Enzyme-Assisted Enantioselective Synthesis of Natural (−)-*β*-Necrodol and Its Enantiomer

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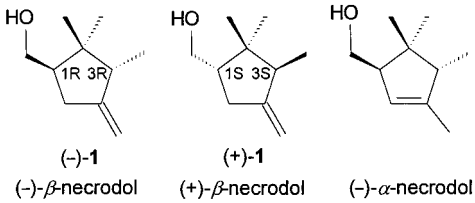
Received September 18, 2000

Introduction

The beetle family Silphidae comprises species of considerable ecological significance that are mostly carrion feeders. Discovered[1] in the defense spray of *Necrodes surinamensis*, the so-called red-lined carrion beetle, (−)-(1*R*,3*R*)-*β*-necrodol ((−)-**1**) and its α-isomer ((−)-α-necrodol) constitute members of a new class of monoterpenes possessing the nonisoprenoid 1,2,2,3,4-pentamethylcyclopentane skeleton.

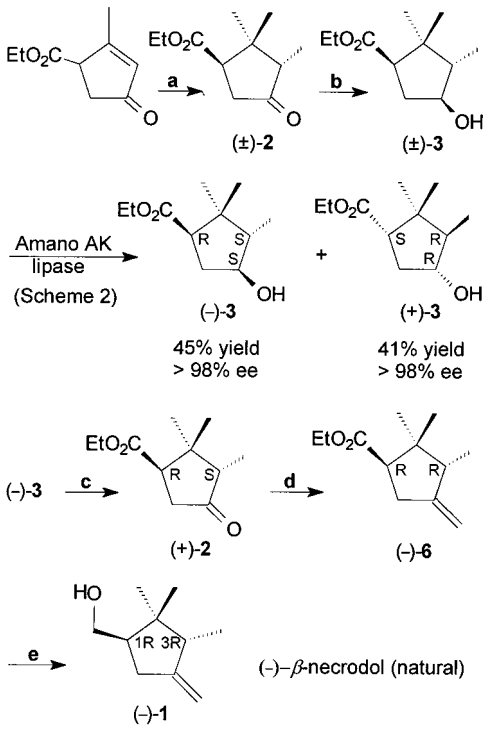


Because of their fascinating structures and insect repellant activity, these compounds continue to be targets of synthetic investigations.[2] The synthetic challenge represented by the necrodanes involves the construction of the sterically hindered cyclopentane core with total control of the thermodynamically unfavorable trans 1,3-stereochemistry. Until now, total diastereoselection has not yet been achieved with mixtures of *trans*- and *cis*-necrodane structures being obtained. We report herein an enantioselective synthesis of natural (−)-*β*-necrodol and its enantiomer in which the complete 1,3-diastereoselection has been achieved and which is based upon an efficient lipase-assisted kinetic resolution.

Results and Discussion

The readily available[3] ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate was converted into the keto ester (±)-**2** in 77% yield by the $Ni(acac)_2$-catalyzed 1,4-addition of dimethylzinc, followed by quenching with methyl iodide in hexamethylphosphoric triamide[4] (Scheme 1).

Scheme 1[a]



[a] Reagents: (a) Me_2Zn, $Ni(acac)_2$, THF then MeI (77%); (b) $NaBH_4$, EtOH (92%); (c) DMSO, $(ClCO)_2$, NEt_3, CH_2Cl_2 (94%); (d) $TiCl_4-CH_2Br_2-Zn$, THF, CH_2Cl_2 (88%); (e) $LiAlH_4$, Et_2O (98%).

The relative trans configuration of the stereocenters in (±)-**2** was assigned using ^1H NMR coupling constants (400 MHz) and NOESY (Figure 1). The proton H_a-C(5) resonated as a ddd at $\delta_H = 2.61$ ppm ($J = 19.2, 2.9, 1.6$ Hz) whereas H_b-C(5) resonated as a dd at $\delta_H = 2.37$ ppm ($J = 19.2, 8.8$ Hz). This indicated that H_a ($J = 2.9$ Hz) and H_b ($J = 8.8$ Hz) are, respectively, trans and cis relative to H-C(1) which resonated as a dd at $\delta_H = 2.81$ ppm ($J = 8.8, 2.9$ Hz), because $^3J_{trans}$ is always notably smaller than $^3J_{cis}$ in five-membered rings which cannot deviate appreciably from planarity.[5] Moreover, H_a-C(5) showed a small cis coupling ($^4J = 1.6$ Hz) with H-C(3) which resonated as a qd at $\delta_H = 2.41$ ppm ($J = 7.1, 1.6$ Hz). NOESY correlations among H-C(1) and the Me-C(3) and/or the Me-C(2), which resonated at $\delta_H = 0.93$ and 0.94 ppm, established the spatial proximities of these protons. A pronounced NOESY correlation between H-C(3) and Me-C(2) which resonated at $\delta_H = 1.10$ ppm, was consistent with their cis orientation. In addition, the stereochemistry was secured later by the X-ray structural analysis of the crystalline derivative (−)-**5** (vide infra).

The stereochemical outcome from the alkylation of endocyclic enolates depends on a balance of several

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10.1021/jo0013812 CCC: $20.00
Published on Web 12/05/2000

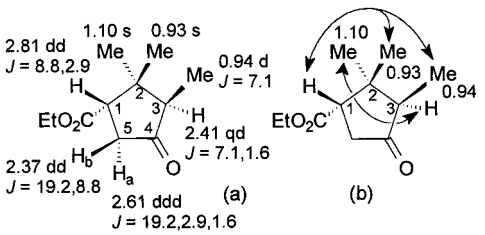
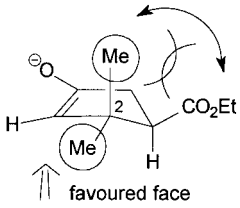


Figure 1. High-field ^{1}H NMR analysis (a) and NOESY correlations (b) of (±)-**2**.

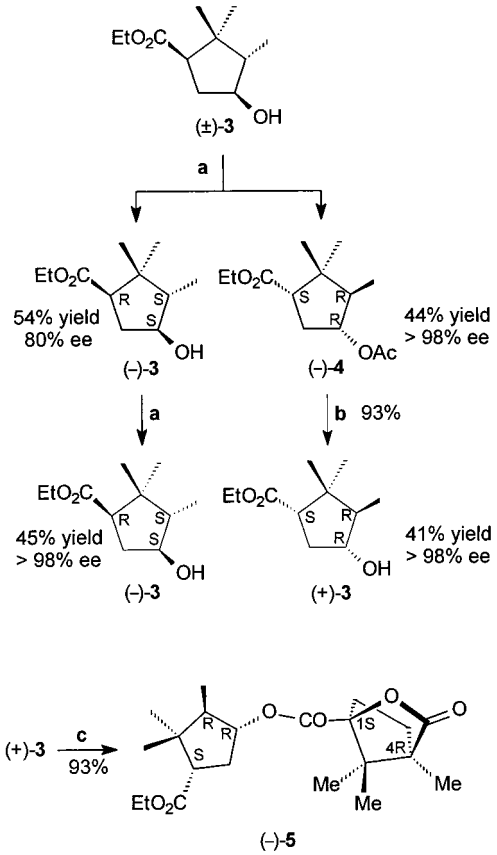
factors,[6] but the need to maintain orbital overlap over three centers in the transition state structure (stereoelectronic effect) leads to the presumption of the requirement of a perpendicular approach of the electrophile to the enolate system.[7] The observed stereoselectivity might be rationalized in terms of the steric hindrance in the transition-state geometry. The low-energy "envelope" conformation, which minimizes the steric interactions between the cis carbethoxy and Me-C(2) groups, presents a less-encumbered lower face, because of the pseudoaxial position of the other Me-C(2) on the upper face. The perpendicular approach of iodomethane to the enolate carbon will be favored from this lower face to give (±)-**2** with complete diastereoselectivity.



Reduction of (±)-**2** with sodium borohydride proceeded with high stereoselectivity (30:1) to give cis alcohol (±)-**3** which could then be isolated in pure form by simple chromatography in 92% yield. Proof of the relative cis configuration between hydroxy and carbethoxy substituents in this derivative was provided below. This stereochemistry shows that, like precedence,[8] there is a preference for $NaBH_4$, which is a nucleophile with relatively small steric demand, to approach along the face bearing the α-Me group, what appears to be the more-hindered trajectory. Steric influences arising from nonbonded interaction between the carbethoxy group and the incoming hydride also favor and strengthen the stereoselective formation of (±)-**3**.

Treatment of racemic **3** with vinyl acetate in the presence of *Pseudomonas* sp lipase[9,10] (Amano AK lipase) gave the results outlined in Scheme 2.

Scheme 2.[a] **Amano AK Enzymatic Resolution of (±)-3 and Synthesis of the Crystalline Ester (−)-5**



[a] Reagents: (a) vinyl acetate, lipase Amano AK; (b) K_2CO_3, EtOH; (c) (−)-(1*S*,4*R*)-camphanic acid chloride, DMAP, Py.

The progress of the reaction was monitored by capillary GC. In parallel, enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by GC separation using a chiral phase (see Experimental Section). The enantiomers of the alcohol were perfectly separable, but those of the acetate not. Accordingly, the enantiomer purity of the acetate was determined after hydrolysis to the corresponding alcohol. After 8 h at room temperature, the active enzyme was recovered for reuse by filtration. Concentration of the filtrate and column chromatography on silica gel afforded a 54% yield of the nonreactive alcohol (−)-**3** (80% ee) and a 44% yield of the acetate (−)-**4**. Acetate (−)-**4** was hydrolyzed with K_2CO_3/MeOH to afford alcohol (+)-**3** in 93% yield (>98% ee, 41% overall yield from racemic **3**). The remaining alcohol (−)-**3** was resubjected in the same conditions to enzymatic transesterification using the recovered enzyme. The progress of the

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reaction was monitored by chiral phase analytical GC until one enantiomer of the starting material was completely consumed. After 24 h, (−)-**3** was obtained in 45% overall yield and >98% ee. To establish the enantiomeric specificity of *Pseudomonas* sp lipase and, in the same time, to confirm the relative configurations of substituents in compounds (±)-**2** and (±)-**3**, the absolute configuration of alcohol (+)-**3** was determined. Thus, the crystalline ester (−)-**5** was synthesized using (1*S*,4*R*)-camphanic chloride[11] as a chiral auxiliary and submitted to X-ray crystallography. The 3D ORTEP diagram[12] of (−)-**5** fully supported the structures assigned on the basis of NMR methods.

Swern oxidation[13] of (−)-**3** afforded the ketoester (+)-**2** in excellent yield (94%). Several Ti-based methylenation procedures have been developed that avoid most of the problems encountered with Wittig-type processes.[14] In our case, the keto group of (+)-**2** was methylenated, without any epimerization, by a zinc−dibromomethane−titanium(IV) chloride mixed reagent[15] in THF to give (−)-**6** in 88% yield. Finally, $LiAlH_4$ reduction of (−)-**6** in Et_2O at room temperature furnished the natural (−)-(1*R*,3*R*)-*β*-necrodol, (−)-**1** in 98% yield and >98% ee. The high enantiomeric purity of the compound was verified by chiral CPG (see Experimental Section). The $[\alpha]^{25}_D$ = −17.7 (*c* 1.0, $CHCl_3$) of (−)-**1** agrees[16a] or disagrees[16b] with those reported in the literature in which there are already discrepancies in the magnitude of the specific rotation. Starting from alcohol (+)-**3**, this synthetic pathway formally constitutes a total synthesis of nonnatural (+)-(1*S*,3*S*)-*β*-necrodol, (+)-**1**.

In conclusion, we have developed a short and efficient enantioselective synthesis of both enantiomers of *β*-necrodol in very high enantiomeric excess via a stereoselective alkylation and an asymmetric enzymatic transesterification.

Experimental Section

General Methods. For analytical thin-layer chromatographies, Merck silica gel F-254 on aluminum plates was used. Column chromatographies were performed with Merck Silica gel 60 (70−230 mesh) and Merck Silica gel (230−400 mesh) for flash chromatography, using mixtures of diethyl ether and petroleum ether as eluent. GC analyses were carried out using a WCOT fused silica column (25 m × 0.32 mm i.d.; CP−Wax-52 CB stationary phase; N_2 carrier gas: 50 kPa). Enantiomeric excess determinations were carried out using a MEGADEX DETTBS*β* fused silica column (30 m × 0.25 mm i.d.; N_2 carrier gas: 75 kPa). Microanalyses were performed at our University. FT-IR spectra were recorded as film or KBr pellet. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, unless otherwise cited. Melting points are uncorrected. Unless otherwise stated, solutions were dried over magnesium sulfate and evaporated in a rotary evaporator under reduce pressure.

Ethyl 2,2,3-Trimethyl-4-oxocyclopentanecarboxylate (2). To a stirred suspension of ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate (2.00 g, 11.9 mmol) and $Ni(acac)_2$ (305 mg, 1.19 mmol) in THF (30 mL) was added dropwise a 2 M toluene solution of dimethylzinc (18.0 mL, 36.0 mmol) at 5 °C, and the mixture was allowed to rise to room temperature. After 12 h the solution was slowly cooled to −70 °C, and HMPA (15 mL, 88.0 mmol) and methyl iodide (12.0 g, 84.5 mmol) in THF (20 mL) were successively added dropwise under vigorous stirring. The solution was allowed to rise to room temperature, poured into a saturated aqueous NH_4Cl solution, and extracted with ether. The organic layers were combined, washed with brine, dried, and evaporated. The oily residue was subjected to rapid column chromatography on silica gel to afford 1.81 g (77%) of **2**. IR (neat): *ν* 1746, 1055 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.18 and 4.13 (ABX_3, *J* = 11.1, 7.2 Hz, 2H), 2.81 (dd, *J* = 8.8, 2.9 Hz, 1H), 2.61 (ddd, *J* = 19.2, 2.9, 1.6 Hz, 1H), 2.41 (qd, *J* = 7.1, 1.6 Hz, 1H), 2.37 (dd, *J* = 19.2, 8.8 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.10 (s, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.93 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 218.4, 174.4, 60.6, 51.6, 49.5, 42.1, 38.6, 24.3, 14.2, 8.1. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.85; H, 9.12.

Ethyl 4-Hydroxy-2,2,3-Trimethylcyclopentanecarboxylate (3). To a stirred solution of **2** (1.27 g, 6.41 mmol) in absolute EtOH (80 mL) at −80 °C was added $NaBH_4$ (268 mg, 7.05 mmol). The reaction mixture was allowed to rise to room temperature and concentrated under reduced pressure. Water (200 mL) and CH_2Cl_2 (200 mL) were added to the residue, and the mixture was stirred for an additional 0.5 h. After extraction with CH_2Cl_2, the combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel to afford 1.17 g (92%) of pure **3** and 40 mg (3%) of *epi*-**3**.

3. IR (neat): *ν* 3450, 1734, 1048 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 4.10 and 4.05 (ABX_3, *J* = 10.8, 7.2 Hz, 2H), 3.84−3.66 (m, 1H), 2.47 (dd, *J* = 7.6, 4.6 Hz, 1H), 2.25 (dt, *J* = 14.1, 7.8 Hz, 1H), 1.81 (dt, *J* = 14.1, 4.8 Hz, 1H), 1.66 (q, *J* = 7.2 Hz, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 176.2, 78.9, 60.3, 53.4, 51.4, 43.7, 35.9, 24.7, 24.5, 14.2, 11.7. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.15; H, 10.05.

epi-**3**. IR (neat): *ν* 3400, 1728, 1048 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 4.32−4.22 (m, 1H), 4.22−4.06 (m, 2H), 2.82 (t, *J* = 8.2 Hz, 1H), 2.32−2.16 (m, 1H), 1.92−1.72 (m, 2H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.10 (s, 3H), 0.93 (d, *J* = 7.3 Hz, 3H), 0.89 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 175.1, 75.8, 60.0, 53.4, 48.2, 42.9, 36.0, 26.4, 25.6, 14.3, 8.8. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.69; H, 10.04.

General Procedure for Lipase-Catalyzed Acylation of (±)-3. To a solution of (±)-**3** (1.00 g) in vinyl acetate (30 mL) was added Amano AK lipase (250 mg). The mixture was stirred magnetically in a hermetically stoppered one-neck flask at room temperature. The course of the reaction was monitored by capillary GC at one and the same time on the chiral and achiral columns. After 8 h and 44% conversion, the reaction was stopped by filtration. Removal of the solvent, followed by silica gel column chromatography, yielded 540 mg (54%) of nonreactive alcohol (−)-**3** (ee = 80%, determined by chiral GC) and 530 mg (44%) of acetate (−)-**4** (ee >98%, determined by analogy with that of alcohol (+)-**3**, vide infra).

(−)-**4**. $[\alpha]^{25}_D$ = −18.4 (*c* 1.0, $CHCl_3$). IR (neat): *ν* 1741, 1243, 1042 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): *δ* 4.72 (broad q, *J* = 8.2 Hz, 1H), 4.16 and 4.10 (ABX_3, *J* = 10.8, 7.0 Hz, 2H), 2.53 (dd, *J* = 8.3, 6.5 Hz, 1H), 2.48−2.30 (m, 1H), 2.06 (s, 3H), 2.00−1.84 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.94 (s, 3 H), 0.89 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): *δ* 174.6, 171.1, 79.8, 60.0, 52.2, 47.2, 42.3, 32.4, 24.5, 24.3, 21.0, 14.1, 11.6. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.61; H, 9.17.

Acetate (−)-**4** (530 mg, 2.18 mmol) was treated with K_2CO_3 (2.90 g, 29.3 mmol) in 30 mL of EtOH for 12 h at room temperature. An excess of NH_4Cl (4.70 g, 87.9 mmol) was added, and the reaction mixture was filtered and concentrated under reduced pressure. Column chromatography gave 406 mg (93%) of (+)-**3** as an oil. Ee >98%, $[\alpha]^{25}_D$ = +35.4 (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (±)-**3**.

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(16) (a) $[\alpha]^{20}_D$ = −17.85 (*c* 1.68, $CHCl_3$).[2c] (b) $[\alpha]^{20}_D$ = −10.74 (*c* 0.65, $CHCl_3$),[2a] $[\alpha]^{20}_D$ = −11.2 (*c* 0.60, $CHCl_3$).[2e]

The nonreactive alcohol (−)-**3** (ee = 80%) was resubjected to the same conditions to lipase-catalyzed acylation using the recovered active enzyme, and the progress of the reaction was monitored by chiral GC. After 24 h, GC analysis showed that one enantiomer was completely consumed. The reaction was stopped by filtration. Removal of the solvent followed by silica gel column chromatography yielded 450 mg (45% overall yield from (±)-**3**) of alcohol (−)-**3**. Ee>98%, $[\alpha]^{25}_D = -35.2$ (*c* 1.0, $CHCl_3$).^{1}H and ^{13}C NMR spectra were identical with those of (±)-**3**.

Reaction of (+)-3 with (−)-(1*S*,4*R*)-Camphanic Acid Chloride. To a solution of (+)-**3** (100 mg, 0.50 mmol) and DMAP (10 mg, 0.08 mmol) in pyridine (15 mL) at 5 °C under argon atmosphere was added (−)-(1*S*,4*R*)-camphanic acid chloride (Fluka, 130 mg, 0.60 mmol). The cooling bath was removed, and the solution was stirred at room temperature. The reaction was monitored by TLC and was complete within 1 h. The mixture was diluted with CH_2Cl_2 and was sequentially washed with water, 1 N HCl until pH 2 (paper indicator), 1 M $NaHCO_3$, saturated $CuSO_4 \cdot 5H_2O$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography and afforded the camphanate derivative (−)-**5** (177 mg, 93%). Crystallization from *n*-hexane afforded white crystals. $[\alpha]^{25}_D = -22.7$ (*c* 1.0, $CHCl_3$), mp = 71−72 °C. IR (neat): ν 1785, 1741, 1728, 1174 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.83 (q, J = 8.1 Hz, 1H), 4.18 and 4.06 (ABX_3, J = 10.8, 7.0 Hz, 2H), 2.60−2.32 (m, 3H), 2.10−1.84 (m, 4H), 1.74−1.58 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H), 1.10 (s, 3H), 1.08 (s, 3 H), 0.95 (s, 6H), 0.90 (d, J = 7.0 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 178.1, 174.4, 167.4, 91.0, 81.3, 60.3, 54.7, 54.0, 52.3, 47.4, 42.4, 32.6, 30.4, 28.9, 24.5, 24.4, 16.8, 16.6, 14.2, 11.7, 9.6. Anal. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48. Found: C, 66.15; H, 8.46.

(+)-(1*R*,3*S*)-Ethyl 2,2,3-Trimethyl-4-oxocyclopentanecarboxylate ((+)-2). A solution of oxalyl chloride (315 mg, 2.48 mmol) in CH_2Cl_2 (20 mL) was cooled to −70 °C, and a solution of dry DMSO (387 mg, 4.95 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred at −70 °C for 15 min, and a solution of alcohol (-)-**3** (330 mg, 1.65 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 30 min at −70 °C, Et_3N (1.40 mL, 9.90 mmol) was added, and the reaction mixture was allowed to warm to room temperature over a period of 3 h. Water was added, and the resultant mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water until neutral, dried, filtered, and concentrated. A column chromatography of the residue yielded 312 mg (94%) of ketone (+)-**2** as a colorless oil. $[\alpha]^{25}_D = +55.4$ (*c* 1.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical with those of (±)-**2**.

(−)-(1*R*,3*R*)-Ethyl 2,2,3-Trimethyl-4-methylidenecyclopentanecarboxylate ((-)-6). Preparation of Lombardo's Reagent. To a suspension of Zn dust (2.87 g, 44 mmol) and CH_2Br_2 (1.01 mL, 14.4 mmol) in THF (25 mL), stirred under an argon atmosphere at −40 °C, was added dropwise neat $TiCl_4$ (1.13 mL, 10.3 mmol). The mixture was then allowed to warm to 5 °C and was stirred for 3 days at this temperature to produce a thick gray slurry of the active reagent.

To a CH_2Cl_2 (6 mL) solution of ketone (+)-**2** (270 mg, 1.36 mmol), stirred at 5 °C under an argon atmosphere, was added the $Zn-CH_2Br_2-TiCl_4$ mixed methylenation reagent (2.5 equiv). After being stirred for 2 h at this temperature, the reaction mixture was diluted with CH_2Cl_2, poured into a cold $NaHCO_3$ saturated aqueous solution, and extracted with ether. The combined extracts were washed with brine, dried, filtered, and concentrated. The residue was subjected to column chromatography to afford 238 mg (88%) of pure (−)-**6** as an oil. $[\alpha]^{25}_D = -14.4$ (*c* 1.0, $CHCl_3$). IR (neat)): ν 3075, 1741, 1665, 878 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.90−4.85 (m, 1H), 4.82−4.77 (m, 1H), 4.16 and 4.10 (ABX_3, J = 10.8, 7.1 Hz, 2H), 2.78−2.32 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 0.96 (s, 3H), 0.92 (d, J = 7.2 Hz, 3H), 0.85 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.4, 155.0, 105.1, 60.0, 52.3, 47.2, 44.4, 33.1, 23.7, 23.3, 14.3, 12.6. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.65; H, 10.28.

(−)-(1*R*,3*R*)-2,2,3-Trimethyl-4-methylenecyclopentanemethanol ((−)-*β*-necrodol, (−)-1). To a slurry suspension of $LiAlH_4$ (85 mg, 2.20 mmol) in 20 mL of dry ether, was added ester (−)-**6** (175 mg, 0.89 mmol), and the mixture was stirred for 0.5 h at room temperature. After cooling in an ice bath, ether (20 mL), Celite (2.2 g), $Na_2SO_4 \cdot 10H_2O$ (2.2 g), and 0.50 mL of H_2O were added. After 30 min, the reaction mixture was filtered through a pad of $MgSO_4$ and concentrated to give 135 mg (98%) of pure (−)-*β*-necrodol, (−)-**1**. $[\alpha]^{25}_D = -17.7$ (*c* 1.0, $CHCl_3$). IR (neat): ν 3358, 3068, 1652, 872 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.84 (qd, J = 2.3, 1.2 Hz, 1H), 4.77 (qd, J = 2.4, 1.2 Hz, 1H), 3.75 and 3.43 (ABX, J = 10.4, 9.5, 5.3 Hz, 2H), 2.58 (ddq, J = 17.4, 8.5, 2.0 Hz, 1H), 2.30 (dt, J = 4.7, 2.4 Hz, 1H), 2.24−2.06 (m, 2H), 1.83 (tt, J = 8.5, 5.2 Hz, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ156.0, 105.0, 64.0, 48.6, 48.3, 42.0, 33.7, 23.6, 22.9, 13.4. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.03; H, 11.72.

Acknowledgment. Dr. M. Giorgi performed the X-ray diffraction experiments. We are grateful to Amano Pharmaceutical Co., Ltd. for the kind gift of lipases.

Supporting Information Available: X-ray structural results of (−)-**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0013812