

On the Stereospecific Synthesis of Methylene-interrupted Di- and Polymethoxy-substituted Fatty Acids

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The four possible stereoisomers of methyl 2,4-dimethoxytridec-12-enoate have been synthesized from the optically active 2-methoxyundec-10-enoic acids. The synthetic route involves stepwise introduction of an asymmetric centre to optically active 2-methoxy-substituted primary iodides with the aid of diethyl methoxymalonate. The diastereoisomers obtained have been separated by preparative gas chromatography or liquid chromatography on silicic acid.

Methyl 2D,4D- and methyl 2L,4D-dimethoxytridec-12-enoate have been cleaved oxidatively to optically active half-esters, which have been chain-lengthened to give methyl 2D,4D- and methyl 2L,4D-dimethoxyheptacosanoate.

The mass spectra of 2D-methoxyundec-10-en-1-ol, methyl 2D,4D-dimethoxytridec-12-enoate, and methyl 2L,4D-dimethoxyheptacosanoate are reproduced.

Long chain optically active aliphatic structures containing several hydroxyl groups have been isolated from the lipids of tubercle bacilli. The structure of phthiocerol, being a complex β -glycol of the type $\text{CH}_3(\text{CH}_2)_n - \text{CHOH} - \text{CH}_2 - \text{CHOH} - (\text{CH}_2)_4 - \text{CH} - \text{CH} - (\text{CH}_2)_m - \text{CH}_3$, $n=20$ or 22 ; $m=0$ or 1 ,



from human and bovine strains has been elucidated by mass spectrometric studies.¹⁻⁴ In the absence of suitable methods for preparation, optically active phthiocerols have as yet not been synthesized, a consequence being that there is still doubt about their stereochemistry.^{5,6}

Very little has been reported in the literature about the preparation of optically active hydroxy- and methoxy-substituted molecules with more than one asymmetric carbon atom. The only relevant work in the field appears to be that of Serck-Hanssen⁷ in which the synthesis of two of the four possible stereoisomers of 2,4-eicosanediol is described. The method appears to be applicable to preparation of molecules with two asymmetric carbon atoms only.

Several optically active polymethyl-branched methylene-interrupted fatty acids have recently been synthesized.⁸⁻¹¹ Asymmetric centres carrying methyl side chains are here introduced by alkylation of diethyl methylmalonate with an optically active 2-methyl-substituted primary halide. The diastereoisomers are separated by means of preparative gas chromatography. The possible stereoisomers of a given polymethyl-branched fatty acid may ultimately be prepared, provided the stereoisomers to be resolved possess reasonably short hydrocarbon end groups. Very long chain methyl-branched fatty acids are best prepared from ω -unsaturated methyl esters. By oxidative cleavage such esters can be converted to half esters which may subsequently be subjected to mixed anodic coupling with a normal chain fatty acid.

It was thought of interest to investigate if methylene-interrupted methoxy-substituted fatty acids can be built up analogously. It has recently been shown that optically active methoxy-substituted fatty acids can be transformed to the corresponding hydroxy-acids with retained optical activity.¹²

We have recently described the synthesis of the optically active methyl 2-methoxyundec-10-enoates.¹³ These can readily be converted to the primary halides required for alkylation. The synthesis of diethyl methoxymalonate has been described previously.¹⁴ The preparation of racemic 2-methoxydecanoic acid by alkylation of diethyl methoxymalonate with *n*-octyl bromide¹⁴ appears to be the only report in the literature of this type of chain-lengthening.

SYNTHESIS

It has now been found that diethyl methoxymalonate can be alkylated with optically active 2-methoxy-substituted primary iodides in the presence of potassium *tert*-butoxide in satisfactory yields. The sequence of the synthesis is outlined in Chart 1. Optically pure methyl 2D-methoxyundec-10-enoate (I) of $[\alpha]_D^{23} + 35.4^\circ$ ¹³ served as starting material. This was reduced to 2D-methoxyundec-10-en-1-ol (II). II was then converted to the corresponding tosyl ester (III), the tosylate group subsequently being replaced by iodine to yield 1-iodo-2D-methoxyundec-10-ene (IV). Alkylation of diethyl methoxymalonate with IV yielded ethyl 2-ethoxycarbonyl-2,4D-dimethoxytridec-12-enoate (V), which after hydrolysis, decarboxylation and esterification afforded the diastereoisomeric pair methyl 2,4D-dimethoxytridec-12-enoate (VI). A gas chromatogram of VI is shown in Fig. 1. It shows as expected two peaks, VII and VIII, originating from the two stereoisomers.

Attempts were made to separate the isomers on a preparative gas chromatographic column (HI-EFF-4B as stationary phase). The diastereoisomers separated excellently, but had unfortunately so strong a tendency to form aerosols, that severe losses were encountered.

Liquid chromatography on silicic acid was therefore tried for resolution. It was found that repeated chromatography on this adsorbent afforded optically pure VII and VIII. Interestingly, the order of elution of VII and VIII on silicic acid is reversed that on the GLC column. Optically pure VIII was obtained in a satisfactory amount after only one run on the column whereas it was necessary to repeat the chromatography three times to obtain VII of satisfactory optical purity.

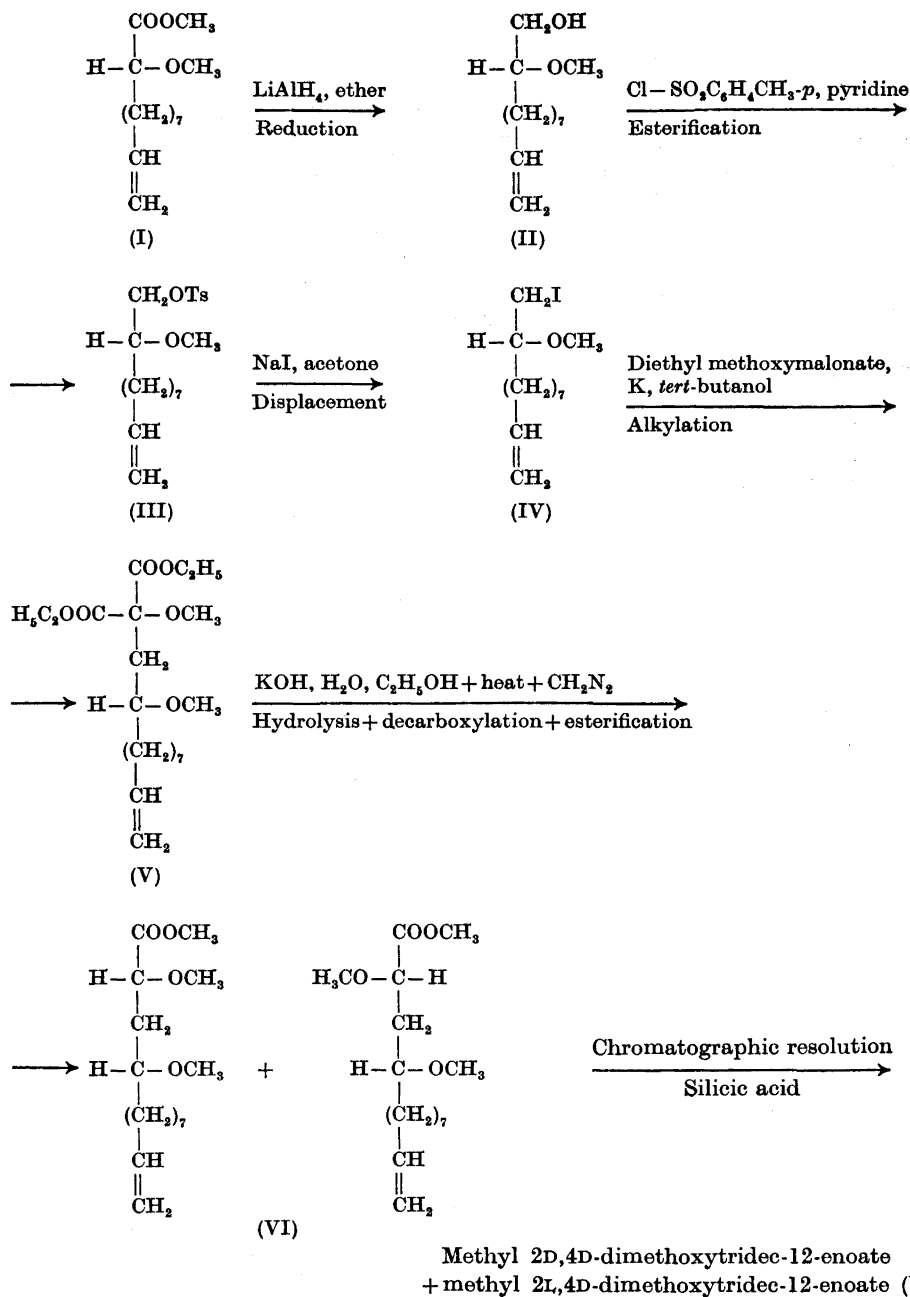


Chart 1.

Starting with methyl 2L-methoxyundec-10-enoate of $[\alpha]_D^{23} - 35.0^\circ$ ¹² the enantiomers of VII and VIII were analogously prepared.

The assignment of steric configuration to VII, VIII, and the corresponding enantiomers may be based on the following considerations. As is also the case for methyl esters of methyl-substituted fatty acids, 2-methoxy-substituted methyl esters show the largest optical rotation among the corresponding positional isomers. For example, the starting material I of D-configuration has $[M] + 80$, whereas a 3D-methoxy-substituted methyl ester of about equivalent chain length only has $[M]_D \approx -6$.¹² When the substituent is further removed from the ester group the optical rotation reaches very small values. All known 2-hydroxy-substituted fatty acids of D-configuration are levorotatory in chloroform in light of the sodium D-line and possess approximately the same molecular rotation.^{15,13} Consequently the methyl ester of the corresponding 2D-methoxy-derivatives may be expected to be dextrorotatory in chloroform ($[M]_D \approx +80$) as is the case for I.

In case of VII and VIII, possessing two asymmetric centres, the sign of the optical rotation is determined by the centre nearest the carboxyl end of the molecule as this centre gives the largest contribution to the rotation. Accordingly VII of $[M]_D^{22} + 23$ must have D-configuration at carbon atom 2 and possess thus the structure methyl 2D,4D-dimethoxytridec-12-enoate. Analogously, VIII of $[M]_D^{22} - 116$ must have the structure methyl 2L,4D-dimethoxytridec-12-enoate. The molecular rotations of VII and VIII indicate that the methoxyl group at carbon atom 4 of D-configuration gives a negative contribution to the total optical rotation. In the *R,S*-system the corresponding notations are *R,R*-VII, and *S,R*-VIII. The enantiomer of VII $[M]_D^{23} - 23$ must be assigned the structure methyl 2L,4L-dimethoxytridec-12-enoate (*S,S*-) and that of VIII $[M]_D^{25} + 122$ the structure methyl 2D,4L-dimethoxytridec-12-enoate (*R,S*-).

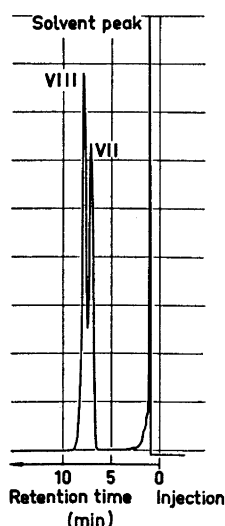


Fig. 1. Gas chromatogram of methyl 2,4D-dimethoxytridec-12-enoate (diastereoisomeric pair) run at a temperature of 170° on a 2 m column with 2.5 % HI-EFF-4B on Chromosorb W 80-100 mesh as stationary phase and n-heptane as solvent. Perkin-Elmer model 900 gas chromatograph. Flame ionization detector.

The structure with the same configuration at the two asymmetric centres VII has shorter gas chromatographic retention time than that whose centres have opposite configuration VIII. This agrees with the findings in case of 2,4-dimethyl-substituted methyl esters.⁸⁻¹⁰

Fig. 1 shows that methyl 2D,4D-dimethoxytridec-12-enoate (VII) and methyl 2L,4D-dimethoxytridec-12-enoate (VIII) are not formed in equal proportions (45 % and 55 %, respectively). It is evident that during the course of decarboxylation the formation of a new asymmetric carbon atom with a configuration opposite that of carbon atom 2 is slightly favoured. Some stereoselectivity is observed also in the synthesis of 2,4-dimethyl-substituted acids involving alkylation of diethyl methylmalonate. However, here a formation of the stereoisomer with the same configuration at carbon atoms 2 and 4 is favoured.⁸⁻¹⁰

Oxidative cleavage of the two stereoisomers of methyl 2,4D-dimethoxytridec-12-enoate by means of potassium permanganate in acetic acid afforded the corresponding half esters. There were obtained from VII (Chart 2) methyl

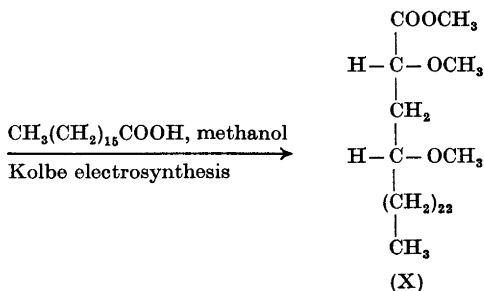
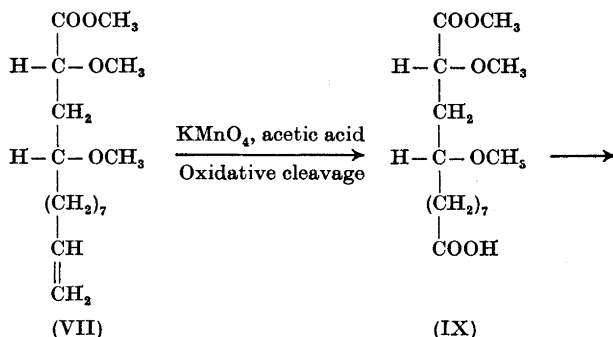


Chart 2.

2D,4D-dimethoxy-11-carboxyundecanoate (IX) and from VIII methyl 2L,4D-dimethoxy-11-carboxyundecanoate. Mixed electrolysis with n-heptadecanoic acid yielded methyl 2D,4D-dimethoxyheptacosanoate (X) and methyl 2L,4D-dimethoxyheptacosanoate.

Table 1.

Ref.	Number of substituents	Structures	Temp. (°C)	$[\alpha]_D$ (°)	$[M]_D$
12	1	Methyl 3D-methoxynonanoate	23	- 2.8	- 6
13	1	Methyl 2D-methoxyundec-10-enoate	23	+ 35.4	+ 81
13	1	Methyl 2L-methoxyundec-10-enoate	23	- 35.0	- 80
	2	Methyl 2D,4D-dimethoxytridec-12-enoate	25	+ 8.1	+ 23
	2	Methyl 2D,4L-dimethoxytridec-12-enoate	25	+ 42.7	+ 122
	2	Methyl 2L,4L-dimethoxytridec-12-enoate	23	- 8.3	- 24
	2	Methyl 2L,4D-dimethoxytridec-12-enoate	22	- 40.5	- 116
	2	Methyl 2D,4D-dimethoxyheptacosanoate	26	+ 2.5	+ 12
	2	Methyl 2L,4D-dimethoxyheptacosanoate	23	- 15.5	- 75

Solvent: chloroform.

The optical rotations of some recently prepared methoxy-substituted methyl esters have been summarized in Table 1.

MASS SPECTROMETRIC INVESTIGATIONS

The mass spectrum of 2D-methoxyundec-10-en-1-ol (II) is reproduced in Fig. 2. The parent peak at m/e 200 is as expected very small. Loss of the fragment CH_2OH results in the base peak at m/e 169. A small peak at m/e 168 formed through loss of a molecule of methanol is also observed. Further

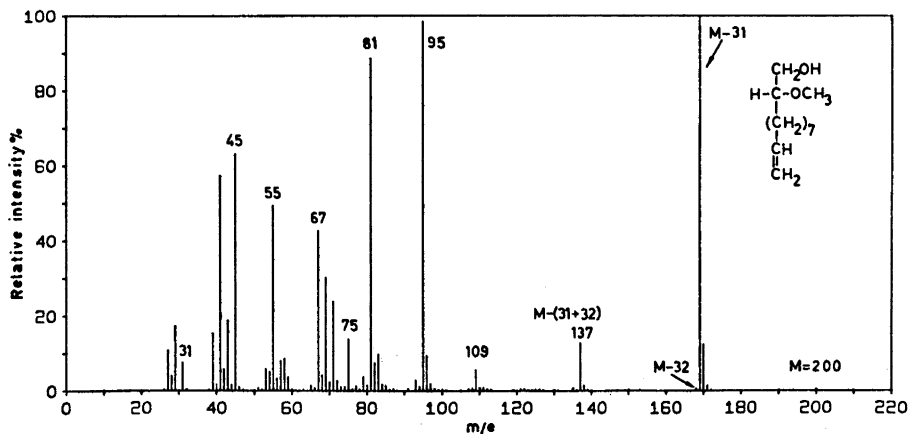


Fig. 2. Mass spectrum of 2D-methoxyundec-10-en-1-ol.

break-down of the ion of m/e 169 results in alkenyl ions of m/e 137 (=M-(31+32)). Subsequent loss of a molecule of ethylene gives rise to the comparatively small peak at m/e 109 whereas loss of 42 or 56 a.m.u. (formally loss of propylene or butylene) results in very abundant ions at m/e 95 or m/e 81.

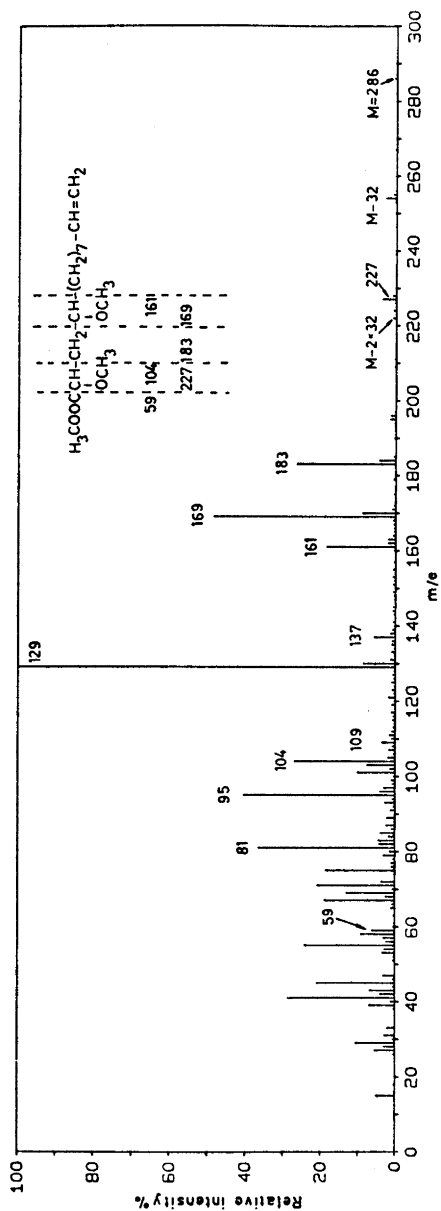


Fig. 3. Mass spectrum of methyl 2D,4D-dimethoxytridec-12-enoate.

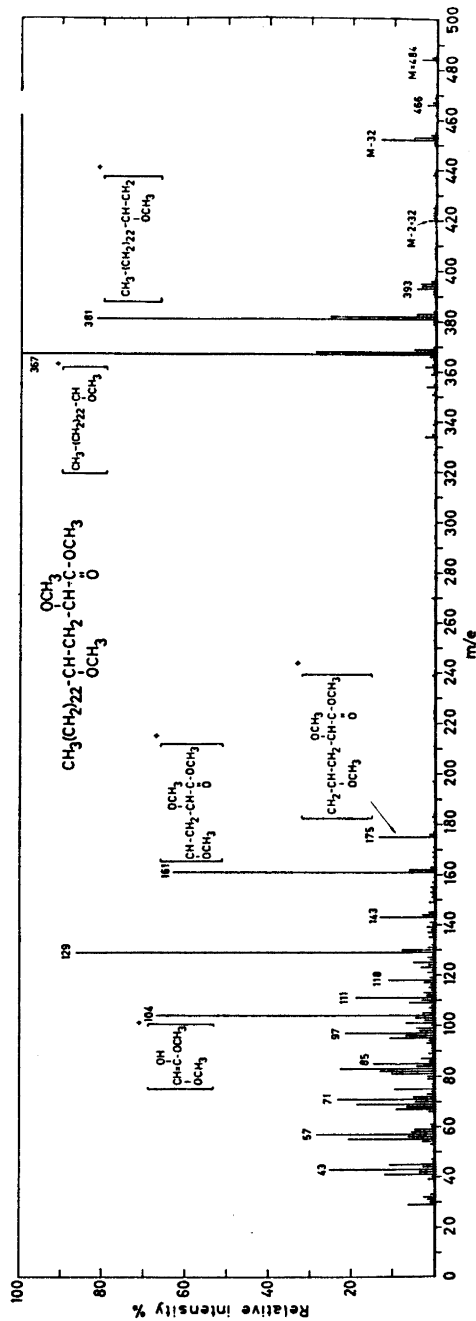


Fig. 4. Mass spectrum of methyl 2L,4D-dimethoxyheptacosanoate. A peak ($\approx 5\%$) at m/e 353 due to the presence of small amounts of methyl 2L,4D-dimethoxyhexacosanoate in the sample has been omitted.

Fig. 3 shows the mass spectrum of methyl 2D,4D-dimethoxytridec-12-enoate (VII). The parent peak at m/e 286 is small. Loss of one or two molecules of methanol results in fragments of m/e 254 or m/e 222. Abundant oxygen-containing ions formed through cleavages α to the methoxy-substituents are observed at m/e 59, m/e 104, m/e 161, m/e 169, m/e 183, and m/e 227. The rearranged ion of even mass at m/e 104 corresponds to the McLafferty type ion. The ions of m/e 161 and m/e 169 show a marked tendency to lose an additional molecule of methanol giving rise to the base peak at m/e 129 and a prominent peak at m/e 137. As was observed in Fig. 2 the alkenyl ions break down further by expulsion of ethylene, propylene, or butylene as indicated by the presence of a prominent peak at m/e 109, m/e 95, or m/e 81.

Fig. 4 shows the mass spectrum of methyl 2L,4D-dimethoxyheptacosanoate. It indicates the expected molecular weight of 484. The general mode of fragmentation is very much the same as observed for VII. However, the strong tendency to expel ethylene, propylene, or butylene shown by the ω -unsaturated compounds is not observed.

EXPERIMENTAL

Diethyl methoxymalonate was prepared from 300 g (2.54 mol) of ethyl methoxyacetate (Fluka AG, Buchs, Switzerland) following the directions given by Ames and Bowman.¹⁴ The crude reaction product was distilled twice through a 0.5 m Nester/Faust spinning band column and the fraction of b.p. 124.5–125.5°, 12 mm (100.6 g) used for the chain-lengthenings.

2D-Methoxyundec-10-en-1-ol (II). 35 ml of dry ether was added to 553 mg (14.5 mmol) of LiAlH_4 . A solution of 3.32 g (14.5 mmol) of I in 35 ml of ether was added dropwise during a period of 10 min to the above slurry. The reaction mixture was refluxed for 20 min and then cooled in an ice-bath. Water was added to destroy the excess of LiAlH_4 and then sulphuric acid in water (1:4 v/v) until the aqueous layer became clear. The organic phase was separated and the aqueous layer extracted with a 50 ml portion of ether. The combined ether solutions were washed, dried (MgSO_4) and evaporated, yielding 2.80 g of II. This was dissolved in ether and filtered through a small amount of aluminium oxide. Yield 2.70 g (91 %). $\alpha_D^{25} - 0.178^\circ$ (chloroform; l , 0.2; c , 4.00), $[\alpha]_D^{25} - 22.3 \pm 0.3^\circ$, $[\text{M}]_D^{25} - 45 \pm 1$. ($\text{C}_{13}\text{H}_{24}\text{O}_2$. Calc.: 200.1776; mass spectrometric: 200.1762.)

2L-Methoxyundec-10-en-1-ol was analogously prepared from 4.4 g (19.3 mmol) of methyl 2L-methoxyundec-10-enoate. 3.56 g (92 %) of the alcohol was obtained. $\alpha_D^{25} + 0.180^\circ$ (chloroform; l , 0.2; c , 4.00), $[\alpha]_D^{25} + 22.5 \pm 0.3^\circ$, $[\text{M}]_D^{25} + 45 \pm 1$.

Tosyl ester of II. 2.7 g (13.5 mmol) of II was dissolved in 14 ml of dry pyridine and the stirred solution cooled in a freezing bath (-5°). Solid *p*-toluenesulphonyl chloride (5.5 g, 29.0 mmol) was added in portions during a period of 30 min and the stirring continued for 2 h. The reaction mixture was left at $+4^\circ$ overnight and then poured on ice and acidified to pH 2 with cold diluted hydrochloric acid. The aqueous phase was extracted twice with ether, the organic layers combined, washed, dried (MgSO_4) and evaporated at room temperature. Yield 4.61 g (97 %) of crude tosyl ester.

Tosyl ester of 2L-methoxyundec-10-en-1-ol was prepared from 3.56 g (17.8 mmol) of the alcohol in the manner described. Yield 6.40 g of crude tosyl ester.

1-Iodo-2D-methoxyundec-10-ene (IV). 7.8 g (52 mmol) of sodium iodide was partially dissolved in 36 ml of stirred, refluxing dry acetone. 4.6 g (13 mmol) of the tosyl ester of II dissolved in 12 ml of acetone was added dropwise to the slurry (15 min) and the heating and stirring continued for 24 h. After cooling, water and light petroleum (b.p. 40–60°) were added. After separation of the organic layer, the aqueous phase was extracted with a further portion of light petroleum. The combined organic solutions were washed, dried (MgSO_4), and evaporated at room temperature. The crude halogen compound was filtered through about 2 g of deactivated aluminium oxide with light petroleum (b.p. 40–60°). Yield 3.8 g (95 %) of IV. This was not further purified.

1-Iodo-2L-methoxyundec-10-ene was analogously prepared from the tosyl ester of 2L-methoxyundec-10-en-1-ol (6.3 g, 18 mmol). 4.5 g (82 %) of the iodo-compound was obtained.

Ethyl 2-ethoxycarbonyl-2,4D-dimethoxytridec-12-enoate (V). 0.48 g (12.3 mmol) of potassium was allowed to react with 15 ml of *tert*-butanol (heated to 50°) in a 60 ml test tube equipped with a calcium chloride drying tube. The stirred solution was heated to 80° and 2.3 g (12.3 mmol) of diethyl methoxymalonate dissolved in 2 ml of *tert*-butanol was rapidly run in. After 5 min the iodide IV (3.8 g, 12.3 mmol) in 3 ml of *tert*-butanol was added dropwise to the reaction mixture. The test tube was stoppered and the heating and stirring continued for 8 h. After cooling ether and water were added. The ether layer was washed and evaporated. The disubstituted malonic ester V was not further purified.

Ethyl 2-ethoxycarbonyl-2,4L-dimethoxytridec-12-enoate. 2.73 g (14.4 mmol) of diethyl methoxymalonate was analogously alkylated with 4.45 g (14.4 mmol) of 1-iodo-2L-methoxyundec-10-ene.

Methyl 2,4D-dimethoxytridec-12-enoate (VI) (mixture of diastereoisomers). To the crude (V) was added a solution of 3.2 g of potassium hydroxide in 4 ml of water and then ethanol (≈ 15 ml) until a homogeneous solution was obtained. This was refluxed for 4 h and extracted with light petroleum (b.p. 40–60°). The aqueous phase was acidified (pH 2) with diluted hydrochloric acid (1:3 v/v) and extracted with ether. The ether layer was washed and dried (molecular sieve type 3A). After evaporation, 2.3 g of crude dialkylated malonic acid was obtained. This was decarboxylated at 140° for 5 h, and the acid formed subsequently esterified by means of diazomethane. The mixture of diastereoisomeric methyl esters was filtered through a small column of silicic acid with ether-light petroleum (b.p. 40–60°) (1:1 v/v). Yield 1.78 g of (VI).

Methyl 2,4L-dimethoxytridec-12-enoate (mixture of diastereoisomers) was analogously prepared from ethyl 2-ethoxycarbonyl-2,4L-dimethoxytridec-12-enoate. Yield 1.92 g.

Resolution of methyl 2,4L-dimethoxytridec-12-enoate. A column of 145 g of silicic acid (Mallinckrodt, 100–200 mesh, activated at 110° overnight) in ether–light petroleum (b.p. 40–60°) (1:20 v/v) was charged with 1.92 g of the diastereoisomeric mixture in 2 ml of the same solvent. 400 ml of this solvent was eluted, and then another 400 ml of the same pair of solvents of 1:13.3 v/v. The polarity of the eluent was then increased to 1:10 v/v and 25 ml fractions were taken. The course of the resolution was followed by analyzing the eluted fractions on the GLC column (*cf.* Fig. 1). Fractions 27–33 (436 mg, 41.5 % of the theoretical) contained methyl 2D,4L-dimethoxytridec-12-enoate of satisfactory optical purity (> 98 %) and were combined. $\alpha_D^{25} + 0.128^\circ$ (chloroform; *l*, 0.1; *c*, 3.00) $[\alpha]_D^{25} + 42.7 \pm 1.0^\circ$, $[M]_D^{25} + 122 \pm 3$. The combined fractions 39–58 (625 mg) containing methyl 2L,4L-dimethoxytridec-12-enoate of an optical purity of 80 % were successively rechromatographed on 60 g, 27 g and 16 g of silicic acid. 117 mg (13.6 % of the theoretical) of the 2L,4L-isomer was obtained. Optically pure methyl 2L,4L-dimethoxytridec-12-enoate had $\alpha_D^{23} - 0.011^\circ$ (chloroform; *l*, 0.1; *c*, 1.20), $[\alpha]_D^{23} - 8.3 \pm 1.6^\circ$, $[M]_D^{23} - 24 \pm 5$. (C₁₆H₃₀O₄. Calc.: 286.2144; mass spectrometric: 286.2130.)

Resolution of methyl 2,4D-dimethoxytridec-12-enoate. This was performed analogously. Repeated chromatography of 1.78 g of methyl 2,4D-dimethoxytridec-12-enoate afforded 210 mg (21.5 % of the theoretical) of methyl 2L,4D-dimethoxytridec-12-enoate (VIII) (optical purity > 98 %). $\alpha_D^{22} - 0.164^\circ$ (chloroform; *l*, 0.1; *c*, 4.00) $[\alpha]_D^{22} - 40.5 \pm 1.0^\circ$, $[M]_D^{22} - 116 \pm 3$.

Methyl 2D,4D-dimethoxytridec-12-enoate was obtained in a yield of 14.6 % of the theoretical (117 mg, optical purity > 97 %). The optically pure 2D,4D-isomer had $\alpha_D^{22} + 0.0285^\circ$ (chloroform; *l*, 0.1; *c*, 3.56), $[\alpha]_D^{22} + 8.1 \pm 0.6^\circ$, $[M]_D^{22} + 23 \pm 2$.

Oxidative cleavage of two ω -unsaturated stereoisomers. 177 mg (0.62 mmol) of methyl 2L,4D-dimethoxytridec-12-enoate and 0.49 g (3.10 mmol) of pulverized potassium permanganate dissolved in 16 ml of acetic acid were kept at 40° for 0.5 h. 10 ml of water and 12 ml of ether were added followed by solid sodium hydrogen sulphite until two colourless layers were obtained. Diluted hydrochloric acid (1:2) was added (pH 2) and the aqueous layer extracted with a further portion of ether. The combined organic phases were washed with water until completely neutral. After drying (molecular sieve type 3A) and evaporation 100 mg of crude methyl 2L,4D-dimethoxy-11-carboxyundecanoate was obtained.

Analogously, from 156 mg (0.55 mmol) of the 2D,4D-isomer, 133 mg of methyl 2D,4D-dimethoxy-11-carboxyundecanoate was obtained. The half-esters were liquids at room temperature.

Chain-lengthening of methyl 2D,4D- and methyl 2L,4D-dimethoxy-11-carboxyundecanoate. 62.2 mg (0.205 mmol) of IX and 166 mg (0.615 mmol) of n-heptadecanoic acid were mixed and converted to the sodium salts by adding 44.2 mg (0.820 mmol) of sodium methoxide in 2 ml of methanol. The mixture was electrolyzed between platinum (anode) and mercury (cathode) at an initial current of 0.5 A (190 V). After 70 min the current had dropped to zero and the electrolysis was stopped. The evaporated reaction mixture was triturated three times with 10 ml portions of ether. After filtration, the solution was evaporated and the product purified by preparative thin-layer chromatography (Silica Gel G, Fluka AG) with hexane:ethyl acetate:acetic acid (90:10:1 v/v/v) as solvent. Iodine vapours served as developer of the spots. 63.0 mg of methyl 2D,4D-dimethoxyheptacosanoate (X) was obtained. This was recrystallized from 1 ml of methanol. Yield 51.8 mg. Gas chromatographic examination showed that the material contained about 5 % of the next lower homologue (methyl 2D,4D-dimethoxyhexacosanoate), presumably formed through partial degradation of the half ester during the oxidative cleavage of the double bond.

In order to remove possible traces of free acids X was filtered through a small amount of neutral Al_2O_3 with ether-light petroleum (b.p. 40–60°) (1:1 v/v) prior to measurement of the optical rotation. $\alpha_D^{25} + 0.0010^\circ$ (chloroform; l, 0.1; c, 0.40) $[\alpha]_D^{25} + 2.5 \pm 0.5^\circ$, $[\text{M}]_D^{25} + 12 \pm 2$.

Methyl 2L,4D-dimethoxyheptacosanoate was prepared analogously. From the electrolytic cross-coupling of 100.0 mg (0.329 mmol) of half ester and 268 mg (0.987 mmol) of n-heptadecanoic acid 55.8 mg of methyl 2L,4D-dimethoxyheptacosanoate was obtained. $\alpha_D^{25} - 0.0170^\circ$ (chloroform; l, 0.1; c, 1.10), $[\alpha]_D^{25} - 15.5 \pm 1.9^\circ$, $[\text{M}]_D^{25} - 75 \pm 9$.

Optical rotations. The optical rotations were measured with a Bendix-Ericsson type 143 photoelectric polarimeter using sodium D light.

Acknowledgements. Grants from the Swedish Natural Science Research Council (to G. Odham) are gratefully acknowledged.

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Received February 1, 1971.