Chiral Tetraalkylmethanes. Two Syntheses of Optically Active Butylethylmethylpropylmethane of Known and High Optical Purity

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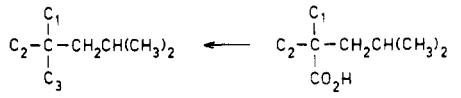
The chiral hydrocarbon butylethylmethylpropylmethane (**10**) has been prepared in a state of known and high optical purity via two independent routes. The first synthesis has as its main feature the addition of 2-thienylmagnesium bromide to the α,β-unsaturated di-(-)-menthyl ester **11**. The two diastereoisomeric adducts **12** were readily separated by crystallization, as confirmed by ^{1}H NMR spectroscopy. Saponification gave the thiophene acid **24**. Further synthetic elaboration finally gave (-)-**10**, $[\alpha]_{578}$ -0.198, having an enantiomeric excess of 95 ± 5%. The second synthesis is based upon the resolution of the racemic diacid **34** via one recrystallization of the corresponding (-)-cinchonidine salts. The (+) diacid was obtained in an enantiomeric excess of 85 ± 5% as was determined by ^{1}H NMR spectroscopy of the corresponding di-(-)-menthyl ester. The racemic diacid **34** could be prepared via the Michael addition of cyanoacetamide to the α,β-unsaturated ketone **28**. Conversion of (+)-**34** to **10** by straightforward reactions gave the (+) hydrocarbon, $[\alpha]_{578}$ +0.185, having an enantiomeric excess of 85 ± 5%.

The synthesis of optically active tetraalkylmethanes presents a challenge in at least two respects.

First, the absolute rotation of chiral tetraalkylmethanes is expected to be very small,[1] due to the almost equal polarizability of normal alkyl groups.[2] This aspect necessitates the construction of a polarimeter either with the capability to measure minute rotations of <0.001° or with the capability to measure rotations at wavelengths where higher rotations can be expected, i.e., at wavelengths around UV absorption maxima.[3] Tetraalkylmethanes have their absorption maxima (σ-σ^* transitions) below 200 nm,[4] thus necessitating vacuum short-wavelength polarimetry. Although short-wavelength CD spectra (below 200 nm) of several chiral compounds have been recorded, this technique has not yet been applied to chiral tetraalkylmethanes.[5] Additional difficulties in recording the chiroptical properties of tetraalkylmethanes may be caused by a low optical purity of the chiral compound.

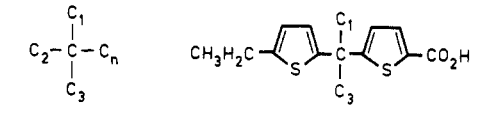
Second, the synthesis of chiral tetraalkylmethanes of known optical purity presents a challenge to the synthetic stereochemist. The difficulties encountered in the synthesis of chiral tetraalkylmethanes[6] are apparent from the fact that only two chiral tetraalkylmethanes have been prepared to date. The first of these is ethylisobutylmethylpropylmethane (**1**, $[M]_{578}$ 0.05), obtained by Streitwieser and Thomson from partially resolved ethylisobutylmethylacetic acid (**2**)[7] [normal alkyl groups attached to the central quaternary carbon atom (or its parent carbon atom) will be abbreviated as C_n, wherein n corresponds to the number of carbon atoms in the normal alkyl chain



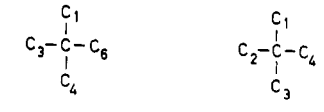
1 **2**

(thus an n-butyl group will be written as C_4)]. Neither the optical purity of the starting acid nor that of the final product was determined unambiguously. The presence of the isobutyl group (instead of a normal alkyl group) in the chiral product makes a comparison between chain length and optical rotatory power difficult. Also, this synthesis is not general, since the desired optically active acids are difficultly accessible (either resolution is difficult or a synthesis by way of asymmetric induction is nearly impossible).[8]

The second chiral tetraalkylmethane that has been synthesized is butylethylhexylpropylmethane (**3**, $[\alpha]_{578}$ 0°), prepared by Wynberg, Hekkert, Houbiers, and Bosch from the dithienylhexane **4**, via the resolved acid **5** and its decarboxylated analogue **6**[9] (Scheme I). Although this route to chiral tetraalkylmethanes seems to have a broad applicability, there are several drawbacks. (i) Resolution of carboxylic acids corresponding to **5** is difficult and time consuming. (ii) Determination of the optical purity of **5** is a major challenge,[10] whereas determination of the optical purity of **3** is impossible by present methods.[11] (iii) Tetraalkylmethanes of the type **7** ($n \geq 4$) cannot be ob-



7 **8**



9 **10**

(1) Thomson, T. R. *J. Am. Chem. Soc.* **1953**, *75*, 6070.

(2) For calculations of molecular rotations, using differences in polarizability of substituents at an asymmetric carbon atom, see: Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5475; *Tetrahedron* **1974**, *30*, 1807. Although Brewster has calculated molecular rotations for chiral tertiary hydrocarbons, such as 3-methylhexane, his calculations have not yet been extended to chiral quaternary hydrocarbons.

(3) Mislow, K. "Introduction to Stereochemistry"; W. A. Benjamin: New York, 1966. Legrand, M.; Rougier, M. J. In "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart, 1977; Vol. 2, p 44.

(4) Tetraalkylmethanes are expected to have a σ-σ^* transition at 176 nm (in n-hexane: Turner, D. W. *Chem. Ind. (London)* **1958**, 626.

(5) The short-wavelength CD spectrum of a steroid hydrocarbon has been reported: Kirk, D. N.; Scopes, P. M.; Tracey, B. M. *Tetrahedron Lett.* **1973**, 1355. For the short-wavelength CD spectra of some other compounds, see: Gedanken, A.; Levy, M. *Rev. Sci. Instrum.* **1977**, *48*, 1661 and references cited therein.

(6) Rabjohn, N.; Phillips, L. V.; DeFeo, R. J. *J. Org. Chem.* **1959**, *24*, 1964. Maire, J. C.; Desgrandchamps, G. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 233.

(7) Streitwieser A., Jr.; Thomson, T. R. *J. Am. Chem. Soc.* **1955**, *77*, 3921.

(8) Meyers, A. T.; Mihelich, E. D. *Angew. Chem.* **1976**, *88*, 321; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem* **1974**, *39*, 2778.

(9) Wynberg, H.; Hekkert, G. L.; Houbiers, J. P. M.; Bosch, H. W. *J. Am. Chem. Soc.* **1965**, *87*, 2635.

(10) The optical purity of **5** has been determined by radiocarbon labeling, giving an absolute rotation for **5**, $[M]_{578}$ 14.2 (benzene). Hulshof, L. A.; Wynberg, H., unpublished results.

(11) Raban, M.; Mislow, K. *Top. Stereochem.* **1967**, *2*, 199.

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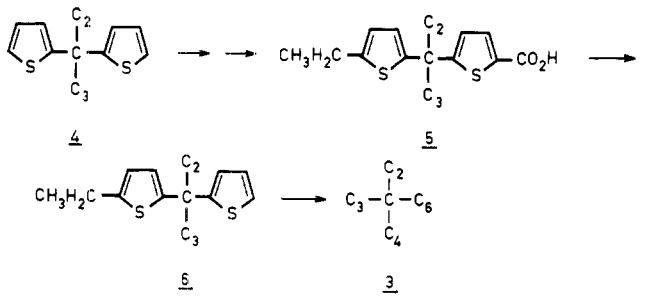
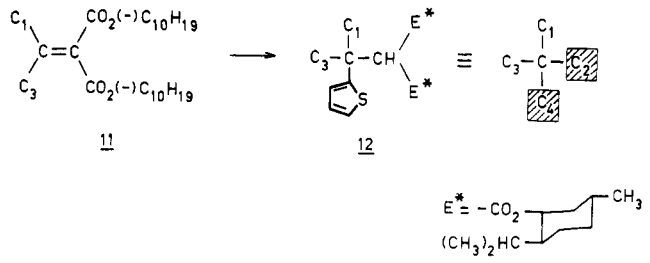
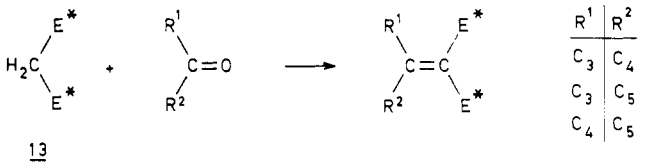
Scheme I



Scheme II



Scheme III

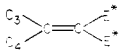
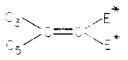
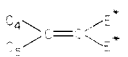
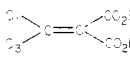
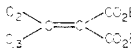


tained. Following the same route, i.e., via resolution of the acid **8**, we have recently prepared the chiral hydrocarbon **9** in our laboratory.[12] The first results indicate that **9**, obtained in this way, shows measurable optical activity. The hydrocarbon **3**, however, showed no measurable rotation in the 280–580-nm range, despite the fact that it was prepared from the optically active acid **5**.

The cause of this zero rotation may be twofold.[13] (i) The absolute rotation of **3** is too small to be measured with present-day instruments. By Thomson's empirical formula,[1] one calculates $[M]_D$ 2.2×10^{-5} for optically pure **3**. In addition, a low optical purity would cause a further drop in the rotation of **3**. (ii) A less acceptable reason for the zero rotation is that at the final stage in the synthesis of **3**—the dithienylhexane **6** was still optically active—racemization has occurred, either during the desulfurization step or, less likely, afterward. As desulfurizations are generally thought to proceed by a radical pathway,[14] a racemization during the desulfurization of **6**, involving tertiary radicals, seems feasible, at least in theory.

In order to confirm that the zero rotation of **3** from optically active precursors was an intrinsic effect not due to any racemization during its synthesis, we set out to prepare the chiral tetraalkylmethane **10**.[15] Butylethylmethylpropylmethane (**10**) is expected to have a higher absolute rotation than **3** ($[M]_D$ 11×10^{-3} for optically pure **10** by using Thomson's formula), and measurable rotations may be expected at shorter wavelengths. The synthesis of optically active **10** would demonstrate that chiral tetraalkylmethanes do not racemize. By choosing a route to **10** which bears close resemblance to the route leading to **3**, we can assume that the results of one route will apply to the other route. This means that the route to **10** should contain an intermediate where a 2-thienyl group is attached to the asymmetric carbon atom (as is the case in the route to **3**). If desulfurization of this intermediate gives a product wherein the rotation has been retained, we may conclude that the rotation has also been retained on desulfurization of **6**. In both routes the possibility of partial racemization still exists when the products are optically active. Since the optical purity of the desulfurized products cannot readily be determined, a second unequivocal route to **10** is necessary. A requirement for this second route is that it should be completely independent; i.e., it should not contain any thiophene ring attached to the asymmetric carbon atom, thereby avoiding the critical desulfurization step.

Table I. Synthesis of α,β-Unsaturated Diesters

entry	R^1, R^2 [c]	procedure[b]	yield, %	product	no.
1	C_3, C_4	B	30[a]		14
2	C_3, C_5	B	62[a]		15
3	C_4, C_5	B	43[a]		16
4	C_1, C_3	A	73		17
		B	64		
5	C_2, C_3	B	58		18

[a] The variation in yields is due to separation difficulties (entry 1) and/or nonoptimized conditions (entries 1 and 3). [b] A, $TiCl_4$/pyr/THF; B, $TiCl_4$/pyr/$CHCl_3$. [c] In $R^1C(O)R^2$.

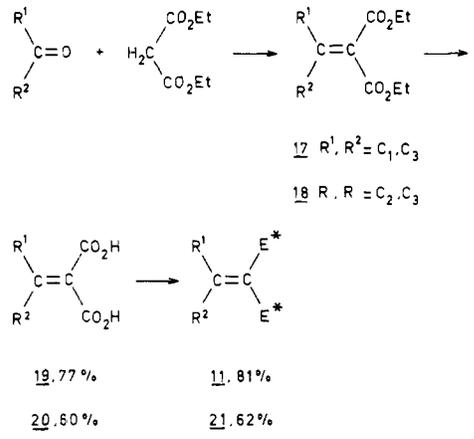
First Synthesis of the Optically Active Hydrocarbon 10

As starting compound for the synthesis of **10** we chose the di-(−)-menthyl ester **11** (the (−)-menthoxycarbonyl group will be designated E* in this paper). Grignard addition of 2-thienylmagnesium bromide should afford the two diastereoisomeric adducts **12** in unequal amounts.[16] Since a 2-thienyl group can easily be transformed to an *n*-butyl group and since the di-(−)-menthylmalonyl residue should be transformable to an ethyl group, the adduct **12** can be considered to be a masked form of the hydrocarbon **10** (masked groups will be denoted as the ultimate group covered with hatching) (Scheme II). Extension of this scheme, if successful, to the synthesis of a series of chiral tetraalkylmethanes seems feasible by simple exchange of the methyl and propyl groups in **11** for other alkyl groups.

The α,β-unsaturated di-(−)-menthyl ester **11** could be obtained via the Lehnert variant of the Knoevenagel condensation.[17] Direct condensation of di-(−)-menthyl malonate (**13**)[18] with 2-pentanone (R^1 and R^2 = C_1 and C_3, respectively, in Scheme III) gave rise to the expected product **11**; however, separation of **11** and **13** was not feasible due to the high boiling points and too small of a difference between these boiling points. These separation

(12) Ten Hoeve, W.; Hulshof, L. A.; Wynberg, H., to be submitted for publication.
(13) Wynberg, H.; Hulshof, L. A. *Tetrahedron* **1974**, *30*, 1775.
(14) Pettit, G. R.; Van Tamelen, E. E. *Org. React.* **1962**, *12*, 356. Hauptmann, H.; Walter, W. F. *Chem. Rev.* **1962**, *62*, 347. Pizey, J. S. "Synthetic Reagents"; Ellis Horwood: Chichester, England, 1974; Vol. 2, p 175.
(15) Mann, G.; Mühlstädt, M.; Braband, J.; Döring, E. *Tetrahedron* **1967**, *23*, 3393.
(16) The reaction of Grignard reagents with β-alkyl, α,β-unsaturated carboxylic esters (the ester moiety is formed from an optically active alcohol) has been studied in some detail: Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 910 and references cited therein. See also: Mukaiyama, T.; Takeda, T; Fujimoto, K. *Ibid.* **1978**, *51*, 3368.
(17) Lehnert, W. *Tetrahedron* **1973**, *29*, 635.
(18) Rule, H. G.; Harrower, J. *J. Chem. Soc.* **1930**, 2319.

Scheme IV



difficulties were encountered in a lesser degree when higher ketones, namely, 4-octanone, 4-nonanone, and 5-decanone, were condensed with di-(−)-menthyl malonate (Scheme III; entries 1, 2, and 3 in Table I). These di-(−)-menthyl esters (**14**, **15**, **16**) were prepared in order to obtain in a later stage a series of chiral tetraalkylmethanes.

Di-(−)-menthyl ester **11** had to be prepared via a detour, namely, via its diethyl ester **17**[19] (Scheme IV), which was easily prepared by using titanium(IV) chloride and pyridine in tetrahydrofuran (Lehnert variant) or in chloroform (which appeared to be more convenient; entry 4). Similarly prepared was the diethyl ester **18** from 3-hexanone (entry 5). Transesterification of **17** using (−)-menthol and a trace of sodium at higher temperatures was only partly successful, since it gave rise to an inseparable mixture of the α,β-unsaturated diester **11** and its β,γ-unsaturated counterpart.[20] Diethyl ester **17** was then saponified to the diacid **19** by using potassium hydroxide in ethanol at reflux temperature. Diacid **20** was obtained from diester **18** by using somewhat milder conditions (stirring at room temperature, methanol/water as solvent) which were necessary because under reflux conditions a considerable amount of the β,γ isomer of **20** was formed.[20] The corresponding diacid chlorides, readily obtained from the diacids by treatment with thionyl chloride, furnished the desired di-(−)-menthyl esters **11** and **21** on reaction with (−)-menthol.

Addition of ester **11** to 2-thienylmagnesium bromide gave indefinite products. The presence of a catalytic amount of cuprous chloride,[21] however, gave a maximum yield of ca. 80% of the adduct **12** (Scheme V). The amount of asymmetric induction was easily determined from the ^{1}H NMR spectrum to be ca. 30% by integration of the singlets associated with the malonic ester proton in each diastereoisomer (at 3.56 and 3.60 ppm, respectively, the signal at 3.60 ppm representing the major isomer). Hence, the differences between a methyl, propyl, and 2-thienyl group (steric and/or electronic) appear to be large enough to show physical differences between both diastereoisomers of **12**. The difference between both isomers was also manifested by the observation that a cooled solution of the partially purified adduct **12** in pentane deposited only one diastereoisomer, the major one (i.e., ≥95% of one diastereoisomer). The other isomer of **12** could only be obtained as an impure oil. An easy separation of both isomers was thus possible, and thereby access to optically pure tetraalkylmethane **10** was achieved. In a similar way the adduct **22** could be obtained (Scheme V) by addition of *n*-butylmagnesium bromide to a mixture of ester **11** and cuprous chloride (inverse addition).[22] The adduct **22** was accompanied by some reduction product[23] **23** as revealed by 100-MHz ^{1}H NMR spectroscopy. A separation between the two singlets stemming from the malonic ester proton in each diastereoisomers of **22** was not observed, however. No separation of these two diastereoisomers was observed by using high-pressure LC techniques. Hence this shorter route to optically active hydrocarbon **10** of known enantiomeric purity and with the exclusion of thiophene intermediates such as **12** or **24** is not possible.

Attempts to perform 1,4-additions of Grignard reagents to other α,β-unsaturated di-(−)-menthyl esters met with little success. For instance, the reaction of 2-thienylmagnesium bromide with esters **15** and **21** furnished a crude product which consisted of a mixture of the expected adduct and the β,γ isomers of **15** and **21**[20] in a ratio of ca. 1:5. Although addition of *n*-butylmagnesium bromide to ester **15** and cuprous chloride (inverse addition) led to a product consisting largely of the expected adduct, the impossibility of determining the enantiomeric purity of this adduct led us to halt further research on the synthesis of other chiral tetraalkylmethanes by this route.

Once the thiophene adduct **12** had been obtained, the remaining steps leading to hydrocarbon **10** consisted of a series of straightforward reactions (Scheme V). Hydrolysis of **12** with potassium hydroxide in ethylene glycol gave the thiophene acid **24** in 89% yield. The major crystalline diastereoisomer of **12** gave the acid having $[\alpha]_{578}$ −20.3° (enantiomeric excess 95 ± 5%). The oily, minor diastereoisomer of **12** gave impure **24** with $[\alpha]_{578}$ +12.0°, whereas the mixture of both diastereoisomers, obtained from the Grignard reaction without subsequent crystallization, gave acid **24** with $[\alpha]_{578}$ −5.6°, corresponding to an optical purity of ca. 27% which is in good agreement with the enantiomeric excess of 30 ± 5% based on ^{1}H NMR spectroscopy.[24]

Desulfurization of **24** using Raney nickel[25] in water gave the aliphatic acid **25** in 85% yield. From **24**, $[\alpha]_{578}$ −20.3°, there was obtained **25** with $[\alpha]_{578}$ −0.68 whereas **24**, $[\alpha]_{578}$ +12.0°, gave **25** with $[\alpha]_{578}$ +0.60° (thus showing an optical purity of 84 ± 5%). The same acid was obtained by saponification of the mixture of diastereoisomers **22**; in this case **25** had $[\alpha]_{578}$ −0.12°, which corresponds to an optical yield of ca. 20% for the addition of *n*-butylmagnesium bromide to di-(−)-menthyl ester **11**.

Alcohol **26** was obtained by lithium aluminum hydride reduction of **25** (90% yield). It had $[\alpha]_{578}$ −0.16° and

(19) Danion-Bougot, R.; Carrié, R. *Bull. Soc. Chim. Fr.* **1969**, 313.

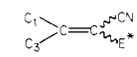
(20) This β,γ isomerization must be due to the acidity of the γ proton and to steric hindrance in the α,β-unsaturated diesters. The presence of the β,γ isomers was indicated in all cases from the ^{1}H NMR spectra which showed a singlet at about δ 4 (malonic ester proton) and a multiplet around δ 5.5 (vinylic protons with coupling to other protons).

(21) Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107. Posner, G. H. *Ibid.* **1972**, *19*, 1.

(22) Nielsen, E. B.; Munch-Petersen, J.; Jørgensen, P. M.; Refn, S. *Acta Chem. Scand.* **1959**, *13*, 1943. Munch-Petersen, J. *Bull. Soc. Chim. Fr.* **1966**, 471.

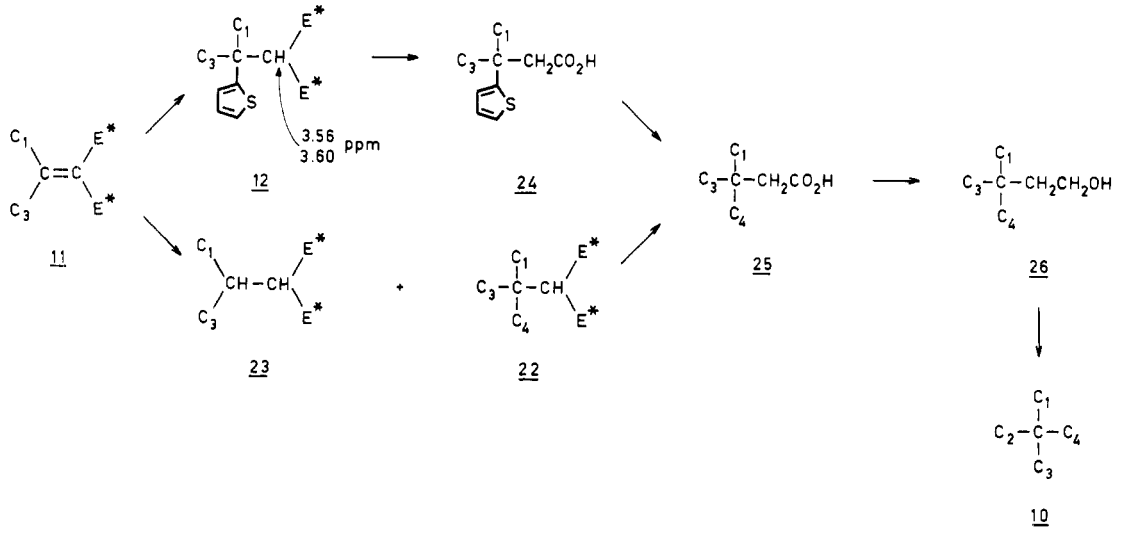
(23) Prout, F. S.; Huang, E. P.-Y.; Hartman, R. J.; Korpics, C. J. *J. Am. Chem. Soc.* **1954**, *76*, 1911.

(24) The addition of 2-thienylmagnesium bromide to the easily synthesized cyano-(−)-menthyl ester (see structure below) proceeds with ca. 20% induction, as was shown via diastereoisomer formation of the thiophene acid **24**. Determination of the enantiomeric excess of the acid **25** by using diastereoisomer formation has been unsuccessful. See: Labuschagne, A. J. H.; Houbiers, J. P. M.; Hulshof, L. A.; Wynberg, H. *Afinidad* **1978**, *35*, 141.

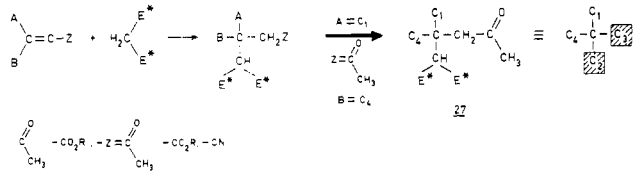


(25) Badger, G. M.; Rodda, H. J.; Sasse, W. H. F. *J. Chem. Soc.* **1954**, 4162. Billica, H. R.; Adkins, H. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3, p 176.

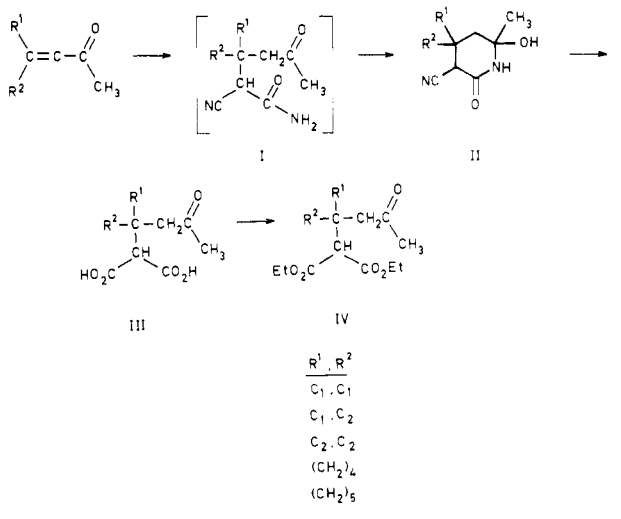
Scheme V



Scheme VI



Scheme VII



+0.14° from acids with $[\alpha]_{578}$ −0.68° and +0.60°, respectively. The corresponding tosylates, obtained by reaction with tosyl chloride in pyridine, were reduced directly with lithium aluminum hydride to afford in ca. 80% yield the optically active tetraalkylmethane **10**. This product was rigorously purified to remove any olefinic and/or other impurities (see Experimental Section). Only the (−) hydrocarbon was obtained in a sufficient amount, and the (+) isomer was obtained via our second route described below; (−)-**10** had $[\alpha]_{578}$ −0.198° which corresponds to $[M]_{578}$ −0.309°.

Second Synthesis of the Optically Active Hydrocarbon 10

Our first synthesis of optically active butylethylmethylpropylmethane (**10**) demonstrates that chiral tetraalkylmethanes do not racemize. However, we are still left with the question of whether *partial* racemization has occurred during the desulfurization of the thiophene acid **24** or not. Answering this question is only possible via an independent synthesis of **10**. Our strategy for this synthesis was directed toward a Michael reaction between a masked ethyl group as the Michael donor, namely, di-(−)-menthyl malonate, or the like, and an α,β-unsaturated compound as the Michael acceptor. The α,β-unsaturated compound might be an α,β-unsaturated ketone, ester, or nitrile. Scheme VI shows our basic thought. In order to arrive at hydrocarbon **10**, one should necessarily choose A to be a methyl group. This led us to choose as Z an acetyl group because the corresponding α,β-unsaturated ester or nitrile is more difficulty accessible. An acetyl group has the further advantage of being easily protected—for instance in the form of its acetal—which is necessary in order to prevent reversal of the Michael reaction during subsequent steps of the synthesis. The choice of an acetyl group (as a masked ethyl group) then leads to the choice of an *n*-butyl group for B. Hence our Michael acceptor is the ketone **28** which is easily prepared by reaction of *n*-butylmagnesium bromide with acetylacetone (Scheme VIII) and distillation of the intermediate β-hydroxy ketone in the presence of iodine.[26] Ketone **28** is presumably contaminated with its β,γ isomer as deduced from the ^{1}H NMR spectrum (multiplet at δ 5.0–5.5). However, this was thought to be of minor importance because under the basic conditions of the Michael reaction, isomerization of the β,γ isomer to the reactive α,β isomer was expected.

Since β,β-dialkyl, α,β-unsaturated ketones such as **28** are poor acceptors in Michael reactions,[27] the addition of di-(−)-menthyl malonate to ketone **28** is not likely to meet with success. Therefore a detour had to be made in order to arrive at the adduct **27** or a derivative thereof. This detour was successfully applied by using the method of Qudrat-I-Khuda, who performed the addition of cyanoacetamide to several α,β-unsaturated ketones (Scheme VII).[28] He did not isolate the initial Michael adducts I, but instead he obtained the crystalline pyridone derivatives II which could be hydrolyzed to the diacids III and then esterified to the diesters IV. These diesters are, in fact, the initial Michael adducts of diethyl malonate to the parent ketones. Access to the di-(−)-menthyl ester **27** seems possible by using this method. To that end the

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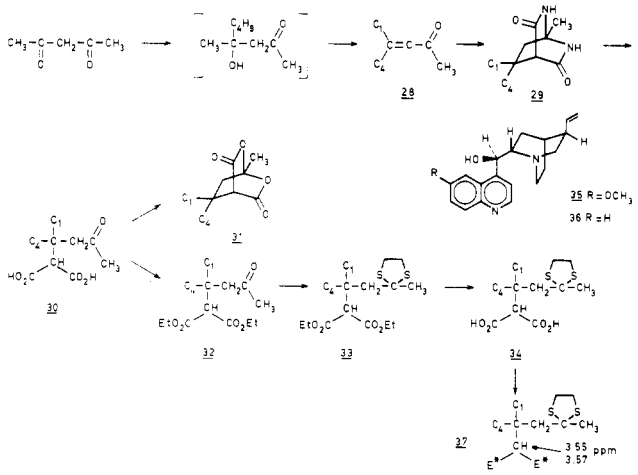
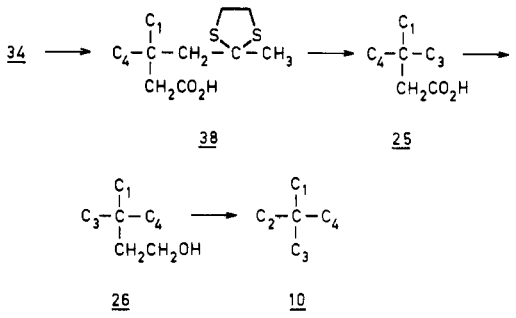
(27) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; pp 595–623.
(28) Qudrat-I-Khuda, M. *J. Chem. Soc.* **1929**, 201, 713, 1913.

Scheme VIII



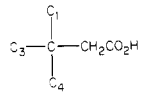
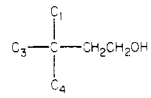
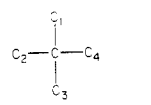
Scheme IX



ketone **28** was treated with cyanoacetamide and sodium ethoxide in ethanol. From the crude reaction product a crystalline pyridone derivative of the type II could not be isolated. However, treatment of the product with hydrochloric acid afforded the bicyclic diamide **28** in good yield (Scheme VIII). Its structure was in accord with the spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR).[29] The diamide was hydrolyzed to the oily diacid **30** which could be dehydrated to the crystalline dilactone **31** with phosphorus oxychloride in benzene. Attempts to obtain the di-(−)-menthyl ester **27** from the diacid failed; however, dilactone formation occurred in some instances (the dilactone **31** can be converted back to the diacid **30** by treatment with base). In order to circumvent either dilactonization and/or retrograde Michael reaction, we protected the ketone function in **30**. Diacid **30** was converted to the diethyl ester **32** (56% yield, based on the starting ketone **28**), which was thioacetalized to form **33** and then saponified to the diacid **34**. Direct thioacetalization of diacid **30** was unsuccessful, since this led to formation of the dilactone **31**.

Two conditions, which have to be met in our second route to the chiral tetraalkylmethane **10**, are that optically enriched material must be made and that the enantiomeric purity of an optically active intermediate has to be determined. Diacid **34** seems a viable candidate to meet these two requirements. Among the optically active bases investigated for the resolution[30] of **34**, quinine (**35**) and cinchonidine (**36**) were the only bases that led to crystallization of diastereoisomeric salts; however, no separation of the salts was observed in the case of quinine. Cinchonidine worked beautifully; however, rapid crystallization occurred after warming a mixture of the diacid **34** and cinchonidine in a small amount of solvent. Furthermore, one recrystallization of the mixture of diastereoisomeric salts (obtained in 63% yield, based on diethyl ester **32**) from methanol gave almost complete separation of the two salts, as was proven via synthesis of the corresponding di-(−)-menthyl esters **37**. Dissociation of each diastereoisomeric salt with acid gave (+)-**34** and (−)-**34** having $[\alpha]_{578}$ +4.81 and −5.10°, respectively (these diacids could not be purified further). From these diacids the corresponding di-(−)-menthyl esters were obtained via the diacid chlorides.[31] Again as in the case of the 2-thienyl adduct **12**, separation between the singlets associated with the malonic ester proton of each diastereoisomer—from racemic **34** and (−)-menthol—was observed in the ^{1}H NMR spectrum although the chemical shift difference was quite small, namely, 0.02 ppm (as compared to 0.04 ppm in the case of **12**). Almost complete separation was observed in the 100-MHz ^{1}H NMR spectrum of **37**, thus revealing the desired enantiomeric excess for the resolved diacids. Compound **34** with $[\alpha]_{578}$ +4.81° was thus calculated to be 85 ± 5% enantiomerically pure, and **34** with $[\alpha]_{578}$ 5.10° was 72 ± 5% enantiomerically pure.

Table II. Specific Rotations and Enantiomeric Excess of Optically Active Intermediates

		route I		route II	
compd	λ, nm	(−)	(+)	(−)	(+)
	578	−0.68[a]	0.60[a]	−1.07[b]	1.51[a]
	546	−0.77	0.67	−1.20	1.69
	436	−1.30	1.15	−1.92	2.72
	365	−2.00	1.84	−2.73	3.87
	578	−0.157[c]	0.140[c]	−0.109[d]	0.126[e]
	546	−0.178	0.161	−0.125	0.139
	436	−0.298	0.273	−0.200	0.235
	365	−0.455	0.426	−0.314	0.357
	578	−0.198			0.185
	546	−0.225			0.212
	436	−0.383			0.344
	365	−0.608			0.516
optical purity (±5%)		95	88	72	85

[a] *c* 24.9, benzene. [b] *c* 24.7, benzene. [c] *c* 24.2, benzene. [d] *c* 17.5, benzene. [e] *c* 23.8, benzene.

After the successful resolution of diacid **34** and the determination of the enantiomeric excesses of the resolved (+) and (−) isomers, the remaining steps leading to tetraalkylmethane **10** are quite simple (Scheme IX). Decarboxylation of **34** gave the acid **38** in 74% yield, based on the cinchonidine salt, which on desulfurization with Raney nickel gave acid **25** (91% yield) that had already been obtained via our previous route. From (+)-**34**, $[\alpha]_{578}$ +4.81°, we obtained **25** with $[\alpha]_{578}$ +1.51°, whereas (−)-**34**, $[\alpha]_{578}$ −5.10°, gave the aliphatic acid **25** with $[\alpha]_{578}$ −1.07°.[32,33] Reduction of **25** with lithium aluminum hydride gave pure alcohol **26** with $[\alpha]_{578}$ +0.126 and −0.109° (from the diacids with enantiomeric purities of ca. 85% and 72%, respectively), in agreement with the values re-

(29) Two other examples of 2,6-diazabicyclo[2.2.2]octane-3,5-diones were found in the literature, prepared in an entirely different way: Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Chem. Commun.* **1975**, 502; Davies, L. B.; Leci, O. A.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1293.

(30) Wilen, S. H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725.

(31) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.

(32) In Table II it will be noted that there exists a discrepancy between the measured rotations of acid **25** and the optical purity. We believe that this discrepancy is due to minor, optically active impurities in the acid obtained by the second route (as was evident from the ^{1}H NMR spectrum). This discrepancy does not, however, affect the final results or the conclusions.

(33) Since both enantiomers of acid **25** are easily accessible, this acid can serve as a suitable precursor for several chiral tetraalkylmethanes, e.g., both enantiomers of butylhexylmethylpropylmethane (**9**) can be prepared in a state of high optical purity by starting from acid **25**.[12]

ported in the previous section. Tosylation and reduction of the (+) alcohol finally gave optically active **10**, $[\alpha]_{578}$ +0.185°, corresponding to $[M]_{578}$ +0.289°. The rotations of optically active intermediates, present in both routes, and their enantiomeric excesses are collected in Table II.

Conclusions

The synthesis of optically active **10** via two separate routes, both affording hydrocarbon **10** with the same absolute rotation, leads to the following conclusions. (i) No evidence for racemization could be found when thiophene derivatives with the 2-thienyl unit directly attached to an asymmetric quaternary carbon atom are desulfurized.[34] (ii) Hydrocarbon **3**, though chiral, retains its unique place in stereochemistry by virtue of the fact that its rotation is too small to be measured. Although the optical purity of **3** is not known with absolute certainty, the work described here leads us to the conclusion that **3** has the same optical purity as the acid **5**, namely, 25%.[10] This optical purity in no way invalidates the conclusion—as stated in the first publication[9]—that "hydrocarbon **3**, though asymmetric, does not exhibit optical activity between 280 and 580 nm", since the rotation of optically pure **3** would still be too small to be measured. Assuming that Thomson's formula gives an absolute rotation which is too low by a factor 30 (as appears to be the case for **10**) and assuming that the specific rotation is higher by a factor 3 at 365 nm (compare Table II), the expected rotation for neat, optically pure **3** in a 1-cm tube will still be only ca. 1×10^{-4} (at 365 nm), which is below the noise level of present-day instruments. Hence measurable optical activity of **3** can only be expected in the far ultraviolet region (below 200 nm).

Experimental Section

General Remarks. Microanalyses were performed in the analytical section of our department. Melting points (uncorrected) were determined on a Mettler FP apparatus. Infrared spectra were recorded on a Unicam SP-200 infrared spectrophotometer. Ultraviolet spectra were measured on a Zeiss PM-QII spectrophotometer. ^{1}H NMR spectra were recorded on a Varian A-60 or a Hitachi Perkin-Elmer R-24B spectrometer. A Varian XL-100 instrument was used for the ^{13}C NMR and 100-MHz ^{1}H NMR spectra. Tetramethylsilane (Me_4Si) was used as an internal standard in the ^{1}H NMR spectra, and chemical shifts are denoted in parts per million relative to Me_4Si at δ 0. Chloroform-*d* ($CDCl_3$) was used as an internal standard in the ^{13}C NMR spectra, and chemical shifts are denoted in parts per million relative to $CDCl_3$ at δ 77.0. Splitting patterns are designated as follows: s, singlet; d, double; t, triplet, q, quartet; m, multiplet. Mass spectra were obtained on an AEI MS-902 instrument by Mr. A. Kiewiet. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Di-(−)-menthyl Malonate (13). A small amount of sodium (0.35 g) was dissolved in (−)-menthol (210 g, 1.346 mol) by heating for ca. 4 h at 100–150 °C. To the brownish solution was added diethyl malonate (100 g, 0.625 mol), and the mixture was heated to distil off the ethanol formed in the transesterification. When no more ethanol distilled (ca. 65 mL of ethanol was obtained), the reaction mixture was cooled and subjected to steam distillation in order to remove the excess of (−)-menthol. The product was extracted with ether, and the ether layer was washed with saturated bicarbonate solution (2 × 100 mL) and with water (100 mL). After the ether layer was dried and the ether evaporated, the residue was distilled under vacuum to give 171 g of product with a boiling point of 160–180 °C (0.03 mm). Recrystallization from methanol gave 158.34 g (0.417 mol, 67%) of product: mp 58–59 °C; ^{1}H NMR (CCl_4) δ 0.7–2.2 (m, 18 H), 3.1 (s, 2 H), 4.4–4.8 (m, 2 H); $[\alpha]_{578}$ −75.8°, $[\alpha]_{546}$ −87.2°, $[\alpha]_{436}$ −143.3°, $[\alpha]_{365}$ −213.6° (*c* 4.83, chloroform).

Diethyl 1-Methylbutylidenemalonate (17). Procedure A. A mixture of titanium(IV) chloride (22 mL) and carbon tetrachloride (50 mL) was added to 125 mL of THF with ice cooling to keep the temperature below 15 °C under a nitrogen atmosphere. To the yellow suspension, kept at 0 °C, was added dropwise 16.1 g of diethyl malonate (0.110 mol) in 5 mL of THF. The mixture was stirred for 0.5 h, and then 2-pentanone (9.5 g, 0.110 mol) was added dropwise (in 5 mL of THF). After the mixture was stirred for 1.5 h at 0 °C, pyridine (37 mL) in THF (20 mL) was added dropwise with ice cooling. The reaction mixture was stirred for another 16 h at room temperature, and then water (100 mL) and ether (100 mL) were added to the brownish paste. The layers were separated, and the aqueous layer was extracted with ether (2 × 100 mL). The organic layers were combined and washed with brine (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL). After the organic layers were dried and distilled, there was obtained 14.49 g of the colorless ester **17**, bp 126–128 °C (9 mm). Redistillation of a forerun [bp 100–126 °C (9 mm)] gave another 2.23 g of product: bp 127–130 °C (10 mm); total amount 16.72 g (0.073 mol, 73%).

Procedure B. A mixture of titanium(IV) chloride (22 mL) and chloroform (90 mL) was cooled to 0 °C under a nitrogen atmosphere. To this solution was added with ice cooling diethyl malonate (15.5 g, 0.097 mol) in chloroform (10 mL) at such a rate that the temperature was kept below 15 °C. The mixture was stirred for 0.5 h at ca. 0 °C, and then 9.45 g of 2-pentanone (0.110 mol) in chloroform (10 mL) was added dropwise and with ice cooling. Stirring was continued for ca. 4 h at room temperature, and then the yellow solution was again ice cooled. A mixture of 40 mL of pyridine and 10 mL of chloroform was added dropwise in 1 h (temperature kept below 10 °C), and the brownish paste was subsequently stirred for 16 h at room temperature. Water (100 mL) was added, the layers were separated, and the aqueous layer was extracted with chloroform (2 × 100 mL). The rest of the procedure was analogous to procedure A, providing 14.06 g (0.062 mol, 64%) of **17**: bp 126.5–128.5 °C (10 mm); ^{1}H NMR (CCl_4) δ 0.7–1.8 (m) and 1.15–1.35 (t, J = 7 Hz) (11 H), 2.0 (s, 3 H), 2.1–2.4 (br t, 2 H), 3.9–4.3 (q, J = 7 Hz, 4 H); IR (neat) 1720 (C=O), 1640 cm^{-1} (C=C).

Diethyl 1-Ethylbutylidenemalonate (18). From 140 mL of titanium(IV) chloride in 400 mL of chloroform, 106.0 g of diethyl malonate (0.663 mol), 66.3 g of 2-hexanone (0.662 mol), and 220 g of pyridine there was obtained (according to procedure B) the product: bp 127–130 °C (10 mm); 92.8 g (0.383 mol, 58%); ^{1}H NMR (CCl_4) δ 0.8–1.9 (m) and 1.2–1.45 (t, J = 7 Hz) (14 H), 2.15–2.6 (m, 4 H), 4.0–4.4 (q, J = 7 Hz, 4 H); IR (neat) 1720 (C=O), 1630 cm^{-1} (C=C). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.32, 64.44; H, 9.15, 9.22.

Di-(−)-menthyl 1-Propylpentylidenemalonate (14). The crude product obtained from 27 mL of titanium(IV) chloride, 41.0 g of di-(−)-menthyl malonate (0.108 mol), 14.08 g of 4-octanone (0.110 mol), 40 mL of pyridine, and chloroform (total amount ca. 250 mL) by following procedure B was distilled by using a preheated Vigreux column (15–20 cm). This gave a forerun [bp 187–201 °C (0.3 mm)] and a main fraction [bp 203–220 °C (0.3–0.5 mm)], yield 18.55 g. The main fraction contained some 10–15% of di-(−)-menthyl malonate as determined by ^{1}H NMR spectroscopy (subtraction of this quantity gives a yield of ca. 30% of **14**). A pure, colorless product was obtained by crystallization from a mixture of methanol and ether: mp 41.5–43 °C; ^{1}H NMR (CCl_4) δ 0.5–2.4 (m, 52 H), 4.2–4.8 (m, 2 H); IR (neat) 1710 (C=O), 1620 cm^{-1} (C=C); $[\alpha]_{578}$ −49.4°, $[\alpha]_{546}$ −56.3°, $[\alpha]_{436}$ −95.0°, $[\alpha]_{365}$ −160.8° (*c* 3.9, chloroform). Anal. Calcd for $C_{31}H_{54}O_4$: C, 75.87; H, 11.09. Found: C, 75.88, 76.10; H, 11.33, 11.14.

Di-(−)-menthyl 1-Propylhexylidenemalonate (15). By use of procedure B, a crude product was obtained from titanium(IV) chloride (44 mL), di-(−)-menthyl malonate (62.92 g, 0.166 mol), 4-nonanone (23.6 g, 0.166 mol), pyridine (90 mL), and chloroform (total amount 200 mL). In this case, the reaction mixture was stirred for 20 h and then left for 3 days. The crude product was purified by distillation using a preheated Vigreux column to afford 51.96 g (0.103 mol, 62%) of slightly yellow **15**, bp 200–202 °C (0.02 mm). A small part was purified by column chromatography

(34) The occurrence of an equal amount of partial racemization in both routes to optically active butylethylmethylpropylmethane (**10**) seems highly improbable, because in both routes two entirely different groups are desulfurized.

(neutral alumina, activity I, benzene as eluent) and then distilled by Kugelrohr methods to give a colorless syrup: ^{1}H NMR (CCl_4) δ 0.7–2.4 (m, 54 H), 4.5–5.1 (m, 2 H); IR (neat) 1720 (C=O), 1630 cm^{-1} (C=C); $[\alpha]_{578}$ −48.7°, $[\alpha]_{546}$ −55.4°, $[\alpha]_{436}$ −96.2°, $[\alpha]_{365}$ −157.1° (*c* 4.13, chloroform). Anal. Calcd for $C_{32}H_{56}O_4$: C, 76.14; H, 11.18. Found: C, 76.04, 76.02; H, 11.25, 11.17.

Di-(−)-menthyl 1-Butylhexylidenemalonate (16). By use of the procedure as described above for **15**, a crude product was obtained from titanium(IV) chloride (45 mL), di-(−)-menthyl malonate (54.7 g, 0.144 mol), 5-decanone (22.47 g, 0.144 mol), pyridine (80 mL), and chloroform (total amount 200 mL). Distillation as described for **14** and **15** gave 31.75 g (0.061 mol, 43%) of slightly yellow **16**, bp 202–204 °C (0.02 mm). A small part was purified as described for **15** to give the colorless product: ^{1}H NMR (CCl_4) δ 0.6–2.5 (m, 56 H), 4.5–5.0 (m, 2 H); $[\alpha]_{578}$ −48.0°, $[\alpha]_{546}$ −54.9°, $[\alpha]_{436}$ −95.2°, $[\alpha]_{365}$ −156.7° (*c* 3.96, chloroform). Anal. Calcd for $C_{33}H_{58}O_4$: C, 76.40; H, 11.27. Found: C, 76.74, 76.56; H, 11.36, 11.28.

1-Methylbutylidenemalonic Acid (19). A 23.05-g sample of diethyl ester **17** (0.101 mol) was added to a solution of potassium hydroxide (27 g) in 96% ethanol (250 mL). The mixture was heated under reflux for 4 h and then evaporated. Ether was added to the brown residue, and after the mixture was shaken, the solid was filtered off. After being washed with ether until almost colorless, the solid was dissolved in water. Acidification and extraction with ether gave, after drying and evaporation, a slightly yellow oil which solidified on standing; yield 13.43 g (0.078 mol, 77%). Purification could be effected by recrystallization from a mixture of benzene and petroleum ether (bp 60–80 °C): mp 108–110 °C; ^{1}H NMR (CH_2Cl_2) δ 0.7–1.8 (m, 5 H), 2.1 (br s, 3 H), 2.2–2.6 (br t, 2 H), 10.7 (br s, 2 H). Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 56.08, 56.21; H, 6.86, 6.89.

1-Ethylbutylidenemalonic Acid (20). A 25.0-g sample of diethyl ester **18** (0.103 mol) was stirred together with potassium hydroxide (30 g), water (100 mL), and methanol (125 mL) for 60 h at room temperature. After partial evaporation to ca. 150 mL, the aqueous solution was extracted with chloroform and then acidified. Chloroform extraction, washing with brine, drying, and evaporation gave the crude acid which was recrystallized from a mixture of benzene and petroleum ether (bp 60–80 °C) to afford 11.45 g (0.062 mol, 60%) of diacid **20**: mp 111–112 °C; ^{1}H NMR ($CDCl_3$) δ 0.8–1.8 (m, 8 H), 2.3–2.8 (br t, 4 H), 12.2 (s, 2 H). Anal. Calcd for $C_9H_{14}O_4$: C, 58.08; H, 7.58. Found: C, 57.97, 58.04; H, 7.65, 7.55.

Di-(−)-menthyl 1-Methylbutylidenemalonate (11). A mixture of purified diacid **19** (9.0 g, 0.052 mol) and thionyl chloride (24.6 g) was warmed for 1.5 h (gentle reflux). The brown mixture was partly evaporated in order to remove most of the excess of thionyl chloride. To the residue was added (−)-menthol (20 g, 0.128 mol), and the mixture was heated at 100–130 °C for 4 h. Ether was added to the cooled reaction mixture, and the ethereal solution was washed with saturated sodium bicarbonate solution (25 mL) and with water (25 mL). After the organic layer was dried and the solvent evaporated, the residue was purified by Kugelrohr distillation to afford 18.9 g (0.042 mol, 81%) of a yellow oil, bp ca. 180 °C (0.02 mm). Chromatography over an alumina column (neutral, activity I, ca. 20 g) with ca. 100 mL of benzene gave the colorless product **11**. A slightly lower yield (ca. 5%) was obtained when unpurified diacid **19** was used: ^{1}H NMR (CCl_4) δ 0.6–2.4 (m, 46 H), 4.4–4.9 (m, 2 H); IR (neat) 1720 (C=O), 1640 cm^{-1} (C=C); $[\alpha]_{578}$ −57.9°, $[\alpha]_{546}$ −66.2°, $[\alpha]_{436}$ −113.1°, $[\alpha]_{365}$ −181.9° (*c* 3.9, chloroform). Anal. Calcd for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 75.16, 74.90; H, 10.70, 10.68.

Di-(−)-menthyl 1-Ethylbutylidenemalonate (21). This ester was prepared in the same way as ester **11** from 6.53 g of diacid **20** (0.035 mol), 20 g of thionyl chloride, and 15 g of (−)-menthol. After Kugelrohr distillation, 10 g (0.022 mol, 62%) of product [bp ca. 200 °C (0.5 mm)] was obtained, which was purified as described above to give the colorless diester **21**: ^{1}H NMR (CCl_4) δ 0.6–2.5 (m, 48 H), 4.4–4.9 (m, 2 H); IR (neat) 1720 (C=O), 1640 cm^{-1} (C=C). Anal. Calcd for $C_{29}H_{50}O_4$: C, 75.28; H, 10.89. Found: C, 75.29, 75.40; H, 10.90, 10.96.

Di-(−)-menthyl 1-Methyl-1-propylpentylmalonate (22). A Grignard reagent, prepared from *n*-butyl bromide (4.15 g, 30 mmol) and magnesium (0.73 g, 30 mmol) in ether, was added under a nitrogen atmosphere to a mixture of the di-(−)-menthyl ester **11** (9.0 g, 20.1 mmol) and 230 mg of copper(I) chloride in ether (at temperatures between −5 and +5 °C, in ca. 1.5 h). The dark brown mixture was stirred overnight at room temperature and then poured onto ice mixed with sulfuric acid. The product, extracted with ether, was washed with water, saturated sodium bicarbonate solution, and water, dried, and evaporated. The crude product was purified by Kugelrohr distillation [at ca. 185 °C (0.02 mm)] to give 7.85 g (15.5 mmol, 77%) of **22**. A small part was further purified by elution over a short alumina column (neutral, activity I) with benzene and subsequent Kugelrohr distillation: ^{1}H NMR (CCl_4, 60 MHz) δ 0.6–2.2 (m, 55 H), 3.3 (s, 1 H), 4.4–5.0 (m, 2 H); the 100-MHz ^{1}H NMR spectrum also showed two doublets (J = 8 Hz) centered around δ 3.05 and 3.85 (assumed to originate from **23**); IR (neat) 1750 and 1720 cm^{-1} (C=O). Anal. Calcd for $C_{32}H_{58}O_4$: C, 75.84; H, 11.54. Found: C, 75.76, 75.80; H, 11.30, 11.52.

Di-(−)-menthyl 1-Methyl-1-(2-thienyl)butylmalonate (12). To a Grignard reagent prepared from 8.54 g of magnesium (0.35 mol) and 58.45 g of 2-bromothiophene (0.36 mol) in ca. 200 mL of ether was added at ca. 5 °C under a nitrogen atmosphere copper(I) chloride (2.65 g) and subsequently at temperatures between −5 and +5 °C a solution of 113.8 g of ester **11** (0.254 mol) in 100 mL of ether (addition time ca. 2 h). After being stirred overnight at room temperature, the reaction mixture was poured onto ice–water (200 mL) and then acidified with dilute sulfuric acid. The product was extracted with three portions of ether. The combined organic layers were washed with water, saturated sodium bicarbonate solution, and water, dried, and evaporated. The residue was dissolved in *n*-pentane (200 mL) and cooled at ca. −50 °C for ca. 5 h. The solvent was decanted from the crystals which had formed, evaporated, and distilled by using a preheated Vigreux column (ca. 20 cm). The distillate [bp 194–225 °C (0.02 mm)] was largely decolorized by elution over a short alumina column (activity I, neutral) with benzene. The eluate was evaporated, dissolved in *n*-pentane, and cooled for 1 week at −50 °C to give another portion of crystals. A total amount of 36.9 g (0.069 mol, 27%) of one diastereoisomer was obtained. Recrystallization from *n*-pentane gave pure **12**, mp 93–95.5 °C. The other diastereoisomer was obtained as an impure oil (based on its ^{1}H NMR spectrum) after evaporation of the final *n*-pentane solution; it weighed 29.4 g (0.055 mol, 22%). In this reaction a rather low yield of **12** was obtained (in other experiments yields up to 80% were obtained); this is presumably due to the large scale employed in this experiment: ^{1}H NMR (CCl_4) δ 0.5–2.0 (m, 46 H), 3.60 (s, 1 H), 4.2–4.7 (m, 2 H), 6.6–7.0 (m, 3 H); the ^{1}H NMR spectrum of the crude product showed a singlet at δ 3.56 in addition to the singlet at δ 3.60 (ratio ca. 1:2); $[\alpha]_{578}$ −46.6°, $[\alpha]_{546}$ −52.6°, $[\alpha]_{436}$ −86.9°, $[\alpha]_{365}$ −130.5° (*c* 3.88, chloroform) (crystalline diastereoisomer). Anal. Calcd for $C_{32}H_{52}O_4S$: C, 72.13; H, 9,84; S, 6.02. Found: C, 72.38, 72.33; H, 9.87, 9.85; S, 6.04, 5.95.

3-Methyl-3-(2-thienyl)hexanoic Acid (24). The crystalline di-(−)-menthyl ester **12** (36.9 g, 69.3 mmol) was heated under reflux for 2 h with potassium hydroxide (63.5 g) and ethylene glycol (400 mL). The (−)-menthol which had formed was then distilled off by using a short distillation head until no more (−)-menthol passed over (some ethylene glycol distilled together with (−)-menthol). The same process, i.e., heating for 2 h under reflux and then distilling the (−)-menthol, was repeated twice. The clear reaction mixture was cooled, mixed with water (200 mL), acidified, and extracted with benzene. The benzene layer was dried and evaporated, and the residue was distilled to give 13.12 g (61.9 mmol, 89%) of the colorless acid: bp 129–130 °C (0.4 mm); IR (neat) 3300–2500 (CO_2H), 1710 (CO_2H), 700 cm^{-1} (thiophene); ^{1}H NMR (CCl_4) δ 0.7–2.0 (m) and 1.4 (s) (10 H), 2.5 (s, 2 H), 6.5–7.0 (m, 3 H), 11.2 (br s, 1 H); $[\alpha]_{578}$ −20.3°, $[\alpha]_{546}$ −23.7°, $[\alpha]_{436}$ −45.1°, $[\alpha]_{365}$ −82.3° (*c* 5.73, chloroform). Anal. Calcd for $C_{11}H_{16}O_2S$: C, 62.23; H, 7.60; S, 15.10. Found: C, 62.10, 62.12; H, 7.74, 7.56; S, 14.78, 14.78.

From 29.4 g of the oily di-(−)-menthyl ester **12** there was obtained in a similar experiment 7.39 g of acid **24** with bp 170–172 °C (4 mm) (presumably containing some impurities that lower its specific rotation): $[\alpha]_{578}$ +12.0°, $[\alpha]_{546}$ +13.9°, $[\alpha]_{436}$ +26.4°, $[\alpha]_{365}$ +48.4° (*c* 5.73, chloroform).

From the crude di-(−)-menthyl ester **12** (only purified by Kugelrohr distillation) the acid **24** was obtained in a similar way,

with the following specific rotations: $[\alpha]_{578}$ −5.6°, $[\alpha]_{546}$ −6.5°, $[\alpha]_{436}$ −12.3° (*c* 5.73, chloroform).

3-Methyl-3-propylheptanoic Acid (25). A Raney nickel catalyst, W-5,[25] prepared from nickel–aluminum alloy (38 g) and sodium hydroxide (48 g) in water (200 mL), was heated under reflux for 3 h with 4.3 g of (−)-**24** (20.3 mmol, $[\alpha]_{578}$ −20.3°), sodium carbonate (3 g), and water (600 mL). The mixture was then filtered while hot, and the catalyst was washed with boiling sodium carbonate solution (150 mL of a 10% solution), boiling ethanol (150 mL), and boiling water (150 mL), respectively. The filtrates were combined, acidified with concentrated hydrochloric acid, and extracted with chloroform (3 × 200 mL). Drying, evaporation, and Kugelrohr distillation gave 3.22 g (17.3 mmol, 85%) of pure acid **25** which on distillation had a boiling point of 110–111 °C (0.6 mm): IR (neat) 3300–2500 and 1710 cm^{-1} (CO_2H); ^1H NMR (CCl_4) δ 0.6–1.5 (m, 19 H), 2.2 (s, 2 H), 11.4 (s, 1 H). Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.66, 70.57; H, 11.91, 11.80.

In the same way there was obtained from 7.1 g (33.5 mmol) of (+)-**24** ($[\alpha]_{578}$ +12.0°) after distillation 4.15 g (22.3 mmol, 67%) of pure acid **25**, bp 110.5–112 °C (0.6 mm).

The same acid can be obtained by saponification of the mixture of diastereoisomers **22** (6.3 g, 12.5 mmol) with potassium hydroxide (10 g) and ethylene glycol (50 mL) as described for the synthesis of the thiophene acid **24**. After Kugelrohr distillation of the crude product there was obtained 1.63 g (8.8 mmol, 70%) of acid **25** which was subsequently distilled [bp 96–98 °C (0.5 mm)]: $[\alpha]_{578}$ −0.12°, $[\alpha]_{546}$ −0.15°, $[\alpha]_{436}$ −0.24°, $[\alpha]_{365}$ −0.38° (*c* 13.1, benzene).

3-Methyl-3-propylheptan-1-ol (26). A 9.06-g sample of (−)-**25** ($[\alpha]_{578}$ −0.68°, 51.5 mmol) in ether (25 mL) was added dropwise to lithium aluminum hydride (10 g) in ether (75 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 3 h and then quenched with water (25 mL) and concentrated hydrochloric acid (50 mL), respectively (ice cooling). After addition of more water, the alcohol was extracted with ether (3 × 100 mL). The combined ether extracts were washed with saturated sodium bicarbonate solution (100 mL) and with water (50 mL), dried, and evaporated. The residue was distilled to give 7.97 g (46.3 mmol, 90%) of alcohol **26**: bp 96–99 °C; ^1H NMR (CCl_4) δ 0.6–1.6 (m, 21 H), 3.35–3.65 (br t, 2 H), 4.0 (br s, 1 H); IR (neat) 3600–3300 (OH). Anal. Calcd for $C_{11}H_{24}O$: C, 76.68; H, 14.04. Found: C, 76.40, 76.46; H, 14.11, 14.01.

4-Ethyl-4-methyloctane (10). (i) To a mixture of 5.10 g of (−)-**26** ($[\alpha]_{578}$ −0.157°, 29.7 mmol) and pyridine (100 mL) cooled at ca. 0 °C there was added *p*-toluenesulfonyl chloride (14.0 g, 73.4 mmol) over a period of 5 min. The mixture was allowed to warm to room temperature and then stirred overnight. Ice–water (200 mL) was added, and the solution was acidified and extracted with chloroform (3 × 150 mL). The combined organic layers were washed with water (250 mL), ca. 10% hydrochloric acid (250 mL), and water (250 mL), dried, and evaporated to leave 8.6 g (26.3 mmol, 89%) of the tosylate of **26**.

(ii) The tosylate of (−)-**26** (4.3 g, 13.2 mmol) dissolved in ether (50 mL) was added dropwise to a mixture of lithium aluminum hydride (3 g) in ether (100 mL) under a nitrogen atmosphere. After the addition was complete, the reaction mixture was heated under reflux for 3.5 h. The mixture was cooled with an ice bath and then quenched with water, and, subsequently, dilute sulfuric acid was added. The layers were separated, and the aqueous layer was extracted with pentane (100 mL). The combined organic layers were washed with water (100 mL), with saturated sodium bicarbonate solution (100 mL), and with water (100 mL). Drying and evaporation to a small volume (ca. 5 mL) gave an oil which was taken up in pentane (5 mL). Concentrated sulfuric acid was added (25 mL), the mixture was shaken for some minutes (giving a brownish acid layer), and the layers were separated. The acid layer was extracted once with 10 mL of pentane. The two pentane fractions were subsequently dropped on a column consisting of silica (bottom, 12 × 1 cm) and alumina (top, 12 × 1 cm) and eluted with pentane (Uvasol quality). The process was essentially the same as that described in ref 35. The eluate was purified by preparative GLC (SE-30 column, helium as carrier gas, column temperature 150 °C, injection port 200 °C, column 6 ft × 0.5 in., F&M 700 apparatus) to give about 1 mL of product. This product was further purified by another column chromatography in the way described above, and subsequent preparative GLC (neat, 1-mm cell, air as reference) gave a product of high purity as shown by its ultraviolet extinctions (wavelength in nanometers as superscript): 0.014^{290}, 0.025^{280}, 0.037^{270}, 0.072^{260}, 0.084^{250}, 0.085^{240}, 0.0164^{230}, 0.218^{225}, 0.297^{220}, 0.490^{215}, 0.910^{210}, 1.480^{205}. The following rotations were obtained for this product (measured neat in a 1-cm cell): α_{578} −0.015°, α_{546} −0.017°, α_{436} −0.026°, α_{365} −0.045°, corresponding to $[\alpha]_{578}$ −0.198°, $[\alpha]_{546}$ −0.225°, $[\alpha]_{436}$ −0.383°, $[\alpha]_{365}$ −0.608° and to $[M]_{578}$ −0.309°, $[M]_{546}$ −0.351°, $[M]_{436}$ −0.597°, $[M]_{365}$ −0.948° (*d* 0.7565, M_r = 156).

In essentially the same way the (+) enantiomer was obtained by reduction of the tosylate of (+)-**26**, $|\alpha|_{578}$ +0.126°, with lithium aluminum hydride in ether. The (+) enantiomer was extensively purified as described for (−)-**10** to give a product with the following ultraviolet extinctions (neat, 1-mm cell, air as reference, wavelength in nanometers as superscript): 0.00^{290}, 0.00^{280}, 0.012^{270}, 0.033^{260}, 0.036^{250}, 0.038^{240}, 0.093^{230}, 0.132^{225}, 0.166^{220}, 0.207^{215}, 0.289^{210}, 0.430^{205}, 0.750^{200}, $1.03^{197.5}$. It had the following rotations (measured neat in a 1-cm cell): α_{578} +0.014°, α_{546} +0.016°, α_{436} +0.026°, α_{365} +0.039°, corresponding to $[\alpha]_{578}$ +0.185°, $[\alpha]_{546}$ +0.212°, $[\alpha]_{436}$ +0.344°, $[\alpha]_{365}$ +0.516° and to $[M]_{578}$ +0.289°, $[M]_{546}$ +0.331°, $[M]_{436}$ +0.537°, $[M]_{365}$ +0.805°.

Although the yield was not determined in the experiments just described, in another experiment the crude product (before the extensive purification) was distilled by Kugelrohr methods to give **10** in ca. 85% yield: ^1H NMR (CCl_4) δ 0.6–1.5 (m); IR (neat) 3000, 1480, 1390 cm^{-1}. Despite the extensive purification, accurate GLC analysis showed that in both enantiomers of **10** a minor trace of an unknown compound was present (having a slightly longer retention time than **10**). This impurity could not be removed by the purification methods used above. Since the impurity gives rise to a CD and UV absorption at 183–196 nm, besides the stronger absorption of **10** at 140–160 nm, further purification will be necessary in order to obtain the CD spectra of the pure enantiomers of **10**. The CD and UV spectra have been recorded by Dr. A. Gedanken and co-workers, Bar-Ilan University, Ramat-Gan, Israel.

4-Methyloct-3-en-2-one (28). Acetylacetone (143 g, 1.43 mol) in ether (250 mL) was added over a period of 1 h to a Grignard reagent prepared for magnesium (77.5 g, 3.19 mol) and *n*-butyl bromide (440 g, 3.21 mol) in ether (300 mL). After the addition was complete, the reaction mixture was stirred for 1 h at room temperature and then for 3 h at reflux temperature. After this mixture cooled, a mixture of ammonium chloride (ca. 140 g) and water (350 mL) was slowly added. The greenish mass was broken up, sucked off, and washed with 1 L of ether. The filtrate was evaporated and the residue then distilled after addition of some iodine; a fraction with a boiling point of ca. 70–100 °C (20 mm) was collected (about 100 mL). The solid residue remaining after the ether washings was added to hydrochloric acid (10%, 750 mL). The product was extracted with ether (2 × 300 mL), and the combined ether extracts were washed with water (250 mL) and with 5% sodium bicarbonate solution (250 mL), dried, and evaporated. The residue was distilled (after addition of some iodine) to give about 50 mL of distillate, bp ca. 70–100 °C (20 mm). The two product fractions were combined and redistilled over some iodine to afford 110.6 g (0.79 mol, 55%) of ketone **28**: bp 72–75 °C (15 mm); ^1H NMR (CCl_4) δ 0.7–2.6 (m, 14 or 15 H), 2.95 (d, *J* = 4 Hz, 0.8 H), 5.0–5.5 (m, 0.4 H), 5.9 (br s, 0.5 H) (the signal at δ 5.9 is assigned to the α,β isomer, and signals at δ 2.95 and 5.0–5.5 are assigned to the β,γ isomer); IR (neat) 1730, 1710 (C=O), 1630 cm^{-1} (C=C).

8-Butyl-2,6-diaza-1,8-dimethylbicyclo[2.2.2]octane-3,5-dione (29). Cyanoacetamide (68 g, 0.81 mol) in hot ethanol (300 mL) was added to a solution of sodium (20 g, 0.87 mol) in ethanol (300 mL). After the suspension was stirred and heated for 10 min ketone **28** (110.6 g, 0.79 mol) in ethanol (100 mL) was added, and heating was continued. A clear solution was obtained after ca. 0.25 h of heating under reflux. After 0.5 h a suspension began to form again, and heating under reflux was continued for 3 h. The solvent was partly evaporated, and water (500 mL) was added. After further evaporation (to remove all of the ethanol) concentrated hydrochloric acid (500 mL) was added to the residue, and

(35) Hesse, G.; Englebrecht, B. P.; Engelhardt, H.; Nitsch, S. *Fresenius' Z. Anal. Chem.* **1968**, *241*, 91.

the solution was completely evaporated on a hot water bath. The remaining yellow paste was recrystallized from water (ca. 500 mL) to which some ethanol had been added. This gave 46.48 g of diamide **29**. Another 55.53 g was obtained after partial evaporation of the filtrate. The filtrate, obtained after the latter crystallization, still contained some **29** as was shown by saponification (see below). The diamide can be further purified by recrystallization from a mixture of benzene and petroleum ether (bp 60–80 °C): mp 193–194 °C; ^{1}H NMR ($CDCl_3$) δ 0.6–1.8 (m, 21 H), 3.0 (br s, 1 H), 8.5 (br d, 2 H); ^{13}C NMR ($CDCl_3$) δ 173.2 (s), 172.8 (s), 66.7 (s), 63.4 (d), 50.4 (t), 41.3 (t), 36.9 (s), 26.1 (t), 25.3 (q), 22.9 (t), 20.8 (q), 13.8 (q); IR ($CHCl_3$) 3300 (NHC=O), 1720–1670 cm^{-1} (C=O); mass spectrum, *m/e* 224. Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.26; H, 8.99; N, 12.49. Found: C, 63.92, 64.04; H, 8.82, 8.89; N, 12.17, 12.14.

1-Acetonyl-1-methylpentylmalonic acid (30). Diamide **29** (46.48 g, 0.208 mol) was heated under reflux for 20 h with potassium hydroxide (70 g) and water (300 mL). After cooling, the reaction mixture was extracted with benzene (100 mL) and then acidified with concentrated hydrochloric acid. The diacid **30** was extracted with chloroform (3 × 500 mL) and weighted ca. 57 g after drying and evaporation.

From 55.53 g of diamide there was obtained in the same way ca. 70 g of crude **30**, while the filtrate described above gave, after evaporation and saponification, ca. 55 g of crude **30**. The diacid did not solidify and could not be obtained crystalline by attempted recrystallizations. It could very well be used, however, in the crude state for the esterification to form **32**: ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 12 H), 2.1 (s, 3 H), 2.7 (s, 2 H), 4.0 (s, 1 H), 12.0 (s, 2 H).

8-Butyl-1,8-dimethyl-2,6-dioxobicyclo[2.2.2]octane-3,5-dione (31). Crude diacid **30** (10 g) was stirred for 4 h at room temperature with phosphorus oxychloride (20 mL) and benzene (70 mL). The reaction mixture was poured onto ice water, the layers were separated, and the benzene layer was washed with water, with saturated sodium bicarbonate solution, and with water. After the benzene layer was dried and the solvent evaporated, the residual oil was crystallized from ethanol to give the colorless dilactone **31** in about 80% yield (based on the diamide **29**): 78.5–79 °C; ^{1}H NMR (CCl_4) δ 0.6–1.5 (m, 12 H), 1.7 (s, 3 H), 2.0 (s, 2 H), 3.3 (s, 1 H). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.76, 63.67; H, 7.98, 7.98. The dilactone can be converted back into the diacid **30** in near quantitative yield by heating **31** under reflux for 1 h with 5% sodium hydroxide solution.

Diethyl 1-Acetonyl-1-methylpentylmalonate (32). The three portions of crude diacid **30** mentioned above were esterified by dissolving in ethanol (500–600 mL for each portion of diacid), passing through dry hydrogen chloride for ca. 3 h, and subsequent heating under reflux for 3 h. After evaporation the residue was distilled to give a small forerun and a main fraction, bp 138–142 °C (0.4 mm) (125.03 g from the three portions of diacid). The combined foreruns were redistilled to give 15.4 g of product [bp 92–95 °C (0.1 mm)]—which we assume is decarbethoxylated **32**, namely, ethyl 3-acetonyl-3-methyl-heptanoate (based on the ^{1}H NMR spectrum; 67.5 mmol, 9% yield, based on the starting ketone **28**)—an intermediate fraction, and a fraction with a boiling point of 117–127 °C (0.1 mm) (7.22 g) which was added to the main portion of diester, thus affording a total amount of 132.25 g of **32** (0.441 mol, 56% yield based on the starting ketone **28**): ^{1}H NMR of decarbethoxylated **32** (CCl_4) δ 0.7–1.6 (m, 15 H), 2.0 (s, 3 H), 2.35 (s, 2 H), 2.5 (s, 2 H), 4.0 (q, J = 7 Hz, 2 H); ^{1}H NMR of **32** (CCl_4) δ 0.7–1.6 (m, 18 H), 2.0 (s, 3 H), 2.7 (s, 2 H), 3.7 (s, 1 H), 4.1 (q, J = 7 Hz, 4 H); IR of **32** (neat) 1770–1720 (C=O). Anal. Calcd for $C_{16}H_{28}O_5$ (**32**): C, 63.97; H, 9.40. Found: C, 64.14, 63.99; H, 9.43, 9.42.

Diethyl 1-Methyl-1-[2,2-(ethylenedithio)propyl]pentylmalonate (33). Diester **32** (132.25 g, 0.441 mol) was thioacetalized in three portions by using a total amount of ca. 800 mL of glacial acetic acid, 91 mL of ethanedithiol, and 92 mL of boron trifluoride etherate. After the mixture was stirred overnight, water (1.5 L) was added, and the diester **33** was extracted with benzene (2 × 1 L). The combined benzene fractions were washed with water (750 mL), dried, and evaporated. The residue was distilled under vacuum (0.1 mm) until all of the ethanedithiol had been removed. The remainder was ester **33** which was pure enough for use in the next step. In another experiment the dithioacetal was purified by distillation, giving a slightly yellow product: bp 158–161 °C (0.1 mm); 86% yield, based on the diester **32**. The product could not be obtained analytically pure, however, since distillation caused some decomposition: ^{1}H NMR (CCl_4) δ 0.6–1.7 (m, 18 H), 1.8 (s, 3 H), 2.35 (s, 2 H), 3.25 (s, 4 H), 3.6 (s, 1 H), 4.1 (q, J = 7 Hz, 4 H).

1-Methyl-1-[2,2-(ethylenedithio)propyl]pentylmalonic Acid (34). The unpurified dithioacetal **33**, described above, was saponified in two portions by using a total amount of 1.5 L of 96% ethanol and 175 g of potassium hydroxide with heating under reflux for 3 h, furnishing a thick paste (heating for a longer time as was done with one portion gives some decarboxylation). Workup of each portion was done by evaporating ca. 0.5 L of ethanol, adding water (1.5 L) to the residue, and extracting with benzene (2 × 250 mL). Acidification of the aqueous layer with concentrated hydrochloric acid, followed by chloroform extraction (2 × 250 mL) and drying and evaporation of the combined chloroform extracts, left the crude **34** behind as a reddish oil (about 150 g from two portions of dithioacetal **33**). This diacid could not be purified and was used as such in the following step: ^{1}H NMR ($CDCl_3$) δ 0.7–2.0 (m) and 1.9 (s) (15 H), 2.5 (2 s, 2 H), 3.3 (s, 4 H), 3.9 (s, 1 H), 11.6 (s, 2 H) (some impurities were also present).

(−)-Cinchonidine Salt of 34. To one portion of crude diacid **34** (ca. 82 g) in warm ethyl acetate (300 mL) was added 78 g of (−)-cinchonidine suspended in warm ethyl acetate (ca. 200 mL) (a solution of (−)-cinchonidine in 200 mL of methanol can be used as well). Immediate salt formation occurred. After the mixture was heated under slight reflux for 5 min, it was cooled to room temperature. The salt was filtered off and washed with methanol (to give ca. 70 g of salt). The filtrate was evaporated, heated under reflux with methanol (200 mL), and evaporated again, and then ethyl acetate was added to give a solid. This solid was filtered off and washed with methanol to give another 7 g of salt. The filtrate was evaporated and dissociated (see below) to afford a residue (ca. 30 g) which consisted mostly of the decarboxylated acid, **38**. This was distilled to give 20.0 g of acid **38**, bp 180–184 °C (0.1 mm). From the other portion of crude **34** (ca. 69 g) there was obtained in the same way ca. 93.5 g of (−)-cinchonidine salt and 8.0 g of acid **38**: total yield ca. 170 g of the (−)-cinchonidine salt (0.277 mol, 63% based on the diester **32**); 28.0 g of acid **38** (0.101 mol, 23% based on the diester **32**).

Resolution of the (−)-Cinchonidine Salt of 34. A 77-g sample of (−)-cinchonidine salt (salt of the first portion described above) was dissolved by heating with 5 L of methanol. The solution was cooled overnight at about 0 °C, and the crystals were filtered and washed with methanol. This gave 41.9 g of salt, mp 172.5–173 °C. The filtrate was concentrated to about 1.5 L, heated until a clear solution was obtained, and cooled again at 0 °C for 3 days. This gave another 2.94 g of salt, mp 171.5–172 °C. The two portions of salt were combined and stirred with ca. 20% sulfuric acid and benzene until two clear layers were obtained. The two layers were separated, and the benzene layer was washed with ca. 20% sulfuric acid and with water, dried, and evaporated to give 26.6 g of (+)-**34** as a viscous oil: $[\alpha]_{578}$ +4.81°, $[\alpha]_{546}$ +5.43° (*c* 9.30, chloroform).

Both diacid enantiomers, obtained in this way, presumably contained some solvent and/or other impurities which could not be removed; hence the specific rotations will be somewhat too low. Anal. Calcd for $C_{33}H_{46}N_2O_5S_2$ [(−)-cinchonidine salt with (+)-**34**]: C, 64.46; H, 7.54; N, 4.56; S, 10.43. Found: C, 64.10, 64.14; H, 7.70, 7.62; N, 4.62, 4.55; S, 10.24, 10.25.

Di-(−)-menthyl 1-Methyl-1-[2,2-(ethylenedithio)propyl]-pentylmalonate (37). To a solution of diacid **34** (0.62 g, 1.94 mmol) in benzene (5 mL) was added oxalyl chloride (0.7 mL) and then 1 drop of *N,N*-dimethylformamide. After the mixture was stirred for 1 h at room temperature, (−)-menthol (1.2 g, 7.70 mmol) was added, and the mixture was evaporated (to remove benzene and the excess of oxalyl chloride) and then heated at 120–140 °C for 1 h. After Kugelrohr distillation the crude product [bp 220 °C (0.02 mm)] was obtained which was eluted over a short alumina column (neutral, activity I) with benzene to give 0.66 g (1.11 mmol, 57%) of colorless **37** after evaporating the eluate: ^{1}H NMR (100 MHz, $CDCl_3$) δ 0.7–2.1 (m, 51 H), 2.3 (d, J = 15 Hz, 1 H), 2.6 (d, J = 15 Hz, 1 H), 3.3 (s, 4 H), 3.55 (s, 0.5 H), 3.57 (s, 0.5 H), 4.4–4.8 (m, 2 H). For this spectrum, (±)-**34** was used as starting com-

pound, thus producing two diastereoisomers which were seen separately via the singlets at δ 3.55 and 3.57 (also a slight difference was observed for the two protons in the propyl side chain: the two doublets, centered around δ 2.3 and 2.6, each consisted of two partially separated doublets). (+)-**34** ([α]$_{578}$ +4.81°) gave the di-(−)-menthyl ester with the singlet at δ 3.55 predominating, while the di-(−)-menthyl ester from (−)-**34** ([α]$_{578}$ −5.10°) had the singlet at δ 3.57 predominating. Anal. Calcd for $C_{34}H_{60}O_4S_2$: C, 68.41; H, 10.13; S, 10.74. Found: C, 68.70, 68.87; H, 10.09, 10.25; S, 10.42, 10.55.

3-[2,2-(Ethylenedithio)propyl]-3-methylheptanoic Acid (38). Distillation of crude (+)-**34** (25.5 g, [α]$_{578}$ +4.81°) gave the decarboxylated acid: bp 168–171 °C (0.03 mm); 14.83 g (53.7 mmol, 74% yield based on the (−)-cinchonidine salt of **34**). It has a very small specific rotation ([α]$_{578}$ +0.1°) which was influenced by small impurities (**38** obtained from other fractions of **34** showed rather variable specific rotations): ^{1}H NMR (CCl_4) δ 0.7–1.6 (m, 12 H), 1.8 (s, 3 H), 2.2 (s, 2 H), 2.45 (s, 2 H), 3.25 (s, 4 H), 12.0 (s, 1 H). Anal. Calcd for $C_{13}H_{24}O_2S_2$: C, 56.48; H, 8.75; S, 23.19. Found: C, 56.61, 56.52; H, 8.86, 8.77; S, 23.06, 23.11.

3-Methyl-3-propylheptanoic Acid (25). A Raney nickel catalyst, W-5, prepared from nickel–aluminum alloy (175 g) and sodium hydroxide (225 g) in water (840 mL) was heated under reflux for 4 h with 4.37 g of **38** (52.1 mmol), sodium carbonate (18 g), water (1300 mL), and ethanol (100 mL). The mixture was filtered while hot, and the catalyst was washed with boiling sodium carbonate solution (300 mL of a 5% solution), boiling ethanol (300 mL), and boiling water (300 mL), respectively. The combined filtrates were acidified with concentrated hydrochloric acid, and the acid **25** was extracted with chloroform (3 × 300 mL). The combined chloroform layers were washed with water, dried, evaporated, and distilled to give **25**: bp 118–120 °C (1 mm); 8.84 g (47.5 mmol, 91%).

In all desulfurizations of **38** with Raney nickel, the product **25** contained small variable amounts of impurities which could not be removed by distillation.

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Registry No. (+)-**10**, 73636-61-0; (−)-**10**, 73636-62-1; **11**, 73651-43-1; **12** (isomer 1), 73636-63-2; **12** (isomer 2), 73679-16-0; **13**, 73636-64-3; **14**, 73636-65-4; **15**, 73636-66-5; **16**, 73636-67-6; **17**, 18795-91-0; **18**, 73636-68-7; **19**, 35205-69-7; **20**, 73636-69-8; **21**, 73636-70-1; **22** (isomer 1), 73636-71-2; **22** (isomer 2), 73679-37-5; (+)-**24**, 73636-72-3; (−)-**24**, 67752-85-6; (+)-**25**, 73636-73-4; (−)-**25**, 67727-45-1; (+)-**26**, 73636-74-5; (+)-**26** tosylate, 73636-75-6; (−)-**26**, 73636-76-7; (−)-**26** tosylate, 73636-77-8; **28**, 60934-88-5; **29**, 73636-78-9; (±)-**30**, 73636-79-0; **31**, 73636-80-3; (±)-**32**, 73636-81-4; (±)-**33**, 73636-82-5; (±)-**34**, 73636-83-6; (±)-**34** (−)-cinchonidine salt, 73636-84-7; (+)-**34**, 73636-85-8; (+)-**34** (−)-cinchonidine salt, 73636-86-9; (−)-**34**, 73636-87-0; **36**, 485-71-2; **37** (isomer 1), 73651-44-2; **37** (isomer 2), 73636-88-1; (±)-**38**, 73636-89-2; (+)-**38**, 73636-89-2; (−)-menthol, 2216-51-5; diethyl malonate, 510-20-3; 2-pentanone, 107-87-9; 2-hexanone, 591-78-6; 4-octanone, 589-63-9; 4-nonanone, 4485-09-0; 5-decanone, 820-29-1; 2-bromothiophene, 1003-09-4; acetylacetone, 123-54-6; cyanoacetamide, 107-91-5; ethyl (±)-3-acetonyl-3-methylheptanoate, 73636-90-5.

Synthesis of Carnitine Homologues. Reactions of Tertiary Amines with Epoxy Esters

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A series of new carnitine homologues, 4-hydroxy-5-(trialkylammonio)pentanoates (**2**) and 5-hydroxy-6-(trialkylammonio)hexanoates (**3**), has been synthesized. The key step in this synthesis was the reaction of an epoxy ester with a tertiary amine to effect epoxide opening and hydrolysis in one step. The generality of this reaction is discussed, and the synthetic approach to **2** and **3** is compared to previously published routes to carnitine and its analogues. Attempts to apply the new reaction scheme to carnitine itself are described.

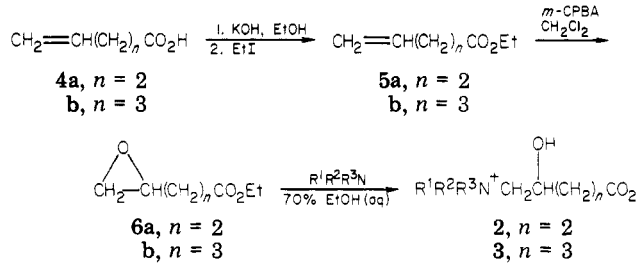
The role of carnitine (**1**), often referred to as vitamin B_T,

$$(CH_3)_3N^+CH_2CH(OH)CH_2CO_2^-$$
1

in the transport of fatty acids across membranes is now well established[1] though research in this area continues.[2] Several analogues of carnitine have also been investigated. For example, Norum studied the effect of various ammoniobutyrates on the carnitine transport system.[3] In 1975 the synthesis and evaluation of several dialkylaminohydroxybutyric acid hydrochlorides and methochlorides as potential hypoglycemic agents were reported.[4]

Our interest in hydroxylated quaternary ammoniocarboxylates led us to the development of an efficient route to their synthesis. We report here the successful preparation of several hydroxylated (trialkylammonio)pentanoates (**2**) and hexanoates (**3**), new carnitine homologues.

Scheme I



$$R^1R^2R^3N^+C^5H_2C^4H(OH)C^3H_2C^2H_2C^1O_2^-$$
2

$$R^1R^2R^3N^+C^6H_2C^5H(OH)C^4H_2C^3H_2C^2H_2C^1O_2^-$$
3

The key step in this sequence is a one-step epoxide ring opening and ester hydrolysis which to our knowledge has

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(2) For example: P. T. Normann, O. C. Ingerbratsen, and T. Flatmark, *Biochim. Biophys. Acta*, **501**, 286 (1978); E. N. Christiansen and E. J. Davis, *ibid.*, **502**, 17 (1978); C. J. Rebouche, *ibid.*, **471**, 145 (1977); M. E. Mitchell, *Am. J. Clin. Nutr.*, **31**, 293, 481, 645 (1978).
(3) K. R. Norum, *Biochim. Biophys. Acta*, **99**, 511 (1965).
(4) S. G. Boots and M. R. Boots, *J. Pharm. Sci.*, **64**, 1949 (1975).

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