, 0.71 mmol) in dichloromethane were added successively *N*,*N*′-dicyclohexylcarbodiimide (180 mg, 0.87 mmol) and phenol (140 mg, 1.49 mmol). The reaction mixture was stirred at room temperature for 3 days. After work-up as described above, the crude product was purified by column chromatography on silica gel [eluant: hexane–ethyl acetate (40:1)] to afford

phenyl ester **1g** (208 mg, 77%) as an oil. IR (neat) 3031, 2926, 2856, 1733, 1634, 1592, 1495, 1455, 1326, 1200, 1163, 1069, 1028, 948, 914, 859, 809, 746, 690 cm^{-1}; ^1H NMR (400 MHz) δ 7.39–7.04 (10H, m, Ph×2), 6.45 (1H, d, J=1.6 Hz, =C*H*H), 5.82 (1H, d, J=1.6 Hz, =CH*H*), 4.56 (1H, d, J=11.6 Hz, OC*H*HPh), 4.53 (1H, d, J=11.6 Hz, OCH*H*Ph), 3.65 (1H, m, C*H*OBn), 2.69 (1H, dd, J=14.0, 6.8 Hz, C*H*H), 2.61 (1H, dd, J=14.0, 5.2 Hz, CH*H*), 1.63–1.18 (12H, m, $(CH_2)_6$), 0.88 (3H, t, J=6.8 Hz, CH_3); ^{13}C NMR (100 MHz) δ 165.6, 150.7, 138.6, 137.1, 129.3, 128.9, 128.2, 127.8, 127.4, 125.7, 121.5, 77.7, 71.2, 37.3, 34.1, 31.9, 29.7, 29.3, 25.4, 22.7, 14.2; MS m/z 287 (M^+−OPh, 20%), 219 (10), 159 (21), 91 (100); HRMS calcd for $C_{19}H_{27}O_2$ (M^+−OPh) 287.2011, found 287.2010.

4.2.7. 4,4-Dimethyl-2-oxotetrahydrofuran-3-yl 2-phenethylpropenoate (4c). To a solution of pantolactone (346 mg, 2.7 mmol) in dry dichloromethane (10 cm^3) were added 4-(dimethylamino)pyridine (29 mg) and 2-phenethylpropenoic acid (417 mg, 2.4 mmol), obtained by hydrolyzing ethyl phenethylpropenoate[6g] as described for the preparation of **19**. The mixture was cooled to 0 °C and *N*,*N*′-dicyclohexylcarbodiimide (580 mg, 2.8 mmol) was added. The mixture was stirred at room temperature for 16 h. Ethyl acetate was added and the resulting precipitate of *N*,*N*′-dicyclohexylurea was eliminated by filtration and the filtrate was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give **4c** (394 mg, 58%) as a colorless solid. Mp 49.5–50.5 °C (from hexane); IR (KBr) 1799, 1717, 1634, 1456, 1308, 1251, 1137, 1079, 1009, 957, 754, 703 cm^{-1}; ^1H NMR (400 MHz) δ 7.32–7.16 (5H, m, Ph), 6.29 (1H, s, =CH*H*), 5.64 (1H, s, =CH*H*), 5.46 (1H, s, COOC*H*), 4.08 (1H, d, J=9.3 Hz, C*H*HO), 4.06 (1H, d, J=9.3 Hz, CH*H*O), 2.83 (2H, t, J=7.8 Hz, PhCH_2), 2.67 (2H, t, J=7.8 Hz, CH_2), 1.24 (3H, s, CH_3), 1.15 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 172.2, 165.5, 141.0, 138.5, 128.4, 128.3, 127.4, 126.0, 76.2, 75.2, 40.4, 34.8, 33.9, 23.1, 20.1; MS m/z 288 (M^+, 2%), 158 (84), 91 (100); HRMS calcd for $C_{17}H_{20}O_4$ (M^+) 288.1362, found 288.1390.

4.2.8. 4,4-Dimethyl-2-oxotetrahydrofuran-3-yl 2-methyl-2-butenoate (4e). Using the procedure as described above, pantolactone (853 mg, 6.6 mmol) was esterified with (*E*)-2-methyl-2-butenoic acid (598 mg, 6.0 mmol) to give **4e** (982 mg, 77%) as a colorless oil. IR (neat) 1791, 1723, 1653, 1249, 1132, 1096, 794 cm^{-1}; ^1H NMR (400 MHz) δ 7.01 (1H, qq, J=6.8, 1.4 Hz, =CH), 5.45 (1H, s, COOC*H*), 4.07 (1H, d, J=8.8 Hz, C*H*HO), 4.06 (1H, d, J=8.8 Hz, CH*H*O), 1.89 (3H, br s, =CCH_3), 1.84 (3H, dq, J=6.8, 1.4 Hz, =CCH_3), 1.22 (3H, s, CH_3), 1.14 (3H, s, CH_3); MS m/z 212 (M^+, 7%), 83 (100), 82 (95); HRMS calcd for $C_{11}H_{16}O_4$ (M^+) 212.1049, found 212.1013.

4.2.9. 1-Benzoyl-3-methylene-5-phenylpyrrolidin-2-one (12). Mp 161.0–161.4 °C (from diethyl ether–hexane); IR (KBr) 1722, 1683, 1652, 1294, 1254, 1202, 1160, 1017, 954, 866, 812, 746, 699 cm^{-1}; ^1H NMR (400 MHz) δ 7.66–7.26 (10H, m, Ph×2), 6.27 (1H, t, J=2.4 Hz, =C*H*H), 5.59 (1H, t, J=2.4 Hz, =CH*H*), 5.48 (1H, dd, J=8.7, 4.8 Hz, C*H*Ph), 3.34 (1H, ddt, J=17.0, 8.7, 2.4 Hz, C*H*H), 2.81 (1H, m, CH*H*); ^{13}C NMR (100 MHz) δ 170.9, 167.2, 141.7, 138.7, 134.3, 132.2, 128.95, 128.87, 127.9, 127.8, 125.7, 121.3, 57.9, 34.3; MS m/z 277 (M^+, 11%), 172 (100), 105 (74), 77 (41); HRMS calcd for $C_{18}H_{15}NO_2$ (M^+) 277.1103, found 277.1088.

4.3. Conjugate reduction

General procedure: to a solution of α,β-unsaturated ester in dry dichloromethane (0.1 mol dm^{-3}) was added $MgBr_2 \cdot OEt_2$ (3 equiv) under N_2 atmosphere. After being stirred at room temperature for 15 min, the reaction mixture was cooled to 0 °C, and Bu_3SnH (2 equiv) was added. The mixture was stirred at 0 °C for 5 h. Then KF and water were added and the mixture was stirred at room temperature for 3 h. After filtration through a pad of Florisil, the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel to afford corresponding reduction product.

4.3.1. Phenyl 2-methyl-4-phenylbutanoate (2d). IR (neat) 2978, 2934, 2851, 1757, 1593, 1493, 1457, 1382, 1195, 1159, 1137, 1110, 915, 748, 689 cm^{-1}; ^1H NMR (400 MHz) δ 7.38–7.06 (10H, m, Ph×2), 2.73 (3H, m, CH_2Ph, C*H*CO_2Ph), 2.16 (1H, m, C*H*HCH_2Ph), 1.86 (1H, m, CH*H*CH_2Ph), 1.34 (3H, d, J=7.1 Hz, CH_3); ^{13}C NMR (100 MHz) δ 174.8, 150.6, 141.3, 129.3, 128.4, 128.3, 125.9, 125.6, 121.4, 39.2, 35.4, 33.5, 17.2; MS m/z 161 (M^+−OPh, 51%), 133 (14), 91 (100); HRMS calcd for $C_{11}H_{13}O$ (M^+−OPh) 161.0966, found 161.0938.

4.3.2. Phenyl (*E*)-2-methyl-3-phenylpropenoate (7). ^1H NMR (400 MHz) δ 7.93 (1H, s, =CH), 7.49–7.15 (10H, m, Ph×2), 2.24 (3H, d, J=1.0 Hz, CH_3); ^{13}C NMR (100 MHz) δ 167.1, 151.0, 140.5, 135.5, 129.7, 129.3, 128.6, 128.4, 127.7, 125.6, 121.6, 14.3; MS m/z 238 (M^+, 4%), 145 (100), 117 (80), 115 (54); HRMS calcd for $C_{16}H_{14}O_2$ (M^+) 238.0994, found 238.1019.

4.3.3. Phenyl *syn*-4-benzyloxy-2-methylundecanoate (*syn*-2g). IR (neat) 3037, 2926, 2855, 1757, 1593, 1493, 1455, 1382, 1352, 1200, 1159, 1119, 1068, 745, 690 cm^{-1}; ^1H NMR (400 MHz) δ 7.37–6.96 (10H, m, Ph×2), 4.55 (1H, d, J=11.6 Hz, OC*H*HPh), 4.47 (1H, d, J=11.6 Hz, OCH*H*Ph), 3.53 (1H, m, C*H*OBn), 3.00 (1H, m, C*H*HCHOBn), 2.04 (1H, m, CH*H*CHOBn), 1.55–1.27 (12H, m, $(CH_2)_6$), 1.33 (3H, d, J=6.8 Hz, CH_3), 0.88 (3H, t, J=6.0 Hz, CH_3); ^{13}C NMR (100 MHz) δ 175.1, 150.7, 138.6, 129.2, 128.3, 128.0, 127.5, 125.5, 121.5, 77.2, 71.3, 39.6, 36.2, 33.9, 31.9, 29.8, 29.3, 25.2, 22.7, 18.3, 14.2; MS m/z 289 (M^+−OPh, 92%), 184 (59), 150 (52), 91 (100); HRMS calcd for $C_{19}H_{29}O_2$ (M^+−OPh) 289.2168, found 289.2185.

4.3.4. Phenyl 4-benzyloxy-2-methyl-4-phenylbutanoate (2h). IR (neat) 3063, 3030, 2970, 2871, 1755, 1593, 1495, 1455, 1381, 1195, 1167, 1107, 1067, 1027, 915, 747, 691 cm^{-1}; MS m/z 267 (M^+−OPh, 93%), 189 (21), 184 (29), 175 (19), 131 (18), 105 (16), 91 (100); HRMS calcd for $C_{18}H_{19}O_2$ (M^+−OPh) 267.1385, found 267.1364.

syn-**2h**: ^1H NMR (400 MHz) δ 7.39–6.95 (15H, m, Ph×3), 4.51 (1H, dd, J=9.6, 3.6 Hz, C*H*OBn), 4.46 (1H, d, J=11.6 Hz, OC*H*HPh), 4.27 (1H, d, J=11.6 Hz, OCH*H*Ph),

3.05 (1H, m, C*H*CO_2), 2.15 (1H, ddd, *J*=14.0, 9.6, 3.6 Hz, C*H*H), 2.02 (1H, ddd, *J*=14.0, 9.6, 4.0 Hz, CH*H*), 1.33 (3H, d, *J*=7.2 Hz, CH_3); ^{13}C NMR (100 MHz) δ 174.8, 150.7, 141.9, 138.1, 129.2, 128.5, 128.3, 128.0, 127.7, 127.5, 126.5, 125.5, 121.5, 79.2, 70.8, 42.5, 36.4, 17.9.

anti-**2h**: ^{13}C NMR (100 MHz) δ 174.9, 150.7, 141.7, 138.1, 129.2, 128.5, 128.3, 127.8, 127.7, 127.5, 126.7, 125.5, 121.5, 79.0, 70.4, 42.1, 37.2, 17.3.

4.3.5. 4,4-Dimethyl-2-oxotetrahydrofuran-3-yl 2-methylpropenoate (5a). IR (neat) 1791, 1750, 1471, 1372, 1147, 1014, 997 cm^{-1}; ^{1}H NMR (400 MHz) δ 5.36 (1H, s, COOC*H*), 4.05 (1H, d, *J*=8.8 Hz, C*H*HO), 4.03 (1H, d, *J*=8.8 Hz, CH*H*O), 2.73 (1H, septet, *J*=7.3 Hz, C*H*$(Me)_2$), 1.24 (6H, d, *J*=7.3 Hz, CH$(Me)_2$), 1.20 (3H, s, CH_3), 1.12 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ 175.7, 172.3, 76.2, 74.6, 40.2, 33.9, 23.1, 19.9, 19.1, 18.8; MS *m*/*z* 201 (M^+, 51%), 71 (100); HRMS calcd for $C_{10}H_{16}O_4$ (M^+) 200.1049, found 200.1043.

4.3.6. Diastereomeric mixture (1:1) of 4,4-dimethyl-2-oxotetrahydrofuran-3-yl 2-methyl-4-phenylbutanoate (5c). IR (neat) 1799, 1717, 1456, 1373, 1275, 1251, 1137, 1079, 1009, 958, 754, 703 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.32–7.16 (5H, m, Ph), 5.40 (1H, s, COOC*H*), 4.06 (1H, d, *J*=8.8 Hz, C*H*HO), 4.04 (1H, d, *J*=8.8 Hz, CH*H*O), 2.73–2.60 (3H, m, PhCH_2, C*H*Me), 2.08 (1H, m, PhCH_2C*H*H), 1.80 (1H, m, PhCH_2CH*H*), [1.27 (d, *J*=6.8 Hz) and 1.26 (d, *J*=7.3 Hz), 3H, Me], [1.22 (s) and 1.21 (s), 3H, CH_3], 1.12 (3H, s, CH_3); ^{13}C NMR (100 MHz) δ (175.2, 175.1), 172.2, (141.36, 141.30), (128.40, 128.37, 128.33), (125.94, 125.87), (76.15, 76.12), (74.72, 74.70), 40.2, 39.1, 38.7, (35.42, 35.37), (33.43, 33.23), 23.1, (20.06, 20.01), (17.27, 17.22); MS *m*/*z* 290 (M^+, 3%), 186 (100), 131 (45), 91 (79); HRMS calcd for $C_{17}H_{22}O_4$ (M^+) 290.1518, found 290.1513.

4.3.7. *N*-(2-Methylpropanoyl)bornane-10,2-sultam (16). Mp 133–134 °C (from diethyl ether–hexane); ^{1}H NMR (400 MHz) δ 3.89 (1H, dd, *J*=6.8, 5.9 Hz, NCH), 3.50 (1H, d, *J*=14.0 Hz, C*H*HSO_2), 3.44 (1H, d, *J*=14.0 Hz, CH*H*SO_2), 3.18 (1H, septet, *J*=6.8 Hz, –C*H*$(Me)_2$), 2.10–2.00 (2H, m, CH_2), 1.95–1.83 (3H, m, CH_2, CH), 1.45–1.30 (2H, m, CH_2), 1.22 (3H, d, *J*=6.8 Hz, Me), 1.17 (3H, s, Me), 1.16 (3H, s, Me), 0.98 (3H, s, Me); ^{13}C NMR (100 MHz) δ 176.7, 65.1, 53.1, 48.3, 47.7, 44.6, 38.5, 34.7, 32.9, 26.5, 20.9, 20.7, 19.9, 18.0; MS *m*/*z* 285 (M^+, 14%), 221 (23), 178 (21), 152 (37), 134 (55), 108 (32), 71 (100); HRMS calcd for $C_{14}H_{23}NO_3S$ (M^+) 285.1439, found 285.1401.

4.3.8. 1-Benzoyl-3-methyl-5-phenylpyrrolidin-2-one (17). MS *m*/*z* 279 (M^+, 22%), 124 (100), 105 (95), 77 (53); HRMS calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1260, found 279.1249.

Major diastereomer: mp 180 °C (from diethyl ether–hexane); ^{1}H NMR (400 MHz) δ 7.73–7.22 (10H, m, Ph×2), 5.25 (1H, m, C*H*Ph), 2.79–2.64 (2H, m, CH_2), 1.73 (1H, m, C*H*Me), 1.34 (3H, d, *J*=6.8 Hz, Me).

Minor diastereomer: ^{1}H NMR (400 MHz) δ 7.64–7.24 (10H, m, Ph×2), 5.57 (1H, dd, *J*=8.3, 2.9 Hz, C*H*Ph), 2.94 (1H, m, C*H*Me), 2.36–2.21 (2H, m, CH_2), 1.25 (3H, d, *J*=7.3 Hz, Me).

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