Diastereoselective Alkylation of 8-Phenylmenthyl Phenylacetate: Aggregated Lithium Enolate *versus* "Naked" Enolate

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It is shown that monoalkylation of 8-phenylmenthyl phenylacetate using lithiated bases leads to poor or no diastereoselectivities (50/50 to 69/31) and high yields (75 to 98%) while alkylation using tBu-P4 (a strong and cation free base, known to provide "naked" anion) leads to high diastereoselectivities (92/8 to 98/2) and high yields (65 to 95%). It is postulated that, in the case of phenylacetates, the degree of aggregation of the lithium enolate is responsible of the poor diastereoselectivities.

Although the synthesis of 2-arylpropionic acids has received considerable attention,[1] only a few studies have been devoted to asymmetric synthesis[2,3] and especially to the alkylation of arylacetic esters.[4] We report here our results concerning the influence of the base upon the asymmetric alkylation of 8-phenylmenthyl phenylacetate (**2**) (Scheme 1) as a three-step route to 2-phenylpropionic acid and analogues.

Assignments of Configurations of Diastereomers 3(a–e)I and 3(a–e)II. The *R* configuration at carbon C2 of diastereomers **3aI** (δH2 = 3.37 ppm, q)[5] and **3bI** (δH2 = 3.15 ppm, t)[5] was determined from the known configurations of the corresponding alcohols obtained: *R*-**5a** (+) neat[6a] and *R*-**5b** (−) benzene[6b] (Scheme 1). In compounds **3c**, **3d**, and **3e**, the same *R* configuration at carbon C2 has been assigned to diastereomers **I** on the basis of similar deshielding of the H2 signals in these diastereomers **I** as compared with diastereomers **II**.[7]

The **I/II** ratios have been determined on crude products using ^{1}H NMR (200 MHz) and the methine H2 signal. In the case of compound **3e** the H2 signal of diastereomer **II** overlaps with the signal of one proton of the CH_2C= group; the ratio was thus determined using the methine H2 signal of **I** and the total signal (**I** + **II**) of the methine H1′ of the ring (a well-isolated double triplet at 4.75 ppm).

Results

8-Phenylmenthyl phenylacetate (**2**) was obtained in 95% yield from phenylacetic acid and (−)-8-phenylmenthol (**I**) using DCC/DMPA in CH_2Cl_2. Alkylations of the enolates were performed with various alkylating agents and the results are given in Tables 1 and 3.

In spite of the fact that kinetic bases[8] and kinetic conditions were used, alkylation of the lithium enolate with MeI led to poor or no diastereoselectivitiy (Table 1, entries 1–8).

Although the diastereoselectivity was poor, the most suitable base for alkylation with MeI in ether and/or THF appeared to be tBuLi with 20% de (Table 1, entry 5). When nBuLi was used as base, there was no diastereoselectivity with MeI but 35% to 38% with EtI, $PhCH_2Br$, $EtOCOCH_2Br$, and CH_2=$CHCH_2Br$ (Table 1, entries 10–13). When Me_2SO_4 was used as alkylating agent, the diastereoselectivity increased to 66% but the yield was poor (37%) even at −30 °C.

It must be noted that no ketone and/or tertiary alcohol (corresponding to reaction of the base with the ester function) were observed with BuLi, but precooled BuLi had to be used.

Isomerization of compound **3a** (Table 2) led to an inversion and a slight increase of the diastereoselectivity which, nevertheless, remained in the range 34–40% and is not synthetically useful although the major *S* configurational isomer is the desired, bioactive isomer.

It is worth noting that upon addition of DMPU[9] (Table 1, entry 4), the diastereoselectivity increased up to 60% (80/20), thus hinting that a decrease in the degree of aggregation could increase the diastereoselectivity. Starting from this hypothesis we decided to use a PN Schwessinger base[10] which would generate a "naked" nonaggregated enolate.

The results are gathered in Table 3. Very interestingly it was found that monoalkylation with almost complete diastereoselectivity (98/2) and high yield (95 to 80%) was obtained upon alkylation with EtI and CH_2=$CHCH_2Br$. Methylation could be performed in high yield (80%) and with a high diastereoselectivity (92/8) by using Me_2SO_4,[11] and only 8% of dialkylation was observed.[12a] Although 15 and 20% dialkylation have been obtained with $PhCH_2Br$ and $EtOCOCH_2Br$, respectively, monoalkylation was preferred and occurred with almost complete diastereoselectivity.[12b] Dialkylated compound **4d** was isolated and identified (*cf.* Experimental Section).

We found recently[13] that under the same alkylation conditions (−78 °C, THF), it was not possible to form

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(2) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. I.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650.

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(5) **3aII**: δH2 = 2.77 ppm (q); $\Delta\delta$(**3aI-3aII**) = 0.6 ppm. **3bII**: δH2 = 2.60 ppm (t); $\Delta\delta$(**3bI-3bII**) = 0.55 ppm.

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(7) δH2: **3cI**, 3.58 ppm (t); **3cII**, 3.10 ppm (t); $\Delta\delta$(**I-II**) = 0.48 ppm. δH2: **3dI**, 3.75 ppm (dd); **3dII**, 3.45 ppm (dd); $\Delta\delta$(**I-II**) = 0.30 ppm. δH2: **3eI**, 3.30 ppm (t); **3eII**, 2.73 ppm (t); $\Delta\delta$(**I-II**) = 0.57 ppm.

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(10) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837 and included references.

(11) The tBu-P4 base undergoes methylation with MeI. Thus, it cannot be used for methylation.

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Scheme 1

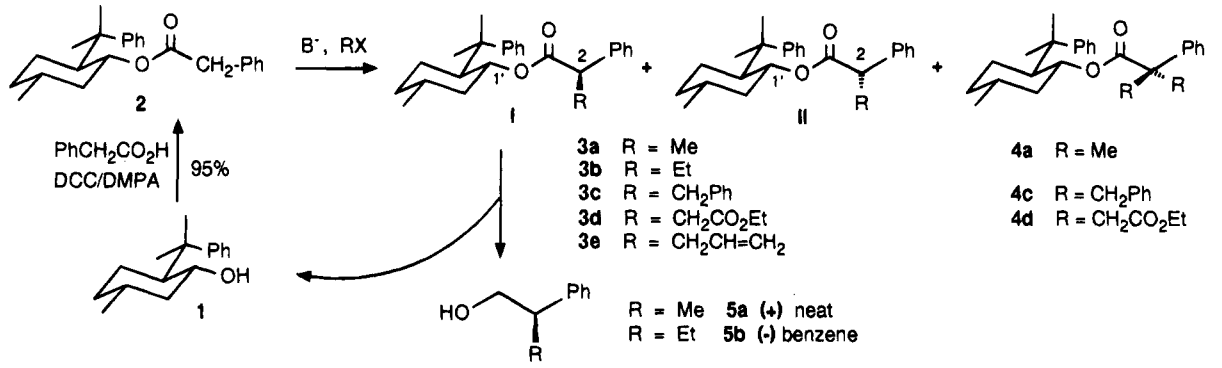


Table 1. Alkylation of Ester 2

RX	base	t, °C	solvent	prodt	yield,[a] %	I/II
MeI	LTHP	−50	THF	**3a**	98	52/48
MeI	LDA	−50	THF	**3a**	95	50/50
MeI	LDA	−50	Et_2O	**3a**	72	46/54
MeI	LDA	−50	THF/DMPU	**3a**	90	80/20
MeI	tBuLi	−50	THF	**3a**	96	60/40
MeI	tBuLi	−50	Et_2O	**3a**	47	48/52
MeI	BuLi	−50	THF	**3a**	75	51/49
MeI	BuLi	−50	Et_2O	**3a**	70	50/50
Me_2SO_4	BuLi	−30	THF	**3a**	37	83/17
EtI	BuLi	−50	THF	**3b**	75	67/32
$PhCH_2Br$	BuLi	−50	THF	**3c**	93	69/31
$EtOCOCH_2Br$	BuLi	−50	THF	**3d**	98	68/32
$CH_2{=}CHCH_2Br$	BuLi	−50	THF	**3e**	89	67/33

[a] % conversion, the complement to 100% is the starting ester **2**.

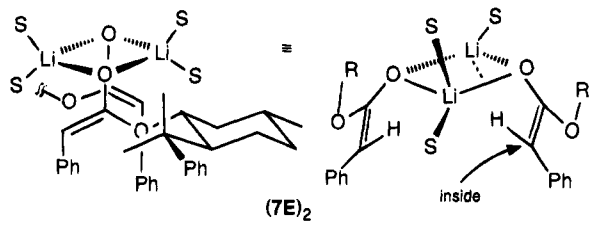


Figure 1.

Table 2. Isomerization and Equilibration

start.	I + II	conditions			I/II	yield,[a] %
3a	51/49	tBuLi	THF, H^+	−78 °C 30 min	33/67	90
3a	80/20	tBuLi	Et_2O, H^+	−78 °C 30 min	30/70	80

[a] Recovered, in weight.

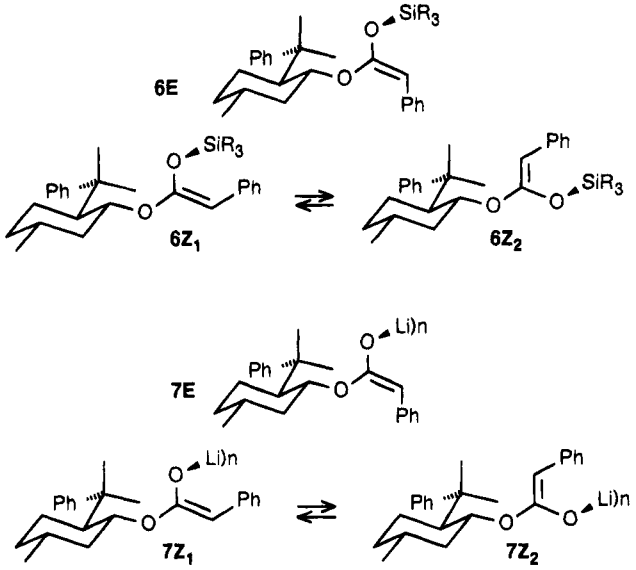
Table 3. Alkylation of Ester 2 Using tBu-P4 as Base

RX	yield,[a] %	monoalkyl. prod.	monoalkyl. I/II[b]	mono/dialkyl.[b]
Me_2SO_4	80	**3a**	93/7	92/8
EtI	95	**3b**	95/5	100/0
$PhCH_2Br$	75	**3c**	98/2	85/15
$EtOCOCH_2Br$	65	**3d**	98/2	80/20[c]
$CH_2{=}CHCH_2Br$	80	**3e**	98/2	100/0

[a] Isolated yields, in weight, of (**I** + **II**). [b] Determined on crude products using NMR. [c] The dialkylated product **4** has been purified and identified, *cf.* Experimental Section.

exclusively the *E*-(trimethylsilyl) ketene acetal **6** of 8-phenylmenthyl phenylacetate (**2**), which indicates that only *E*/*Z* mixtures of the corresponding lithium enolate **7** were probably formed from the various bases used (LDA, tBuLi, and BuLi), Figure 1.

It was also observed (using NOESY) that the phenyl substituent on the menthyl group was trans to the chain in both *E* and *Z* isomers of the silyl ketene acetal **6** and that conformation Z_2 was significantly populated. If these conformations are the reactive species of the lithium enolate **7**, as already envisaged by Corey et al.,[14] the face differentiation at C2 would, of course, be decreased. As a consequence, the presence of both *E* and *Z* isomers as well as of the various conformations suffices to explain the poor to nil diastereoselectivity observed upon alkylation of the lithium enolate **7**.



It must be kept in mind, however (i) that lithium enolates and even lithium enolates of phenylacetates are aggregated at the concentration used (0.2 M)[15a] and (ii) that dimers, which might well be (at −78 °C) the reactive species, are probably folded as found by Seebach *et al.*[15b] (Figure 1).

Examination of models shows that aggregation competes with the chiral auxiliary by hampering the face

(12) (a) The percentage of dialkylated compound **4a** was determined from the ^1H NMR spectrum of the crude product using the nonequivalent *gem*-dimethyl: δ = 1.52 and 1.45. (b) The percentage of dialkylated compounds **4c** and **4d** were determined from the ^1H NMR spectra of the crude products using the two nonequivalent AB systems corresponding to the two CH_2Ph and CH_2CO_2Et groups. **4c**: A, 3.41 (d, J_{AB} = 14 Hz); B, 3.13 (d, J_{AB} = 14 Hz); AB, 3.25 ($\Delta\nu_{AB}$ = ~5 Hz). **4d**: A, 3.51 (d, J_{AB} = 16 Hz); B, 3.27 (d, J_{AB} = 16 Hz); AB, 3.35 ($\Delta\nu_{AB}$ = ~6 Hz, J_{AB} = 15 Hz).

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(15) (a) Although the lithium enolate of *tert*-butyl phenylacetate exists exclusively as monomeric ion pairs in dilute (~10^{-4} M) THF solutions (see: Kaufman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602), at higher concentration (0.25 M) in THF it exists as dimers (*cf.* ref 19). (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

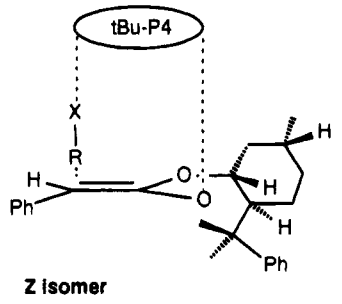

Figure 2.

(concave side) which would be favored by the chiral auxiliary. The poor diastereoselectivity could thus be also due to the geometry of the aggregates.

By working at very low temperature and by using the very strong and cation-free tBu-P4 base (pK_a = 28 in THF)[16] which is known to generate "naked" anions, one could reasonably expect a reactant-like transition state and formation of the desired corresponding free enolate.

The very high diastereoselectivity obtained with tBu-P4 base (Table 3) hinted that our premise concerning the role of aggregation on the diastereoselectivity was correct. One could also conclude from these results that only one isomer (*E* or *Z*) of the free enolate was formed.

If one accepts, as suggested by Seebach *et al.*[10] that the highly delocalized $P4H^+$ assists the approach of the alkylating agent and that the bottom face is obstructed by the *gem*-dimethyl phenyl group of the (−)-8-phenylmenthol used, then the observed *R* diastereoselectivity at C2 can be explained by a top-face approach on the *Z*-enolate[17] (Figure 2).

Exclusive formation of the *Z*-enolate in this cation-free medium is consistent with Ireland's previous suggestion that the increased *Z* stereoselectivity in the presence of HMPT was a consequence of the lesser coordinating ability of lithium in this solvent.[18]

Conclusion

It has been shown that upon alkylation of 8-phenylmenthyl phenylacetate (**2**), the use of a strong cation-free base (tBu-P4) known to generate "naked" anions, in place of the usual lithiated bases, increased the diastereoselectivity from ~50/50 to 92−98/8−2. These results strongly support our hypothesis that the degree of aggregation of the lithium enolate is, in this case, responsible for the poor diastereoselectivities obtained. Our hypothesis is based on the fact that while aggregation tends to favor the *E*-isomer,[19] phenylacetic esters tend to give, upon proton abstraction, the *Z*-isomer,[13] thus leading to complex *E*/*Z* mixtures.

We recently described a case in which reinforcing the aggregate led to increased diastereoselectivities (95−98/5−2).[20] In this case avoiding aggregation led to higher diastereoselectivities, thus illustrating the fickle role of aggregation.

Experimental Section

All starting materials were commercially available research-grade chemicals and used without further purification. The tBu-P4 base was purchased from Fluka. THF was distilled after refluxing over Na/benzophenone and Et_2O was distilled from $LiAlH_4$. Diisopropylamine and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were dried over CaH_2 and freshly distilled under argon prior to use. All reactions were run under argon. The (−)-8-phenylmenthol (free from other diastereomers), $[\alpha]_D$ = −26 EtOH), was prepared from (+)-pulegone and purified according to a modified procedure.[21] Silica gel 60 F_{254} was used for TLC, and the spots were detected with UV. Flash chromatography was carried out with Merck silica gel 60.

8-Phenylmenthyl Phenylacetate (2). To a well-stirred solution of (−)-8-phenylmenthol (6.0 g, 260 mmol) in Et_2O (45 mL) were added successively DCC (5.34 g, 25 mmol), DMPA (0.30 g, 2.4 mmol), and a solution of phenylacetic acid (3.18 g, 23.4 mmol) in Et_2O (45 mL). The mixture was stirred at rt for 3 h. The white solid formed was then filtered and rinsed with Et_2O (3 × 10 mL). The combined organic layers were successively washed with water (3 × 15 mL), 5% acetic acid (3 × 15 mL), water (3 × 15 mL), and brine (1 × 10 mL) and then dried over $MgSO_4$. After concentration of the solution, the colorless liquid was purified by flash chromatography (hexane/ether, 8/2) to give a colorless oil (80%): IR (neat) 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34−7.08 (10H, m), 4.82 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 2.98 (2H, AB system, J_{AB} = 15 Hz), 2.05 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 1.90−0.81 (16H among which 1.28 (3H, s), 1.20 (3H, s), 0.85 (3H, d)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.9, 151.9, 134.3, 129.4, 128.5, 128.2, 125.6, 127, 125.3, 74.6, 50.4, 41.7, 41.3, 39.7, 34.7, 31.4, 28.7, 26.6, 27.6, 22. Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found: C, 82.50; H, 8.35.

Methylation Using LDA as Base. To a solution of diisopropylamine (0.12 mL, 0.82 mmol) in THF (2 mL) at −78 °C was added a 1.5 M solution of BuLi in hexane (0.55 mL, 0.82 mmol) dropwise, and the solution was stirred for 30 min at −78 °C. A solution of ester **2** (230 mg, 0.66 mmol) in THF (0.5 mL) was then slowly added, and the solution was stirred for 30 min at −78 °C. After addition of methyl iodide (0.25 mL), stirring was maintained at −78 °C for 15 min, and the temperature was then allowed to slowly rise to −50 °C. A 1 N HCl solution (2.5 mL) was then added, and the mixture was allowed to reach rt. The organic layer was decanted, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (3 × 2 mL) and dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash column chromatography (hexane/ether, 8/2). In the case of the reaction run in the presence of DMPU (Table 1, entry 4), the same protocol was followed, but DMPU (0.7 mL) was added after BuLi.

Alkylation Using Alkyllithiums as Base. To a solution of ester **2** (230 mg, 0.66 mmol) in THF (2.0 mL) was added dropwise at −78 °C a solution of BuLi, 1.5 M in hexane, or tBuLi, 1.7 M in pentane (0.82 mmol). After 30 min at −78 °C, the desired halide (3.30 mmol) was added and all operations continued as above.

Alkylation Using tBu-P4 as Base. To a stirred solution of ester **2** (0.5 mmol) in THF (2.5 mL) was added an excess of alkylating agent (3 equiv) and then, after cooling to −100 °C, a solution of tBu-P4 (1 M in hexane, 0.55 mmol, 0.55 mL) in dry THF (1.55 mL) in such a way that the temperature of the mixture did not rise above −95 °C. After being stirred for 1 h at −95 °C, the reaction mixture was warmed to rt. The solvent was evaporated under reduced pressure, and Et_2O was added to the resulting oil. A precipitate was formed which was filtered. Concentration of the filtrate gave the crude product, which was purified by flash column chromatography (hexane/ether, 8/2).

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(17) The *E*-isomer would necessitate a bottom approach (the hindered face) to explain the *R*-configuration observed at C2.

(18) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

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(21) Ort, O. *Org. Synth.* **1987**, *65*, 203−213.

8-Phenylmenthyl 2-phenylpropionate (3a) (I/II = 60/40): colorless oil (96%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.1 (10H, m, I + II), 4.80 (1H, m, I + II), 3.37 (1H, q, ^3J = 7 Hz, I:60%), 2.80 (1H, q, ^3J = 7 Hz, II:40%), 2.1–0.6 (20H, among which 1.37 (d, I:60%), 1.34 (s, II/40%), 1.32 (d, II:40%), 1.25 (s, II:40%), 1.14 (s, I:60%), 1.10 (s, I:60%), 0.90 (d, I:60%), 0.80 (d, II:40%)). Anal. Calcd for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85. Found: C, 82.52; H, 8.94.

(−)-8-Phenylmenthyl 2-phenylpropionate (3aI): colorless oil (70% isolated, from tBu-P4 base); $[\alpha]_D$ = −19 (c = 0.9, $CHCl_3$); IR ($CHCl_3$) 1705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36–7.14 (10H, m), 4.77 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 3.33 (1H, q, ^3J = 7Hz), 1.90–0.72 (20H, among which 1.45 (d), 1.10 (s), 1.05 (s), 0.85 (d)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.8, 150.9, 140.3, 128.4, 128.2, 127.9, 127.2, 125.6, 125.1, 75.3, 50.4, 45.8, 41.3, 39.9, 34.5, 31.3, 27.7, 27, 25.5, 21.8, 19. Anal. Calcd for $C_{25}H_{32}O_2$: C, 82.37; H, 8.85. Found: C, 82.42; H, 8.68.

8-Phenylmenthyl 2-phenylbutyrate (3b) (I/II = 67/33): colorless oil (75%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–6.97 (10H, m, I + II), 4.73 (1H, m, I + II), 3.10 (1H, t, ^3J = 8 Hz, I:67%), 2.56 (1H, t, ^3J = 8 Hz, II:33%), 2.10–0.69 (22H, among which 1.26 (s), 1.20 (s), 1.15 (s), 1.10 (s)). Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.56; H, 9.14.

(−)-8-Phenylmenthyl 2-phenylbutyrate (3bI): colorless oil (90% isolated, from tBu-P4 base); $[\alpha]_D$ = −18 (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–6.96 (10H, m), 4.71 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 3.08 (1H, t, ^3J = 8 Hz), 2–0.70 (22H, among which 1.07 (s), 1.03 (s), 0.83 (d), 0.77 (t)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.5, 150.8, 138.8, 128.6, 128.4, 128, 127.2, 125.7, 125.2, 75.5, 53.7, 50.6, 41.9, 40.1, 34.7, 31.4, 28.1, 27.5, 27.2, 25.5, 21.9, 12.3. Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.36; H, 8.92.

8-Phenylmenthyl 2-diphenylpropionate (3c) (I/II = 69/31): colorless oil (93%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5–7.1 (15H, m, I + II), 4.75 (1H, m, I + II), 3.58 (1H, t, ^3J = 7 Hz, I:69%), 3.3 (1H, A part of an ABX, J_{AB} = 13 Hz, I + II), 3.12 (1H, t, ^3J = 6 Hz, II:31%), 3.0 (1H, B part of an ABX, J_{AB} = 13 Hz, I:69%), 2.85 (1H, B part of an ABX, J_{AB} = 13 Hz, II:31%), 2–0.65 (17H, m among which 1.14 (s, II), 1.10 (s, I + II), 1.04 (s, I), 0.85 (d, I), 0.78 (d, II)). Anal. Calcd for $C_{31}H_{36}O_2$: C, 84.50; H, 8.23. Found: C, 84.66; H, 8.07.

1-Ethyl 4-(8-phenylmenthyl) 3-phenylsuccinate (3d) (I/II = 68/32): pale yellow oil (98%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4–7.0 (10H, m, I + II), 4.74 (1H, m, I + II), 4.12 (2H, m, I + II), 3.86 (1H, dd, X part of an ABX system, J_{AX} = 9 Hz, J_{BX} = 6Hz, I:68%), 3.44 (1H, dd, X part of an ABX system, J_{AX} = 9 Hz, J_{BX} = 6 Hz, II:32%), 3.00 (1H, m, A part of an ABX system, I + II), 2.6 (1H, m, B part of an ABX system, I + II), 2.10–0.68 (20H, among which 1.34 (s, II), 1.28 (t, II), 1.24 (t, I), 1.18 (s, II), 1.0 (s, I), 0.86 (s, I), 0.81 (d, I), 0.76 (d, II)). Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.58.

(−)-1-Ethyl 4-(8-phenylmenthyl) 3-phenylsuccinate (3dI): white solid (50% isolated, from tBu-Pr base); mp = 102–104 °C; $[\alpha]_D$ = −36 (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.04 (10H, m), 4.73 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 4.09 (2H, q, ^3J = 7 Hz), 3.87 (1H, X part of an ABX system, J_{AX} = 9 Hz, J_{BX} = 6 Hz), 3.02 (1H, A part of an ABX system, J_{AB} = 17 Hz), 2.65 (1H, B part of an ABX system, J_{AB} = 17 Hz), 2.10–0.69 (20H, among which 1.20 (t), 1.0 (s), 0.86 (s), 0.82 (d)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.2, 171.5, 150.5, 137.3, 128.7, 128.4, 128, 125.7, 127.7 125.3, 76.3, 60.7, 50.5, 47.8, 41.6, 40.1, 38.3, 34.6, 31.4, 29, 27.3, 24.3, 21.8, 14.2. Anal. Calcd for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.23.

Diethyl 3-phenyl-3-(8-phenylmenthyloxycarbonyl)glutarate (4d): colorless oil (10%); IR ($CHCl_3$) 1690 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.14 (10H, m), 4.73 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 4.11 (2H, AB part of an ABX_3), 3.92 (2H, q, ^3J = 8 Hz), 3.40 (4H, two overlapped AB), 2.20–0.68 (23H among which 1.57 (s), 1.25 (t), 1.02 (t), 0.96 (s), 0.80 (s), 0.75 (d)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.3, 171.3, 171.1, 150.6, 138.9, 128.4, 127.9, 126.3, 125.6, 127.5, 125.1, 77.3, 60.5, 60.2, 50.4, 49.5, 40.8, 39.9, 39.7, 37.2, 34.5, 31.3, 29.3, 27.5, 23.5, 21.7, 14.2, 13.9. Anal. Calcd for $C_{32}H_{42}O_6$: C, 77.53; H, 8.09. Found: C, 77.62; H, 7.96.

8-Phenylmenthyl 2-phenylpent-4-enoate (3e) (I/II = 67/33): colorless oil (89%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–6.97 (10H, m, I + II), 5.62 (1H, m, I + II), 5.02 (1H, br d, I + II), 4.95 (1H, br d, I + II), 4.74 (1H, m, I + II), 3.29 (1H, t, ^3J = 7 Hz, I:67%), 2.70 (m, 1H of II:33% and 1H of I + II), 2.40 (1H, m, I + II), 2.00–0.73 (17H, among which 1.3 (s, II), 1.2 (s, II), 1.05 (s, I), 1.00 (s, I), 0.82 (d, I), 0.55 (d, II)). Anal. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77. Found: C, 83.16; H, 8.92.

(−)-8-Phenylmenthyl 2-phenylpent-4-enoate (3eI): colorless oil (75% isolated, from tBu-P4 base); $[\alpha]_D$ = −25 (c = 0.5, $CHCl_3$); IR ($CHCl_3$) 1700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37–6.98 (10H, m), 5.65 (1H, ddt, J_t = 17 Hz, J_c = 10 Hz, ^3J = 7 Hz), 5.02 (1H, br d, J_t = 17 Hz), 4.94 (1H, br d, J_c = 10 Hz), 4.75 (1H, td, $^3J_{aa}$ = 10 Hz, 10 Hz, $^3J_{ae}$ = 5 Hz), 3.30 (1H, t, ^3J = 7 Hz), 2.65 (1H, br quint), 2.42 (1H, br quint), 2.00–0.75 (17H, among which 1.07 (s), 1.02 (s), 0.85 (d)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 172.8, 150.8, 138.2, 135.4, 128.5, 128.5, 128, 125.7, 127.3, 125.2, 116.8, 75.8, 51.6, 50.5, 41.9, 40.1, 38.2, 34.6, 31.4, 28.2, 27.2, 25.3, 21.8. Anal. Calcd for $C_{27}H_{34}O_2$: C, 83.03; H, 8.77. Found: C, 83.16; H, 8.88.

Correlation of 3aI with (*R*)-(+)-2-Phenyl-1-propanol (5a). A 75/25 mixture of **3aI** and **3aII** (311 mg, 0.85 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. A 1 M solution of DIBAL in toluene (2.12 mL, 2.5 equiv) was then added dropwise under stirring, and the temperature was allowed to reach rt (2 h). After addition of MeOH (3 mL) and brine (30 mL), the mixture was extracted with CH_2Cl_2 (5 × 10 mL), and the organic phase was dried over Na_2SO_4 and concentrated under vacuum to give a colorless oil (92%).

(+)-2-Phenyl-1-propanol: $[\alpha]_D$ = +9 (neat) lit.[22] $[\alpha]_D$ = +21 neat for pure *R*); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.15 (5H, m, H_{arom}), 3.70 (2H, d, CH_2), 2.97 (1H, sext, CH), 1.5 (1H, s, OH), 1.25 (3H, d, Me).

Correlation of 3bI with (*R*)-(−)-2-Phenyl-1-butanol (5b). A suspension of $LiAlH_4$ (12 mg, 0.32 mmol) in THF (1.0 mL) was refluxed for 30 min. After cooling at 0 °C, a solution of (−)-**3bI** (120 mg, 0.32 mmol) in THF (0.5 mL) was added dropwise under stirring. The temperature was allowed to reach rt (3 h). The mixture was cooled to 0 °C, and then a saturated solution of NH_4Cl (0.5 mL) and brine (10 mL) were successively added. After extraction with Et_2O (6 × 5 mL), the combined organic layers were dried over $MgSO_4$ and concentrated. The crude alcohol was purified by flash column chromatography (hexane/diethyl ether, 1/1): colorless oil (90%); $[\alpha]_D$ = −11 (c = 0.8, benzene) (lit.[22] $[\alpha]_D$ = −11.4 (c = 3.1, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.12 (5H, m, H_{arom}), 3.75 (2H, m, CH_2O), 2.72 (1H, m, CH), 1.65 (2H, m, AB part of an ABX_3M, CH_2), 0.8 (3H, t, ^3J = 7 Hz, CH_3). Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.01; H, 9.20.

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