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Synthesis of Some New Cholesteryl Esters of Chiral Alkanoic Acids

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Six new cholesteryl esters have been prepared from chiral alkanoic acids. Oxidation of 2(S)-methylbutanol and 2(S)-ethyl-3-methylbutyraldehyde gave the corresponding butyric acids, while condensation of the tosylates of the corresponding alcohols with diethyl malonate led ultimately to the substituted hexanoic acids. 2(R)-Methylpentanoic and (−)-2-ethylhexanoic acids were commercially available.

INTRODUCTION

Structural trends in mesomorphic properties of cholesteryl alkanoates exist[1]. The results indicate that steric effects in the neighbourhood of the ester carbonyl and to a lesser extent further along the alkanoate chain profoundly effect the mesomorphic properties. This means that the conformation of the alkanoate portion plays an important role. Likewise configuration, i.e., the spatial interrelationship of substituents attached to the asymmetric carbon, in chiral alkanoates should influence the mesomorphic properties of these esters. Thus, an examination of the effect of chiral centers at various distances from the carbonyl carbon was undertaken. In the present report the syntheses are detailed; other reports will describe mesomorphic parameters.[2]

DISCUSSION

Synthesis of cholesteryl alkanoates

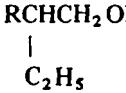
Our previous work[1] indicated that the largest effects would be manifest when the chiral center was adjacent to the carbonyl function. For that reason most (four) of the systems are of this type. Two systems in which the assymmetrically substituted carbon is γ to the carbonyl were also prepared.

For the study of mesomorphic properties high purity is desirable and since cholesterol is normally contaminated with other steroids, primary standard grade cholesterol which had been specially purified was used throughout this work. Special care was also taken to use high purity acids for the esterifications. Also the product esters were carefully purified, generally by column chromatography followed by recrystallization. Throughout this paper the cholesteryl moiety is represented by Ch.

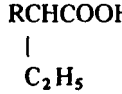
Esters with chiral center α to carbonyl carbon

a) Cholesteryl 2(S)-Methylbutyrate (7)

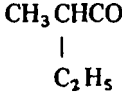
'Primary active amyl alcohol' 2(S)-methylbutanol (*1*), of 97% optical purity was oxidized to 2(S)-methylbutyric acid (*3*) with some loss of optical purity to 84%. The acid was converted with thionyl chloride to 2(S)-methylbutryl chloride (*6*) of 84% optical purity. Reaction of *6* and cholesterol gave 76% of the desired ester *7*.



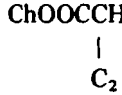
1, R=CH_3 (S)
2, R=i–C_3H_7 (S)



3, R=CH_3 (S)
4, R=n–C_4H_9 (–)
5, R=i–C_3H_7 (S)



6, (S)

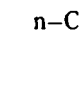


7, R=CH_3 (S)
8, R=n–C_4H_9
9, R=i–C_3H_7 (S)

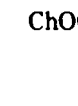
b. Cholesteryl 2(R)-Methylpentanoate (11)

Reaction of 2(R)-methylpentanoic acid (*10*) of 88% optical purity with cholesterol in the presence of 1,1'-carbonyldiimidazole[3] gave a low yield (25%) of the

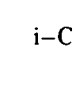
desired ester *11*. Since yields of 60 – 95% have been obtained by this method using straight chain acids,[4] the lower yield here is attributed to steric hindrance caused by the 2-methyl substituent of *10*.



10, (R)

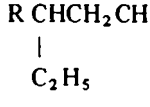


11, (R)

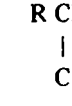


12, (S)

13, $R = CH_3$ (S)
14, $R = i\text{-}C_3H_7$ (S)



15, $R = CH_3$ (S)
16, $R = i\text{-}C_3H_7$ (R)



17, $R = CH_3$ (S)
18, $R = i\text{-}C_3H_7$ (R)

c. Cholesteryl (–)-2-Ethylhexanoate (8)

(–)-2-Ethylhexanoic acid (*4*) of 97% optical purity was converted to its acid chloride and thence without isolation in 94% yield to desired ester *8*. The absolute configuration of the starting acid is unknown

d. Cholesteryl 2(S)-Ethyl–3-methylbutyrate (9):

2(S)-Ethyl-3-methylbutyraldehyde (*12*) ($[\alpha]_D$ + 24.6° (neat)) was oxidized with nitric acid to the acid *5* ($[\alpha]_D$ + 0.16° (neat)). This was converted to its acid chloride and the latter without isolation to the desired ester *9*. The highest previously values of $[\alpha]_D$ are + 37° for *12*[5,6] and –2.24° for *5*[7], the latter prepared from a sample of *12* with $[\alpha]_D$ + 35.9° (dioxane) by permanganate oxidation. Assuming optically pure aldehyde has $[\alpha]_D$ + 37° and no loss of optical purity during the permanganate oxidation, *5* was *7%* optically pure.

Another sample of aldehyde *12* of $[\alpha]_D$ + 39.6° (neat) gave *5* of $[\alpha]_D$ + 0.25° (neat); this oxidation proceeds with loss of about 90% of the optical purity.

$$\mathrm{ChOOCCH_2CH_2CHR}$$
$$\qquad\qquad | $$
$$\qquad\qquad \mathrm{C_2H_5}$$

19, R=CH_3 (S)
20, R=i–C_3H_7 (R)

Esters with chiral center γ to carbonyl carbon

a. Cholesteryl 4(S)-Methylhexanoate (19)

Alcohol *1* (97% optically pure) was converted to tosylate *13* of 92% optical purity with p-toluenesulfonyl chloride. The tosylate *13* was reacted with the sodium salt of diethyl malonate which led to a 100% yield of diethyl (2(S)-methylbutyl)malonate (*15*), $[\alpha]_D$ + 13.7° (neat). The highest reported $[\alpha]_D$ for *15* is + 7.19° [8]. Our material seems to be the most optically pure sample to date; maximum purity is 92%. *15* was subjected to hydrolysis and decarboxylation to afford 78% of 4(S)-methylhexanoic acid (*17*), optical purity 94%. The desired ester *19* was prepared via reaction of the unpurified acid chloride of *17* with cholesterol in 94% yield.

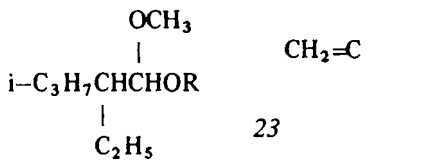
b. Cholesteryl 4(R)-Ethyl-5-methylhexanoate (20)

Attempted catalytic reduction of aldehyde *12*, $[\alpha]_D$ + 39.6° (neat), with palladium on carbon failed, even in the presence of ferric chloride.[9] 2(S)-Ethyl-3-methylbutanol (*2*) of maximum optical purity 89% was obtained in 95% yield by sodium borhydride reduction of *12*.

Distillation of *12* through a Teflon spinning band led to what is believed to be an azeotrope of acetals *21* and *22*, apparently formed by dehydration, due to a combination of longer exposure to high temperature and low pressure and possibly catalysis by the column. The alcohol *2* was converted to its tosylate *14*, $[\alpha]_D$ –6.60° (neat), in 91% yield. The maximum reported rotation for a sample prepared from alcohol $[\alpha]_D$ –9.47° (neat) is $[\alpha]_D$ –8.05° (neat)[6]; thus the optical purity of the present sample would be 82% but must not be lower than the starting alcohol since the asymmetric carbon is not involved in the reaction. Apparently the reported $[\alpha]_D$ did not take into account density; on this basis the reported $[\alpha]_D$ = 7.52[6] and our sample is 87% optically pure. Attempted distillation at 0.5mm led as expected from the literature[6] to decomposition, apparently formation of degradable olefin *23* via loss of *p*-toluenesulfonic acid.

The anion of diethyl malonate was reacted with tosylate *14* to yield 87% of diethyl (2(R)-ethyl-3-methylbutyl)malonate *16*. This compound has not been previously reported but its optical purity must be equal to that of the tosylate *14*,

i.e. 87%, since the chiral center is not involved in the reaction. Note that, while the absolute configuration of the asymmetric carbon is unchanged during conversion of *14* to *16*, the sequence rules for the substituent groups[10] now require a changeover in nomenclature from S in *14* to R in *16*.



23

21, $R = CH_3$ (S)

22, $R = CH_2CHC_3H_7$-i (S,S)

C_2H_5

Hydrolysis and decarboxylation of *16* led to a 72% yield of 4(R)-ethyl-5-methylhexanoic acid *18*; this also is the first isolation of this optically active compound. *18* was converted to its acid chloride, which without characterization was reacted with cholesterol to yield 79% of the desired cholesteryl 4(R)-ethyl-5-methylhexonoate (*20*).

Optical Purity of Cholesteryl Alkanoates

Isomerization of the cholesteryl moiety, the acid chloride and the resultant esters under reaction conditions can be ruled out on the basis of previous esterifications of cholesterol to yield known cholesteryl esters and the preparation of esters in the presence of pyridine and other amines from acid chlorides with an asymmetric carbon bearing a hydrogen adjacent to the carbonyl carbon.[7,11,12]

However, the reaction leads to a mixture of diastereomers from optically impure acids. Diastereomers have different physical properties. Thus, for example recrystallization and/or column chromatography can be expected to separate them. In fact this is a classical method of resolution of optically active materials, i.e., by formation and purification of diastereomeric derivatives from optically active reagents.[10] The use of cholesterol as such a reagent has not heretofore been reported, so its efficiency for resolution is not known.

In view of the fact that starting materials of high optical purity (except for 2-ethyl-3-methylbutyric acid) were employed and the careful purification (generally chromatographic) techniques used, the esters are of very high if not 100% diastereomeric purity. However, the esters prepared from racemic acids previously[1] may not contain equal amounts of the two diastereomers. This will, of course, effect the mesomorphic properties (see below).

Mesomorphic properties

Of the six new esters synthesized in this study one, *8*, possesses an enatiotropic mesophase, two others, *11* and *9*, possess monotropic smectic phases and the rest are non-mesomophic in the pure state. In mixtures with other cholesterol derivatives, however, all show mesomorphic properties. The pitches and heats of transitions of the pure materials[2] and phase diagrams of binary mixtures with cholesteryl nonanoate have been determined and will be reported in detail separately. It suffices here to say that correlations between the crystalline and mesomorphic phases are observed through pitches, ΔH_f and interfacial energies.[2] The position of the chiral (or branch) center plays a role in determination of these properties.

The effect of the configuration of the acid portion is exemplified by the change in specific rotation, $[\alpha]_D$, from $-33.7\pm0.3^\circ$ for the ester[1] from 2(R,S)-methylbutyric acid to $-28.6\pm0.3^\circ$ for that[7] from 2(S)-methylbutyric acid; the heat of fusion, ΔH_f, rises from 4.98 to 5.45 kcal/mole in comparing the esters from the racemic and active (S) acids. The reflection wavelength of the former is 585 nm while that of the latter is 617 nm[2]. The ester from the S-acid shows a decreased tendency toward liquid crystalline behavior as judged from phase diagrams. In comparing other cholesteryl esters of racemic and resolved chiral acids similar, but sometimes more dramatic, differences are observed. For example, the cholesteryl derivates from (−)- and (±)-2-ethylhexanoic acids have reflective wavelenghts of 420 and 115nm, respectively.

These results show the importance of the configuration of the acid portion of the molecule. This fact provides another avenue for the study of the cohesive forces of mesophases. At the same time this feature affords us another means of controlling mesomorphic properties.

Acknowledgement

The author acknowledges a generous gift of 2(S)-ethyl-3-methylbutyraldehyde (d-α-ethylisovaleraldehyde) from the Upjohn Company, Kalamazoo, Mich. and encouragement from Dr. W. H. H. Gunther. The technical assistance of Mr F. C. Baily is gratefully acknowledged.

EXPERIMENTAL

General: Infrared spectra were determined on a Perkin Elmer 137 instrument, nmr spectra on a JOELCO C-60H, optical rotations at 25° on a Rudolf manual polarimeter and a Cary 60 ORD/CD instrument. Melting points are corrected; boiling points are not. Elemental analyses were by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

2(S)-Methylbutanol (1) was purchased from Eastman, $[\alpha]_D - 5.73^\circ \pm 0.02^\circ$ (neat); highest reported[13] $[\alpha]_D - 5.90^\circ$ (neat); optical purity 97%.

2(S)-Methylbutyric Acid (3) was obtained by oxidation of the alcohol *1* with nitric acid by the method reported for oxidation of 3-chloropanol.[14] Distillation gave an 80% yield of liquid, bp 83-90°/15-20 mm (aspirator) and $[\alpha]_D$ + 16.55° ± 0.02° (neat); reported bp 63-68°/12 mm,[12] highest reported $[\alpha]_D$ + 19.76° (neat).[11a] Optical purity was therefore 84%.

2(S)-Methylbutyryl Chloride (6) was prepared by refluxing 20.0g of the (S)-acid *3* and 31ml of thionyl chloride for 18 hrs followed by distillation. The fraction boiling 112 - 120° (11.7g, 50%) had $[\alpha]_D$ + 11.55 ± 0.02° (neat); reported[11a] bp 114-115°, highest $[\alpha]_D$ = + 13.78° (neat). The optical purity was thus 84%.

General procedure for preparation of cholesteryl alkanoates from alkanoyl chlorides

To a stirred solution of 27.4g (0.0708 mole) of cholesterol (Eastman primary standard grade purified through the dibromide, $[\alpha]_D$ – 36.8° to 38.0° ± 0.2° ($CHCl_3$), reported[15] $[\alpha]_D$ = – 39° $CHCl_3$)) in 60 ml dry pyridine containing a few drops of dry dimethylformamide was added 0.0885 mole of the acid chloride dropwise. The reaction was maintained at 100° under a dry atmosphere for 2-5 hrs and poured into 700 ml 2% HCl-ice water, filtered and dried. The solid was extracted with *n*-hexane (cholesterol is only slightly soluble) and washed with 10% HCl, water, saturated sodium bicarbonate and water. After drying over sodium sulfate, the hexane layer was concentrated to afford the crude ester.

Cholesteryl 2(S)-Methylbutyrate (7) The crude ester obtained in 76% yield was recrystallized twice from *n*-hexane and chromatographed on Woelm neutral alumina by elution with *n*-hexane. Four recrystallizations yielded the desired ester as colorless crystals, mp 106.0 - 108.9°, $[\alpha]_D$ – 28.6 ± 0.3° (c 0.0468, $CHCl_3$). Analysis, calculated for $C_{32}H_{54}O_2$: C-81.64%, H-11.56%; found: C-81.64%, H-11.69%.

Cholesteryl 2(R)-Methylpentanoate(11) 2(R)-Methylpentanoic acid (*10*), $[\alpha]_D$ =–16.21° ± 0.02° (neat), was obtained from Norse Laboratories; the reported maximum rotation for (S)-enantiomer $[\alpha]_D$ + 18.5°.[16] Therefore, the optical purity was 88%. A solution of 2.44g (0.0210 mole) of the acid and 3.24g (0.0200 mole) of N,N'-carbonyldiimidazole in 35ml benzene under dry nitrogen was warmed gently until no further carbon dioxide evolved (∼ 40 min.). A solution of 7.74g (0.0200 mole) of primary standard cholesterol (see above) in 75ml benzene was added and the mixture was stirred at 70° for 18 hrs. The solvent was removed and the residue was dissolved in hot *n*-hexane and cooled; 4.07g of cholesterol, mp 147.0 - 149.0° precipitated, The hexane solution was charged to a silica gel column. Elution with hexane gave the desired ester *8*; elution with 9:1 benzene-methylene chloride gave 1.25g of cholesterol, mp 147.0 - 149.0°. The ester, 0.76g (25% yield based on unrecovered cholesterol),

was recrystallized from *n*-hexane as colorless crystals, mp 89.7 - 90.4°, monotropic smectic 67.6°, $[\alpha]_D = -37.8 \pm 0.5°$ (c 0.0290, $CHCl_3$). Analysis calculated for $C_{33}H_{56}O_2$:C-81.76%, H-11.64%; found: C-81.70%, H-11.66%.

Cholesteryl (−)-2-Ethylhexanoate (8)
(−)-2-Ethylhexanoic acid (*4*) (Norse Laboratories) had $[\alpha]_D - 7.60 \pm 0.04°$ (neat), maximum reported $[\alpha] -7.88°$,[17] optical purity 97%. It was converted by reaction with thionyl chloride to the acid chloride which was reacted without purification with cholesterol. The ester *8*, obtained in 94% crude yield, was eluted from neutral alumina with *n*-hexane as a colorless oil stable at room temperature for weeks, but when frozen (-15°) existed at room temperature as crystals which became completely smectic at 48.7° and isotropic at 57.0°; $[\alpha]_D -28.8 \pm 0.3°$ (c 0.0765, $CHCl_3$). Analysis calculated for $C_{35}H_{60}O_2$: C-81.97%, H-11.79%; found: C-82.05%, H-11.56%.

2(S)-Ethyl-3-methylbutyric Acid (5)
2(S)-Ethyl-3-methylbutyraldehyde (*12*) a gift from the Upjohn Co., Kalamazoo, Michigan, $[\alpha]_D + 24.6°$ (neat) (maximum reported $[\alpha]_D + 37°$ (neat)),[6] was oxidized with nitric acid by the method used for 2-chloropropanol.[14] The (S) acid *5*, density 0.9217 g/ml, bp 107.0-109.5/12.5mm, $[\alpha]_D - 0.16 \pm 0.005°$ (neat) was obtained in 67% yield; maximum reported $[\alpha]_D - 2.24°$,[7] reported density 0.915,[7] reported bp 105°/17mn,[5] 104-105°/15mm.[18] Using *12* of $[\alpha]_D + 39.6°$ (neat) *5* had $[\alpha]_D - 0.25 \pm 0.02°$ (neat).

Cholesteryl 2(S)-Ethyl-3-methylbutyrate (9) The acid chloride obtained in 87% yield from (S)-acid *5*, $[\alpha]_D - 0.16°$, was reacted with cholesterol to afford 92% crude yield of the desired ester *9*, which after purification by column chromatography on alumina follwed by recrystallization from ethanol-ethyl acetate yielded colorless crystals, mp 111.5 - 113°, monotropic smectic 92°, $[\alpha]_D = -27.4 \pm 0.3°$ (c 0.1572, $CHCl_3$). Analysis calculated for $C_{34}H_{58}O_2$: C-81.86%; H-11.72%; found: C-81.89%, H-11,79%.

2(S)-Methylbutyl Tosylate (13) To a stirred solution of 43.9g (0.230 mole) of *p*-toluenesulfonyl chloride in 75ml dry pyridine at 0° over 1.5 hrs was added a solution of 10ml dry pyridine and 19.86g (0.225 mole) of 2(S)-methylbutanol (*1*), $[\alpha]_D - 5.73°$ (neat), optical purity 97% (Eastman). After storage at −20° for 18 hrs and 0° for 5.5 hrs and while kept at 0°, 1ml water was added; then 1 min later another ml water was added and this was repeated. After 5 min 5ml water was added and this was repeated. After 5 min it was poured into 500ml water. The ether extract was washed successively with water, 10% hydrochloric acid and water. After drying over sodium sulfate, the solution was evaporated, leaving 49.75g (91%) of nearly colorless oil, density 1.10g/ml, $[\alpha]_D + 3.70 \pm 0.03°$ (neat), reported[19] $[\alpha]_D + 3.75°$ (neat) from alcohol of $[\alpha]_D -5.50°$; calculated

maximum $[\alpha]_D$ +4.03° for *12*; optical purity 92%. Nmr (50% CCl_4). 0.3–2.08δ (m,10H), 2.46δ (s,3H), 3.86δ (d,J=6; 1H), 7.63δ (q,j=9,25; 4H).

Diethyl [2(S)-methylbutyl] malonate (15)

To a solution prepared from 2.30g (0.100g at) of sodium and 50ml absolute ethanol was added 19.2g (0.120 mole) of diethyl malonate; a white precipitate formed. Then 24.3g (0.100 mole) of 2(S)-methylbutyl tosylate (*13*) was added over 0.5 hrs, during which time the white precipate disappeared, but a dark precipate later appeared. After 19 hrs reflux, ethanol was distilled and the residue was shaken with 80 ml water. Extraction with ether afforded 26.0g of an oil; distillation gave 23g (100%) of colorless liquid, density 0.9675 g/ml, bp 90/0.4mm, $[\alpha]_D$ + 13.7 ± 0.1° (neat); reported density 0.9666 g/ml[20], bp 180-210°/15mm,[9] 150 - 152°/45mm,[21] highest reported $[\alpha]_D$ +7.19°.[20] Nmr (50% CCl_4): 0.7 - 2.3δ (m,17H), 3.34δ (t,J=7,1H), 4.20δ (q,J=7,4H). Analysis calculated for $C_{12}H_{22}O_4$: C-62.58%, H-9.63%; found: C-62.96%, H-9.53%.

4(S)-Methylhexanoic Acid (17)

To a stirred solution of 15.0g (0.233 mole) of 87% potassium hydroxide and 15ml of water was added 15.0g (0.0651 mole) of diester *15* over 0.5 hrs. After 2 hrs refluxing 15ml water was added and 15ml of distillate was collected. The residual solution was cooled (∼ 10°) and a cold solution of 24.0g (0.237 mole) of conc. sulfuric acid and 34g water was added dropwise with vigorous stirring. After 3 hrs refluxing the crude product, 7.42g (87%), was collected in a Dean Stark trap by separation of the aqueous azeotrope. Distillation gave a colorless oil, bp 88 - 90°/ 1.0mm, $[\alpha]_D$ + 10.9 ± 0.1° (c 0.2295, $CHCl_3$): reported bp 115 - 116°/18mm,[22] calculated maximum $[\alpha]_D$ + 11.18 ($CHCl_3$)[22,23] for (S)-enantiomer. Optical purity 98%.

Cholesteryl 4(S)-Methylhexanoate (19)

The acid chloride prepared from 4(S)-methylhexanoic acid (*17*) was used without purification in the reaction with cholesterol to afford 20.9g of crude material and 10.2g of cholesterol; yield of *19* based on unrecovered cholesterol 94%. After one recrystallization from *n*-hexane and four recrystallization from ethanol-ethyl acetate, *19* was obtained as colorless needles, mp 111.9 - 113.0°, $[\alpha]_D$ – 26.8 ± 0.2° (c 0.0588,$CHCl_3$). Analysis calculated for $C_{34}H_{58}O_2$: C-81.86%, H-11.72%; found: C-82.14%, H-11.91%.

2(S)-Ethyl-3-methylbutanol (2)

To a stirred solution of 50g (0.438 mole) of 2(S)-ethyl-3-methylbutyraldehyde (*12*) (a gift from the Upjohn Co., Kalamazoo, Michigan, $[\alpha]_D$ + 39.6 (neat)) in 300ml absolute ethanol maintained at room temperature in a water bath was added 10.00g (0.264 mole) of sodium borohydride over 0.75 hr. After stirring for 2 hrs, the solution was poured into 1ℓ of 0.5% sodium hydroxide. The ether extract was dried (sodium sulfate) and distilled through a Bantamware Vigreaux

column to yield 13.4g of recovered aldehyde *12*, bp 30 - 43/60mm (reported bp 67 - 69/74mm[6]) and 35.3g (95% based on unrecovered *12*) of desired alcohol *2*, bp 50°/3.2mm, $[\alpha]_D$ −8.38° ± 0.02 (neat). Ir (neat): 3300 $cm.^{-1}$ (OH), no C=O. Reported bp 91.5°/50mm,[6] 65 - 66°/14mm[24], maximum $[\alpha]_D$ −9.47° (neat).[6] Optical purity 89%.

In a duplicate experiment using methanol as solvent the product was carefully distilled (reflux ratio 10 - 15:1, total time 4 hrs) through a Teflon spinning band column. A 70% yield of colorless liquid, density 0.8391g/ml, bp 52°/13.8mm, $[\alpha]_D$ + 6.57 ± 0.03 (neat), i r (neat) no OH, was obtained. It gave only a single peak when vapor phase chromatographed on an SE-30 silicone column. Nmr (neat): 0.6 - 2.28 (m), 2.9 - 3.7 (m), 4.03 (distored d). Analysis calcd for $C_9H_{20}O_2$ (*21*): C-67.45% H-12.58%; calcd for $C_{15}H_{32}O_2$ (*22*): C-73.71%, H-13.20% Calcd for 1:1 azeotrope of *21* and *22*: C-70.58% H-12.89%. Found: C-70.92%, H-13.08%.

2(S)-Ethyl-3-methylbutyl Tosylate (14)

The (S)-alcohol (*2*) was treated with *p*-toluenesulfonyl chloride in the same manner as for the preparation of *13* (see above). A pale yellow oil ir,(neat) no OH, density 1.069g/ml, nmr (neat) 0.75δ(d,J=6) and 0.4 - 1.9δ (total 13H); 2.24δ (s,3H); 3.75δ (broad s,2H); 7.12δ (AB q, J=8, 15;4H); $[\alpha]_D$−6.60 ± 0.02° (neat), was obtained in 91% yield. Attempted distillation at 0.5 - 1.0mm led to decomposition. Reported[6] for *14* density 1.073g/ml, bp 116°/0.007mm, decomposition at 5mm under nitrogen, maximum $[\alpha]_D$ − 8.05°. The optical purity of the present sample is thus at least 82%.

Diethyl [2(R)-Ethyl-3-methylbutyl] malonate (16)

The (S)-tosylate *14* was reacted with diethyl malonate in the manner used to prepare *15* (see above). There resulted an 87% crude yield, which upon distillation afforded *16* as a colorless oil, density 0.9605g/ml bp 91 - 94°/0.05mm, $[\alpha]_D$ + 5.41 ± 0.01° (neat); ir (neat) C=O, 1725cm^{-1}; nmr (neat): 0.80δ (d,J=7). 1.17δ (t,J=6), 0.6 - 2.2δ (m, total 21H), 3,13δ(t,J=7,1H), 3.09δ (q,J=6, 4H). Analysis calculated for $C_{14}H_{26}O_4$: C-65.08%, H-10.14%, found: C-65.51%, 10.10%.

4(R)-Ethyl-5-methylhexanoic Acid (18)

The hydrolysis and decarboxylation of *16* carried out by the method used to prepare *17* afforded a 72% crude yield of *18* as a colorless liquid which upon distillation had bp 130°/9mm, $[\alpha]_D$ + 4.0 ± 0.1° (c 0.2034, $CHCl_3$), ir (neat) C=O, 1700 cm^{-1}; OH, 2500 - 3400 cm^{-1}. Reported[25] for d,l-compound bp 129°/10mm. Analysis calculated for $C_9H_{18}O_2$: C-68.31%, H-11.47%; found: C-68.37%, H-11.31%.

Cholesteryl 4(R)-Ethyl-5-methylhexanoate (20)

The acid *18* was converted to its acid chloride, which was reacted with choles-

terol to give a 79% crude yield of the desired ester *20*, which after four recrystallizations from *n*-hexane had mp 79.6 - 80.3°, $[\alpha]_D$ – 27.7 ± 0.3° (c 0.0604, $CHCl_3$). Analysis calculated for $C_{36}H_{62}O_2$: C-82.06%, H-11.86%; found: C-82.19%, H-11.75%.

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