A New General Method To Obtain Chiral 2-Alkylglycidic Acid Derivatives: Synthesis of Methyl (*R*)-(+)-Palmoxirate

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Received July 15, 1993[⊕]

The hydrolysis of the diastereomerically pure cyanohydrins, obtained by reaction of Et_2AlCN with homochiral α-sulfinyl ketones, yielded β-sulfenyl esters or amides, which evolved into the corresponding 2-alkylglycidic acid derivatives (ee >97%) by treatment with $Me_3O^+BF_4^-$ and $NaHCO_3$. The use of this sequence to synthesize optically pure (*R*)-(+)-palmoxirate, a powerful hypoglicemic agent, is also described.

Methyl 2-tetradecyloxirane-2-carboxylate (1) (methyl palmoxirate) has been found to be a potent inhibitor of the fatty acid oxidation and a powerful hypoglicemic agent of several animal species including man.[1] It seems that all the activity resides in the (*R*)-enantiomer[2,3] (Scheme 1) whereas the (*S*)-enantiomer is essentially inactive.[4] The enantioselective synthesis of (*R*)-1 has been achieved by chemical and enzymatic methods. The former[4,5] uses, as the key step, the Sharpless chiral epoxidation of the nontrivial allylic alcohol 2[1d] (Scheme 1), which gives rise to 1 in a yield of less than 28%. The enzymatic method is less convenient since the overall yield is quite low, and the enzymatic resolution gives rise to only 87% ee.[6]

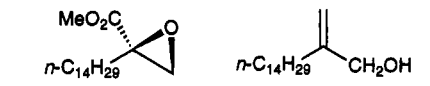
Recently, we have reported a simple and highly stereoselective method to obtain β-sulfinyl cyanohydrins by reaction of Et_2AlCN and chiral α-sulfinyl ketones.[7] The obtained cyanohydrins can be conveniently modified to become precursors of 2-alkylglycidic acid derivatives. In this paper, a new general method to synthesize optically pure amides and esters derived from 2-alkylglycidic acids and its application to the synthesis of enantiomerically pure alkyl (*R*)-palmoxirates are reported.

Results and Discussion

In order to design a new general method to prepare optically pure 2-alkylglycidic acid derivatives, we envisaged the sequence shown in Scheme 2. The first step, involving asymmetric hydrocyanation of ketones, can be achieved by reaction of α-sulfinyl ketones with Et_2AlCN,[7] which is an efficient and highly stereoselective method to obtain β-sulfinyl cyanohydrins. Moreover, the sulfinyl group has been used as a precursor of a good leaving group in the synthesis of optically pure epoxides,[8] although only in cases in which the starting materials were secondary β-hydroxy sulfoxides. Hydrolysis of the cyano group to carboxylic acid derivatives (CN → COY) and formation of the oxirane ring must take place in mild conditions in order to avoid epimerization at the chiral carbon.

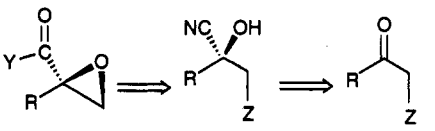
The optically pure cyanohydrins 3–5 selected as starting materials (Scheme 3) had been previously prepared by reaction of the corresponding α-sulfinyl ketones $RCOCH_2SOTol$ and Et_2AlCN.[7] The strong tendency of compounds 3–5 to eliminate HCN, evolving into the sulfinyl ketones,[7]

Scheme 1

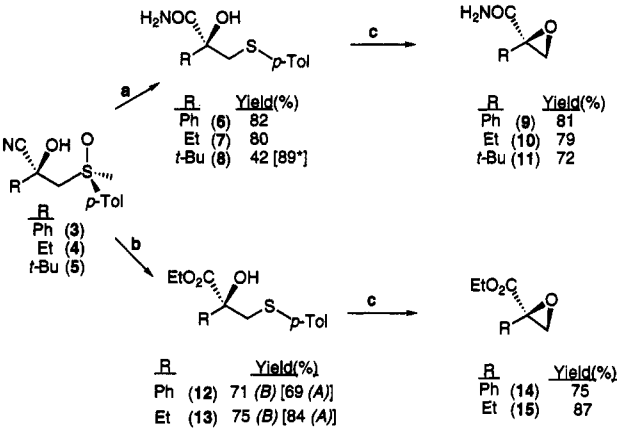


(*R*)-methyl palmoxirate (1) (2)

Scheme 2



Scheme 3[a]



[a] Key: (a) 1. HCl (g)–Et_2O, 0 °C, 2 h; 2. H_2O, 3 h; (b) HCl–EtOH, reflux, 24 h (method A) or 1. HCl (g)–EtOH, rt, 6 days. 2. H_2O, 24 h (method B) (see text); (c) 1. $Me_3O^+BF_4^-$; 2. K_2CO_3. *Concentrated HCl, reflux, 24 h.

[⊕] Abstract published in *Advance ACS Abstracts,* December 15, 1993.

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(3) The active drug, formed *in vivo* after administration of (*R*)-1, is the (*R*)-2-tetradecyloxiranecarboxylic acid CoA ester. The biological activity of the ester 1 and its precursor acid has been demonstrated to be similar (see refs 1d and 2), the first being chosen for clinical trial on the basis of greater stability (see ref 4).

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suggested that the hydrolysis of the CN group into CO_2R and $CONH_2$ (which cannot behave as leaving groups) should be the first step of the sequence.

Reaction of compounds **3** and **4** with a saturated solution of HCl (g)[9] in diethyl ether at 0 °C took place with concomitant reduction of the sulfinyl group, yielding the β-sulfenyl carboxamides **6** and **7**. These results as well as the fact that the used conditions were unusually mild to achieve the hydrolysis of nitriles suggested the anchimeric assistance of the sulfinyl group.[10] Under identical conditions, compound **5** evolved into a mixture of compound **8** and its corresponding *S*-oxide derivative. In this case it was necessary to use stronger acid conditions (reflux with concentrated HCl or concentrated HCl–EtOH) to get the sulfide **8** in high yield, which must be a consequence of the steric hindrance of the *tert*-butyl group.

Hydrolysis of the CN group of the sulfinyl cyanohydrins to CO_2Et was performed by heating at reflux for 24 h in a 1:1 mixture of concentrated HCl–EtOH. At room temperature this transformation required 5–6 days in a saturated HCl (g) solution of absolute EtOH. In both conditions, the reduction of the sulfinyl group was also observed, and the sulfenyl esters **12** and **13** were isolated from the cyanohydrins **3** and **4** (Scheme 3). The hydrolysis of the *tert*-butyl derivative **5** only evolved into the carboxamide **11**, which suggests that amides must be intermediates in the transformation of the cyanohydrins into the esters and that the steric hindrance of the *tert*-butyl group precludes the hydrolysis of the $CONH_2$ group in compound **11**. The influence of temperature and reaction time on the chemical yields is small but very important on the stereoselectivity of the process (*vide infra*).

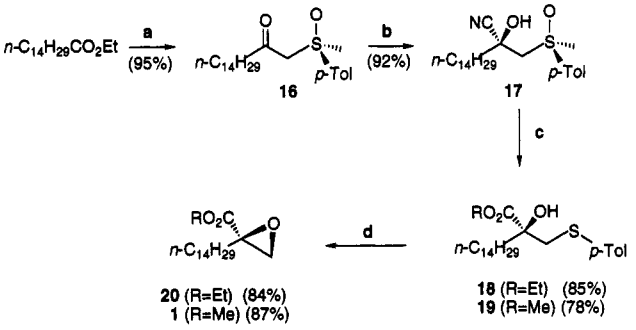
Treatment of the sulfenyl derivatives **6–8** with trimethyloxonium tetrafluoroborate in anhydrous CH_2Cl_2 followed by aqueous K_2CO_3[8] afforded the epoxyamides **9–11**. Analogously, the epoxy esters **14** and **15** were obtained from **12** and **13**, respectively. Although the starting carbinols are tertiary, high yields were obtained in all cases.

The optical purity of the final epoxides was determined by ^1H NMR by using Eu(tfc)$_3$ as chiral lanthanide shift reagent. The ee's of **9** and **10** were >97%, but that of **11** was only 94% determined on a sample of epoxide obtained from the sulfenyl carboxamide **8** resulting from reflux of **5** with concentrated HCl. The ee of **11** became >97% when the epoxide derived from the carboxamide **8** was obtained at 0 °C in diethyl ether saturated with HCl (g), which suggests that the temperature was the factor responsible for the slight epimerization observed in the first case. A similar situation was observed in the epoxy esters **14** and **15**. Their ee's were only 34% and 90%, respectively, determined on the compounds obtained from samples of **12** and **13** resulting from reflux of **3** and **4** in a concentrated HCl–EtOH mixture (24 h), whereas both ee's became >97% when hydrolysis of the cyanohydrins was carried out at room temperature with a saturated solution of HCl (g) in absolute EtOH (6 days).

(9) Hydrolysis of sulfinyl cyano derivatives to sulfenyl amides or sulfenyl esters was not trivial, and other less successful hydrolytic conditions and reagents were tried. The use of basic conditions results in the retrohydrocyanation of cyanohydrins.

(10) The nucleophilic intramolecular attack of the sulfinylic oxygen on the protonated nitrile would yield a cyclic species. Its evolution into final sulfenyl carboxamide may occur through a sulfurane intermediate. The essays needed to confirm the above mechanistic proposal, including the use of ^{18}O-labeled compound, are currently being carried out.

Scheme 4[a]



[a] Key: (a) (*R*)-*p*-Tol-SOMe/LDA, 0 °C, 3 h; (b) Et_2AlCN, 0 °C, 2 h; (c) HCl–ROH, reflux, 24 h; (d) 1. $Me_3O^+BF_4^-$; 2. K_2CO_3.

We have applied this method to the synthesis of methyl and ethyl (*R*)-(+)-2-tetradecyloxirane-2-carboxylates [(*R*)-(+)-palmoxirates, **1** and **20**] (Scheme 4). The reaction of commercially available ethyl pentadecanoate with (*R*)-(+)-methyl *p*-tolyl sulfoxide in the conditions previously reported[7,11,12a] yielded the α-sulfinyl ketone **16**, the hydrocyanation of which with Et_2AlCN in toluene afforded diastereomerically pure cyanohydrin **17** in 92% yield. The hydrolysis of **17** with a 1:1 mixture of concentrated HCl–ROH yielded the sulfenyl esters **18** and **19**, which were transformed into the enantiomerically pure glycidic acid derivatives **20** and **1** (^1H-NMR, by using Eu(tfc)$_3$ as chiral lanthanide shift reagent) by alkylation and further base treatment of the obtained sulfonium salts (Scheme 4). In this case, the epimerization at the hydroxylic carbon was not observed despite the conditions used for hydrolysis. By this method we have achieved the synthesis of the optically pure methyl (*R*)-(+)-palmoxirate **1** with an overall yield of 59%, substantially higher than those previously reported (<18%).[4,13]

The absolute configuration of compound **1** was established by comparison of the specific optical rotation of the sample obtained by us with that previously reported in the literature.[4]

In conclusion, we describe a new general method to obtain optically pure 2-alkylglycidic derivatives which have been succesfully used to synthesize alkyl (*R*)-(+)-palmoxirates. Currently, we are using this method to prepare other structurally similar compounds and extending its scope to the synthesis of trisubstituted oxiranes.

Experimental Section

Details concerning the recording of NMR, IR, MS spectra, the analytical instruments used, the determination of melting points, elemental analyses, enantiomeric purity, and chromatographic procedures (flash chromatography and TLC) have been previously described.[12] Dry THF and ethyl ether were distilled from sodium/benzophenone ketyl, and toluene and CH_2Cl_2 were dried over P_2O_5. Eluting solvents for chromatography are indicated in parentheses in the text. ^1H NMR (200.1 MHz) and ^{13}C NMR (50.3 MHz) spectra were measured in $CDCl_3$ solutions. *J* values are given in Hz. Tol refers to the tolyl group. HRMS were obtained in the electron impact (EI) mode at 70 eV. All

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compounds prepared were shown to be over 97% pure by NMR analysis. The syntheses of compounds 3–8 have been previously described.[7]

(R)-1-[(4-Methylphenyl)sulfinyl]hexadecan-2-one (16). To a solution of 1 mmol of LDA in 20 mL of THF at −78 °C was added dropwise 154 mg (1 mmol) of (R)-(+)-methyl p-tolyl sulfoxide in 20 mL of THF. The temperature was then allowed to reach 0 °C, and the mixture was stirred for 30 min. Then 607.5 mg (2.25 mmol) of ethyl pentadecanoate in 20 mL of THF was added. The reaction mixture was stirred at 0 °C for 2 h and decomposed with 20 mL of a saturated NH_4Cl solution. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to yield a residue which was crystallized from hexane to give 16 (176.7 mg, 95%): mp 86–87 °C; $[\alpha]^{20}_D$ +107.5° ($CHCl_3$, c = 1.0); δ 7.54 and 7.33 (AA'BB' system, 4H, C_6H_4), 3.88 and 3.75 (AB system, 2H, J = 13.5, CH_2S), 2.46 (m, 2H, CH_2CO), 2.41 (s, 3H, CH_3Ar), 1.39–1.10 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, J = 6.5, CH_3CH_2). Anal. Calcd for $C_{23}H_{38}O_2S$: C, 72.96; H, 10.12. Found: C, 72.99; H, 10.44.

(S_2,R_8)-2-Hydroxy-2-[[(4-methylphenyl)sulfinyl]methyl]hexadecanenitrile (17). A solution of 372 mg (1 mmol) of 16 in 10 mL of toluene was dropwise added to a solution of 4 mmol of Et_2AlCN in 10 mL of toluene, and the mixture was stirred at −78 °C for 2 h. The reaction mixture was cannulated (by applying a positive nitrogen pressure to the reaction flask) into a mixture of 25 mL of MeOH and 15 mL of concentrated HCl, previously cooled at −78 °C. The resulting mixture was vigorously stirred at −78 °C for 1 h, poured into a mixture of 20 mL of concentrated HCl and 30 mL of ice–water, and extracted with CH_2Cl_2. The extracts were washed with water (30 mL), dried (Na_2SO_4), concentrated, and purified by crystallization to give the sulfinyl cyanohydrin 17 (367.1 mg, 92%): mp 79–80 °C; $[\alpha]^{20}_D$ +125.0° ($CHCl_3$, c = 1.0); δ 7.59 and 7.39 (AA'BB' system, 4H, C_6H_4), 5.94 (bs, 1H, OH), 3.02 and 2.92 (AB system, 2H, J = 13.2, CH_2S), 2.45 (s, 3H, CH_3Ar), 1.78 and 1.54 (m, 2H, CH_2COH), 1.43–1.07 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, J = 6.8, CH_3CH_2). Anal. Calcd for $C_{24}H_{39}NO_2S$: C, 71.05; H, 9.69; N, 3.45. Found: C, 70.66; H, 9.68; N, 2.94.

Hydrolysis of Cyanohydrins into Hydroxy Esters. Method A. A solution of 1 mmol of cyanohydrin in 10 mL of a 1:1 mixture of concentrated HCl–ROH (R = Et or Me) was stirred at reflux for 24 h. The reaction mixture was cooled at rt and concentrated in vacuo. The residue was diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), and concentrated. **Method B.** 20 mL of absolute EtOH previously saturated with HCl (g) was added to a flask containing 0.8 mmol of cyanohydrin, and the mixture was stirred at rt for 6 days. Then ice–water (20 mL) was added, and the stirring was kept at rt for 24 h. The workup was as in method A.

Ethyl (S)-2-hydroxy-3-[(4-methylphenyl)sulfenyl]-2-phenylpropanoate (12) was prepared by hydrolysis of 3 (method B). It was purified by flash chromatography (hexane–ethyl acetate (8:1)): yield 71% (oil); HRMS calcd for $C_{18}H_{20}O_3S$ 316.1133, found 316.1126; $[\alpha]^{20}_D$ −15.9° ($CHCl_3$, c = 0.15); δ 7.62 (m 2H, aromatic protons (Ph)), 7.35 (m, 3H, aromatic protons (Ph)), 7.34 and 7.09 (AA'BB' system, 4H, C_6H_4), 4.09 (m, 2H, CH_2O), 4.05 (bs, 1H, OH), 3.79 and 3.43 (AB system, 2H, J = 13.5, CH_2S), 2.31 (s, 3H, CH_3Ar), 1.18 (t, 3H, J = 7.2, CH_3CH_2).

Ethyl (S)-2-hydroxy-2-[[(4-methylphenyl)sulfenyl]methyl]butanoate (13) was prepared by hydrolysis of 4 (method B). It was purified by flash chromatography (hexane–ethyl acetate (8:1)): yield 75% (oil); HRMS calcd for $C_{14}H_{20}O_3S$ 268.1133, found 268.1132; $[\alpha]^{20}_D$ −35.4° ($CHCl_3$, c = 0.2); δ 7.32 and 7.08 (AA'BB' system, 4H, C_6H_4), 4.00 (m, 2H, CH_2O), 3.54 (bs, 1H, OH), 3.31 and 3.17 (AB system, 2H, J = 13.7, CH_2S), 2.30 (s, 3H, CH_3Ar), 1.77 (m, 2H, CH_2CH_3), 1.17 (t, 3H, J = 7.2, CH_3CH_2O), 0.87 (t, 3H, J = 7.4, CH_3CH_2).

Ethyl (S)-2-hydroxy-2-[[(4-methylphenyl)sulfenyl]methyl]hexadecanoate (18) was prepared by hydrolysis of 17 (method A). It was purified by flash chromatography (hexane–ethyl acetate (12:1)): yield 85% (oil); HRMS calcd for $C_{19}H_{36}O_3S$ 312.2664, found 312.2671; $[\alpha]^{20}_D$ +9.7° ($CHCl_3$, c = 0.5); δ 7.34 and 7.10 (AA'BB' system, 4H, C_6H_4), 4.11 and 3.90 (m, 2H, CH_2O), 3.34 and 3.19 (AB system, 2H, J = 13.6, CH_2S), 2.33 (s, 3H, CH_3-Ar), 1.87–1.60 (m, 2H, CH_2COH), 1.41–1.23 (m, 24H, $(CH_2)_{12}$-CH_3), 1.19 (t, 3H, J = 7.2, CH_3CH_2O), 0.90 (t, 3H, J = 6.4, CH_3CH_2).

Methyl (S)-2-hydroxy-2-[[(4-methylphenyl)sulfenyl]-methyl]hexadecanoate (19) was prepared by hydrolysis of 17 (method A). It was purified by flash chromatography (hexane–ethyl acetate (14:1)) (yield 78%) and crystallized from hexane, mp 61–62 °C; $[\alpha]^{20}_D$ −17.8° ($CHCl_3$, c = 0.4); δ 7.31 and 7.08 (AA'BB' system, 4H, C_6H_4), 3.90 (s, 3H, CH_3O), 3.32 and 3.14 (AB system, 2H, J = 13.8, CH_2S), 2.30 (s, 3H, CH_3Ar), 1.71 (m, 2H, CH_2COH), 1.38–1.18 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, J = 6.5, CH_3CH_2). Anal. Calcd for $C_{25}H_{42}O_3S$: C, 71.04; H, 10.02. Found: C 70.77; H, 10.36.

Synthesis of 2-Alkylglycidic Acid Derivatives. These compounds were prepared following the procedure described by Pirkle[8] modified as follows: To a solution of 1.01 mmol of sulfenyl hydroxy acid derivative in 2 mL of CH_2Cl_2 was added 177.4 mg (1.2 mmol) of trimethyloxonium tetrafluoroborate. The mixture was stirred at rt for 2 h, and then a solution of 270.0 mg (2.0 mmol) of $NaHCO_3$ in 1.5 mL of water was added. The resulting mixture was vigorously stirred at rt for 17 h. The organic layer was separated, dried (Na_2SO_4), and concentrated.

(R)-2-Phenyloxirane-2-carboxamide (9) was prepared by reaction of 6. It was purified by flash chromatography (hexane–ethyl acetate (3:2)) (yield 81%) and crystallized from hexane–acetone (10:1): mp 106–107 °C; $[\alpha]^{20}_D$ +12.3° ($CHCl_3$, c = 0.275); δ 7.64–7.57 (m, 2H, aromatic protons), 7.41–7.34 (m, 3H, aromatic protons), 6.43 (bs, 1H, NH), 5.90 (bs, 1H, NH), 3.27 and 3.12 (AB system, 2H, J = 5.6, CH_2). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.13; H, 5.47; N, 8.29.

(R)-2-Ethyloxirane-2-carboxamide (10) was prepared by reaction of 7. It was purified by flash chromatography (hexane–ethyl acetate (2:1)) (yield 79%) and crystallized from hexane: mp 100–101 °C. HRMS (MS–GC) calcd for $C_5H_9NO_2$ 115.0633, found 115.0635; $[\alpha]^{20}_D$ +19.7° ($CHCl_3$, c = 0.15); δ 6.31 (bs, 1H, NH), 5.85 (bs, 1H, NH), 2.90 and 2.87 (AB system, 2H, J = 5.0, CH_2O), 2.35 (m, 1H, CH(H)Me), 1.56 (m, 1H, CH(H)Me), 1.00 (t, 3H, J = 7.4, CH_3).

(R)-2-*tert*-Butyloxirane-2-carboxamide (11) was prepared by reaction of 8. It was purified by flash chromatography (hexane–ethyl acetate (1:1)) (yield 72%) and crystallized from hexane: mp 97–98 °C; HRMS calcd for $C_7H_{13}NO_2$ 143.0946, found 143.0909; $[\alpha]^{20}_D$ −35.2° ($CHCl_3$, c = 0.15); δ 6.40 (bs, 1H, NH), 5.58 (bs, 1H, NH), 2.96 and 2.75 (AB system, 2H, J = 4.6, CH_2), 1.11 (s, 9H, $(CH_3)_3C$).

Ethyl (R)-2-phenyloxirane-2-carboxylate (14) was prepared by reaction of 12. It was purified by flash chromatography (hexane–ethyl acetate (6:1)): yield 75% (oil); HRMS (MS–GC) calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0743; $[\alpha]^{20}_D$ −10.6° ($CHCl_3$, c = 0.2); δ 7.51 (m, 2H, aromatic protons), 7.38 (m, 3H, aromatic protons), 4.26 (c, 2H, J = 7.1, CH_2CH_3), 3.43 and 2.96 (AB system, 2H, J = 6.4, CH_2O), 1.29 (t, 3H, J = 7.1, CH_3).

Ethyl (R)-2-ethyloxirane-2-carboxylate (15) was prepared from 13. (Solutions of this compound had to be concentrated on a rotary evaporator at 0 °C because of its low bp.) It was purified by flash chromatography (hexane–ethyl acetate (6:1)): yield 87% (oil); $[\alpha]^{20}_D$ +10.7° ($CHCl_3$, c = 0.67) δ 4.23 (m, 2H, CO_2CH_2), 3.04 and 2.80 (AB system, 2H, J = 5.9, CH_2O), 2.12 and 1.75 (m, 2H, CH_2Me), 1.30 (t, 3H, J = 7.2, CH_3CH_2O), 1.02 (t, 3H, J = 7.4, CH_3CH_2C).

Ethyl (R)-2-tetradecyloxirane-2-carboxylate (20) was prepared from 18. It was purified by flash chromatography (hexane–ethyl acetate (9:1)), yield 84%. It crystallized upon standing: HRMS calcd for $C_{19}H_{36}O_3$ 312.2664, found 312.2671; $[\alpha]^{20}_D$ +6.8° ($CHCl_3$, c = 0.2); δ 4.22 (m, 2H, CO_2CH_2), 3.03 and 2.78 (AB system, 2H, J = 5.9, CH_2O), 2.07 and 1.64 (m, 2H, CH_2CH_2C), 1.31 (t, 3H, J = 7.1, CH_3CH_2O), 1.53–1.08 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, J = 6.5, $CH_3(CH_2)_{13}$).

Methyl (R)-2-tetradecyloxirane-2-carboxylate (1) was prepared from 19. It was purified by flash chromatography (hexane–ethyl acetate (13:1)), yield 87%. It crystallized upon solution in hexane and slow evaporation of the solvent: mp 56–57 °C (lit.[4] mp 43 °C); $[\alpha]^{20}_D$ +10.12° ($CHCl_3$, c = 0.4) [lit.[4] $[\alpha]^{20}_D$ +10.27° ($CHCl_3$, c = 0.5)]; δ 3.76 (s, 3H, CH_3O), 3.04 and 2.79 (AB

system, 2H, J = 5.9, CH_2O), 2.07 and 1.67 (m, 2H, CH_2C), 1.54–1.12 (m, 24H, $(CH_2)_{12}CH_3$), 0.88 (t, 3H, J = 6.5, $CH_3(CH_2)_{13}$). Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.43; H, 11.49.

Acknowledgment. We thank Dirección General de Investigación Científica y Técnica (Grant PB92/162) for financial support. We also thank Prof. H. M. Walborsky for many helpful discussions. One of us (J.L.G.R.) gratefully acknowledges the financial support to complete a sabbatical stay at Florida State University from the DGICYT.

Supplementary Material Available: IR and ^{13}C NMR data for **1** and **9–20**, MS data for **1**, **9–14**, **16**, **17**, **19**, and **20**, and ^1H NMR spectra of **10–15**, **18**, and **20** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.