A Selective and General Access to Trisubstituted Oxetanes

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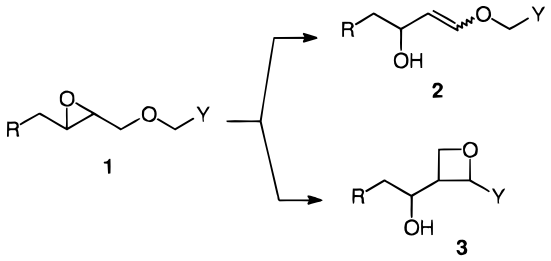
Received March 7, 1996

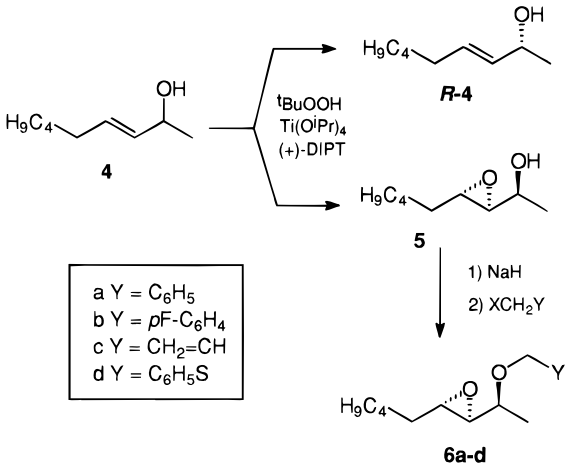
During our previous studies[1,2] on the base-promoted isomerization of oxiranes, we have found[2] that oxiranyl ethers **1**, derived from primary allylic alcohols, rearrange to hydroxy enethers **2** or hydroxyalkyl oxetanes **3** by treatment with the equimolar mixture butyllithium/diisopropylamine/potassium *tert*-butoxide (LIDAKOR).[3] When Y is a phenyl group, the reaction is very selective, the oxetane being formed as the only product in the *anti*-



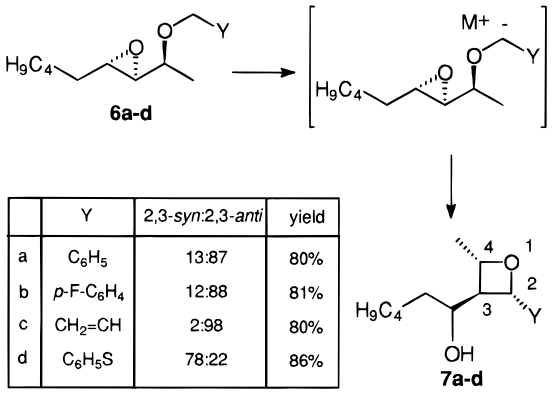
configuration. Unfortunately the oxetane formation is not general. When the phenyl is replaced by a *para*-substituted aromatic ring or another electron-withdrawing group, a mixture of isomers **2** and **3** results after treatment with the organometallic base. This result prompted us to extend our study to a number of oxiranyl ethers derived from secondary allylic alcohols, in hopes that the alkyl substitution α to the ethereal oxygen could prevent the elimination reaction leading to products **2** thus favoring the formation of oxetanes. We wish to report here preliminary results which show that a stereoselective synthesis of trisubstituted oxetanes is easily accomplished from oxiranyl ethers derived from secondary alcohols.

Compounds **6a**−**d** have been prepared by the Sharpless kinetic resolution[4] of racemic 3-nonen-2-ol **4** with *tert*-butyl hydroperoxide, titanium isopropoxide, and (L)-(+)-diisopropyl tartrate, followed by reaction with sodium hydride and a suitable alkylating agent. Careful control of reaction conditions during the oxidation step yields the *anti*-epoxy alcohol **5**, leaving the *R*-enantiomer of 3-nonen-2-ol unreacted.

Substrates **6a**−**d** were then treated with a mixed metal reagent in tetrahydrofuran at −50 °C. All these substrates rearrange by the formation of a carbanion α to the substituent Y followed by a 4-*exo* ring closure.[5,6]



Compounds **6a**, **6b**, and **6d** were isomerized by the LIDAKOR mixture, while **6c** was completely inert under the same reaction conditions. Schlosser's base[7] (LICKOR = butyllithium/potassium *tert*-butoxide) was necessary in order to produce oxetane **7c**. The carbanionic rearrangement is completely regioselective, with oxetanes **7a**−**d** being the only detected products. This is true despite the observation that analogous aryloxy oxiranyl ethers, derived from primary allylic alcohols, give mixtures of rearranged products when submitted to treatment with bases.[2]



	Y	2,3-*syn*:2,3-*anti*	yield
a	C_6H_5	13:87	80%
b	*p*-F-C_6H_4	12:88	81%
c	CH_2=CH	2:98	80%
d	C_6H_5S	78:22	86%

The reaction is also remarkably stereoselective. The relative stereochemistry of substituents on carbon 3 and 4 of the ring is always *anti* and is due to the *anti* configuration of the starting oxiranyl ethers. Substituents on carbon 2 and 3 may be either in a *syn* or an *anti* arrangement depending on the ring closure mode. Oxetane **7c** is formed exclusively as the *anti* stereoisomer while **7a**,**b** are predominantly *anti* and **7d** is actually a 78:22 mixture of 2,3-*syn* and 2,3-*anti* products (both in a 3,4-*anti* configuration), as determined by ^{1}H-NMR analysis (by integration of the signals relative to hydrogen atoms on position 2, that are well separated in the two stereoisomers).

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(2) Mordini, A.; Bindi, S.; Pecchi, S.; Degl'Innocenti, A.; Reginato, G.; Serci, A. *J. Org. Chem*., submitted.

(3) Mordini, A.; BenRayana, E.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401.

(4) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H; Sharpless, K. B. *J. Am. Chem. Soc.* **1987,** *109*, 5765.

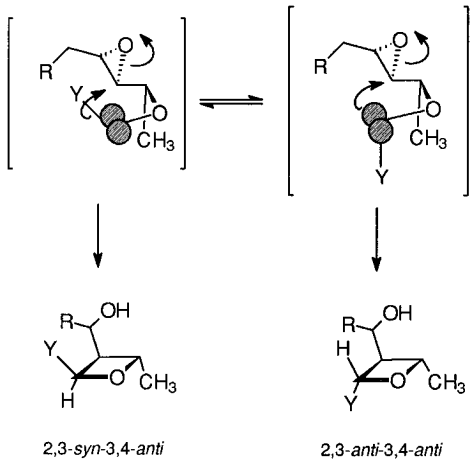
(5) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268; Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270.

(6) For a previous example of oxetane formation via nucleophilic substitution of allylic carbanions on oxiranes, see Still, W. C. *Tetrahedron Lett.* **1976**, *25*, 2115.

(7) Schlosser, M. *J. Organomet. Chem*. **1967**, *8*, 9. Reviews: Mordini, A. In *Comprehensive Organometallic Chemistry II*; Pergamon Press: Oxford, 1995, Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; McKillop, A., Vol. Ed.; 1995, Vol. 11, p 93. Mordini, A. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, p 1. Schlosser, M. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; Vol. 6, p 227.

S0022-3263(96)00459-8 CCC: $12.00

We presume that the *anti*-arrangement in **7a**−**c** is due to steric repulsion between substituents Y and the alkyl chain on the epoxide in the transition state for the carbanion attack on the oxirane. The lower selectivity found in the two benzyl ethers compared to the allyl one is probably due to some steric repulsion between the phenyl group and the methyl on the same side of the ring plane. To confirm the steric influence of the methyl group on the stereoselective outcome of the ring closure, we can compare the results obtained with the benzyl oxiranyl ethers **1** and **6a**, the former derived from 2,3-epoxyoctanol and the latter from 3,4-epoxy-2-nonanol. Ether **1** gives the *anti*-oxetane as the only detectable stereoisomer while **6a**, having the methyl group on the methylene α to the oxirane ring, affords a mixture of stereoisomers (with a predominant *anti*-selectivity). The same steric effect is probably responsible for the reverse selectivity found in the ring closure of **6d**. It seems that in this particular case, the methyl plays a more important role than the alkyl chain, such that the SC_6H_5 is free to stay away from the latter but is closer to the methyl, which is located on the same side of the ring plane.



Therefore our approach allows the synthesis of trisubstituted oxetanes with very good stereocontrol over four stereocenters. The stereocontrol is due to both the method we have used to obtain the starting material (Sharpless kinetic resolution) and the base-promoted ring closure mode.

Experimental Section

General. Air and moisture sensitive compounds were stored in Schlenk tubes or in Schlenk burettes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. The temperature of dry ice−ethanol baths is consistently indicated as −78 °C, that of the ice bath as 0 °C, and "room temperature" as 25 °C. If no reduced pressure is specified, boiling ranges were determined under ordinary atmospheric conditions (720 ± 35 mmHg). Purifications by flash column chromatography were performed using glass columns (10−50 mm wide); silica gel 230−400 mesh was chosen as stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 200 or 500 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Coupling constants (*J*) are measured in Hz. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of a doublet), m (multiplet), bs (broad singlet), bt (broad triplet), bq (broad quartet). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 or 75.5 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm). Mass spectra were obtained at a 70 eV ionization potential.

Materials. Starting materials were commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropyl amine, which was distilled over calcium hydride. Anhydrous tetrahydrofuran distilled from sodium diphenylketyl. Dimethylformamide was distilled over calcium hydride and then stored over 4-Å molecular sieves. Methylene chloride was dried over calcium chloride and stored over 4-Å molecular sieves. Petroleum ether, unless specified, was the 40−70 °C boiling fraction.

1. Preparation of Oxiranyl Ethers 6a−d. Molecular sieves (4 Å), CH_2Cl_2 (40 mL), (*E*)-3-nonen-2-ol (**4**) (1.42 g, 10.0 mmol), and (L)-(+)-diisopropyl tartrate (0.35 g, 1.5 mmol) were mixed under N_2 and cooled to −23 °C. Ti(O^iPr) (0.28 g, 1.0 mmol) was then added with a syringe and the mixture maintained at −23 °C for 30 min before ^{t}BuOOH (0.63 g of a 3 M solution in isooctane, dried over molecular sieves, 7.0 mmol) was slowly added. After 3 h, 10 mL of an aqueous solution obtained by dissolving 3.3 g of $FeSO_4 \cdot H_2O$ and 1.1 g citric acid in 10 mL of H_2O, was added and the mixture warmed up to room temperature. The two phases, which were formed after stirring, were separated; the water phase was extracted with CH_2Cl_2 (2 × 30 mL), and the organic solution was dried and evaporated. An aqueous solution (obtained by dissolving 0.5 g of NaCl and 3.0 g of NaOH in 9.0 mL of H_2O) was then added to the residue and, after 30 min stirring, worked up as described previously. After evaporation of the solvent, 1.44 g of a 42:58 mixture of (*R*)-(*E*)-3-nonen-2-ol [(*R*)-**4**] and *anti*-(*E*)-3,4-epoxy-2-nonanol (**5**) (de 80%) were obtained and purified by chromatography (hexane/ethyl acetate 2:1) to afford 0.37 g of pure [(*R*)-**4**] and 0.68 g (72%) of pure **5** with a 92% diastereomeric excess. ^{1}H-NMR ($CDCl_3$, 200 MHz): 3.96 (1H, m); 2.99 (1H, app td, *J* = 5.2, 2.2); 2.76 (1H, dd, *J* = 2.7, 2.2); 1.87 (1H, d, *J* = 2.7); 1.6−1.2 (8H, m); 1.25 (3H, d, *J* = 6.2); 0.89 (3H, t, *J* = 6.6). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 64.7; 61.7; 55.0; 31.5; 31.5; 25.7; 22.5; 18.7; 14.0. MS (*m*/*z* %): 149 (23); 125 (10); 109 (26); 91 (14); 86 (49); 84 (53); 83 (44); 71 (29); 69 (18); 58 (100); 55 (55). The epoxy alcohol **5** (0.68 g, 4.3 mmol) was dissolved in DMF (6.5 mL) and, after cooling to −5 °C, a suspension of NaH (0.13 g, 5.6 mmol) in DMF (6.5 mL) is added during 30 min. After an additional 30 min, a solution of the suitable halide (5.0 mmol; a: $C_6H_5CH_2Br$, b: *p*F-$C_6H_4CH_2Cl$, c: CH_2═$CHCH_2Br$, d: $C_6H_5SCH_2Cl$/NaI) in DMF (6.5 mL) was added and the mixture warmed up to 25 °C and then stirred for 15 h, before it was treated with H_2O (5 mL) and extracted with ether (3 × 10 mL). The organic phase was washed with H_2O (4 × 10 mL), and NaCl saturated (2 × 20 mL) and dried. After evaporation of the solvent, the oxiranyl ethers **6a**−**d** were purified by chromatography.

***(E)*-2-(Benzyloxy)-3,4-epoxynonane (6a).** Purification: eluent petroleum ether/ether 3:1; yield: 80%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.4−7.2 (5H, m); 4.44 (2H, AB system); 3.34 (1H, app quint., *J* = 6.2); 2.87 (1H, app td, *J* = 5.2, 1.8); 2.67 (1H, dd, *J* = 6.0, 1.8); 1.28 (3H, d, *J* = 6.2); 1.6−1.2 (8H, m); 0.89 (3H, t, *J* = 6.2).

***(E)*-2-[(4-Fluorobenzyl)oxy]-3,4-epoxynonane (6b).** Purification: eluent petroleum ether/ether 3:1; yield: 85%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.4−7.0 (4H, m); 4.54 (2H, AB system); 3.38 (1H, app quint, *J* = 6.2); 2.88 (1H, app td, *J* = 5.4, 2.0); 2.69 (1H, m); 1.28 (3H, d, *J* = 6.2); 1.6−1.2 (8H, m); 0.90 (3H, t, *J* = 6.2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 162.3 (d, J_{CF} = 245.4); 134.4; 129.2 (d, J_{CF} = 8.0); 115.2 (d, J_{CF} = 21.2); 74.5; 70.7; 60.5; 57.6; 31.7; 31.6; 25.6; 22.5; 17.8; 14.0. Anal. Calcd for $C_{16}H_{23}O_2F$: C, 72.15; H, 8.70. Found: C, 71.95; H, 9.10.

***(E)*-2-(2-propenoxy)-3,4-epoxynonane (6c).** Purification: eluent petroleum ether/ether 6:1; yield: 50%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 5.90 (1H, ddt, *J* = 17.2, 10.2, 5.7); 5.26 (1H, app dq, *J* = 17.2, 1.4); 5.17 (1H, dq, *J* = 10.2, 1.4); 4.04 (2H, AB system); 3.30 (1H, app quint, *J* = 6.2); 2.89 (1H, app td, *J* = 5.6, 2.2); 2.63 (1H, dd, *J* = 5.8, 2.2); 1.6−1.2 (8H, m); 1.26 (3H, d, *J* = 6.2); 0.89 (3H, t, *J* = 6.6). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 135.0; 116.8; 74.4; 70.2; 60.5; 57.9; 31.8; 31.6; 25.6; 22.5; 17.8; 14.0. MS (*m*/*z* %): 155 (3, $M^+ - C_3H_7$); 141 (9); 99 (22); 95 (11); 86 (16); 85 (59); 84 (26); 83 (40); 82 (12); 81 (29); 71 (100); 68 (14); 67 (16); 58 (34); 57 (63); 55 (99). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.64; H, 11.06.

***(E)*-2-[(Phenylthio)methoxy]-3,4-epoxynonane (6d).** Purification: eluent petroleum ether/ethyl acetate 17:1; yield:

56%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.6−7.4 (5H, m); 5.04 (2H, AB system); 3.78 (1H, qd, J = 6.5, 5.5); 2.87 (1H, td, J = 5.5, 2.0); 2.66 (1H, dd, J=5.5, 2.0); 1.6−1.2 (8H, m); 1.25 (3H, d, J = 6.5) 0.89 (3H, t, J = 6.2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 135.7; 130.0; 128.9; 126.7; 74.2; 72.0; 60.1; 57.6; 31.7; 31.6; 25.6; 22.5; 17.33; 14.0. MS (m/z %): 280 (1, M^+); 123 (52); 110 (19); 109 (18); 87 (33); 83 (41); 81 (16); 77 (11); 71 (28); 69 (19); 65 (14); 59 (13); 57 (66); 55 (100); 51 (11). Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.82; H, 8.70.

2. Isomerization of Oxiranes. Hexane was stripped off from a solution of BuLi (3.7 mL of a 1.5 M solution, 0.55 mmol) and precooled THF (1.0 mL) was added at −78 °C under N_2, followed by diisopropylamine (56 mg, 0.55 mmol) and potassium *tert*-butoxide (62 mg, 0.55 mmol). The mixture was stirred at −78 °C for 45 min after which the oxirane (0.50 mmol) was added and allowed to react for 15 h at −50 °C; the reaction was then quenched with H_2O (2.0 mL) and extracted twice with Et_2O (2 × 5.0 mL), after warming to 25 °C. The organic layers were combined and washed with brine and dried; evaporation of the solvent gave of the desired product as an oil which upon purification by flash chromatography yielded pure oxetane. For compounds **7a** and **7b** only data relative to the *anti* isomers are reported; the *syn* products were lost during purification.

(2,3-*anti*/3,4-*anti*)-2-Phenyl-3-(1-hydroxyhexyl)-4-methyloxetane (*anti,anti*-7a). Purification: eluent petroleum ether/ethyl acetate 1:1; yield: 81%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.4−7.2 (5H, m); 5.39 (1H, d, J = 7.4); 4.86 (1H, app q, J = 6.6,); 3.9 (1H, m); 2.47 (1H, app q, J = 6.8); 1.7−1.0 (9H, m); 1.50 (3H, d, J = 6.4); 0.86 (3H, t, J = 7.0). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.67; H, 9.85.

(2,3-*anti*/3,4-*anti*)-2-(4-Fluorophenyl)-3-(1-hydroxyhexyl)-4-methyloxetane (*anti,anti*-7b). Purification: eluent petroleum ether/ethyl acetate 1:1; yield: 81%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.6−7.0 (4H, m); 5.36 (1H, d, J = 7.0); 4.86 (1H, app q, J = 6.2,); 4.0−3.8 (1H, m); 2.44 (1H, app q, J = 6.8); 1.7−1.0 (9H, m); 1.50 (3H, d, J = 6.6); 0.87 (3H, t, J = 7.0). ^{13}C-NMR ($CDCl_3$, 75.45 MHz); 162.5 (d, J_{CF} = 246.3); 138.3 (d, J_{CF} = 3.0); 127.6 (d, J_{CF} = 8.1); 115.4 (d, J_{CF} = 21.1); 79.8; 77.1; 71.9; 57.6; 35.1; 31.7; 24.9; 23.7; 22.5; 13.9. Anal. Calcd for $C_{16}H_{23}O_2F$: C, 72.15; H, 8.70. Found: C, 71.98; H, 8.95.

(2,3-*anti*/3,4-*anti*)-2-Vinyl-3-(1-hydroxyhexyl)-4-methyloxetane (*anti,anti*-7c). Purification: eluent petroleum ether/ethyl acetate 15:1; yield: 80%. ^{1}H-NMR ($CDCl_3$, 200 MHz): 6.03 (1H, ddd, J = 17.2, 10.2, 6.6); 5.29 (1H, app dt, J = 10.2, 1.6); 5.16 (1H, app dt, J = 10.6, 1.6); 4.8−4.6 (2H, m); 3.9−3.7 (1H, m); 2.28 (1H, app q, J = 7.0); 1.6−1.2 (9H, m); 1.41 (3H, d, J = 6.2); 0.89 (3H, t, J = 6.2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 139.4; 116.3; 79.7; 77.5; 72.4; 54.9; 35.0; 31.7; 24.9; 24.2; 22.5; 14.0. MS (m/z %): 109 (11); 99 (25); 97 (10); 86 (22); 84 (16); 83 (29); 81 (21); 79 (11); 71 (100); 69 (15); 67 (10); 57 (16); 55 (23). Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.47; H, 11.41.

(2,3-*syn*/3,4-*anti*)-2-(Phenylthio)-3-(1-hydroxyhexyl)-4-methyloxetane (*syn,anti*-7d). Purification: eluent petroleum ether/ethyl acetate 4:1; yield: 80%. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.4−7.2 (5H, m); 6.08 (1H, d, J = 8.0); 5.09 (1H, app quint, J = 6.0); 4.05 (1H, m); 2.96 (1H, app q, J = 6.5); 1.92 (1H, d, J = 4.5); 1.6−1.2 (8H, m); 1.48 (3H, d, J = 6.0); 0.90 (3H, t, J = 6.2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 132.8; 131.1; 129.0; 127.2; 89.3; 79.1; 69.9; 52.5; 35.7; 31.6; 25.1; 23.0; 22.6; 14.0. MS (m/z %): 279 (M^+ − H); 263 (10); 245 (14); 219 (52); 163 (48); 161 (12); 153 (11); 149 (36); 147 (20); 135 (23); 129 (12); 123 (25); 116 (14); 115 (15); 110 (22); 109 (100); 105 (13); 91 (21); 86 (33); 85 (27); 84 (78); 81 (17); 77 (28); 73 (17); 71 (42); 69 (35); 67 (22); 63 (33); 57 (22); 55 (41), 52 (21); 51 (20). Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.72; H, 8.72.

(2,3-*anti*/3,4-*anti*)-2-(Phenylthio)-3-(1-hydroxyhexyl)-4-methyloxetane (*anti,anti*-7d). ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.4−7.2 (5H, m); 5.72 (1H, d, J = 7.0); 4.66 (1H, app quint, J = 6.0); 3.85 (1H, m); 2.46 (1H, app q, J = 6.5); 1.6−1.2 (9H, m); 1.24 (3H, d, J = 6.5); 0.89 (3H, t, J = 6.2). ^{13}C-NMR ($CDCl_3$, 75.45 MHz): 135.0; 131.1; 128.8; 127.8; 85.9; 76.8; 71.3; 54.6; 35.0; 31.7; 25.0; 23.0; 22.6; 14.0.). Anal. Calcd for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.68; H, 8.75.

Acknowledgment. Financial support by the Consiglio Nazionale delle Ricerche, Roma, is much appreciated. We also thank Mrs. Anna Bigi for her helpful assistance in the preparation of compounds **6a** and **7a**.

JO9604595