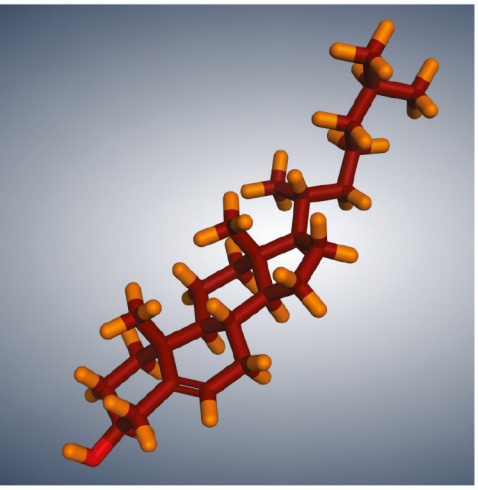
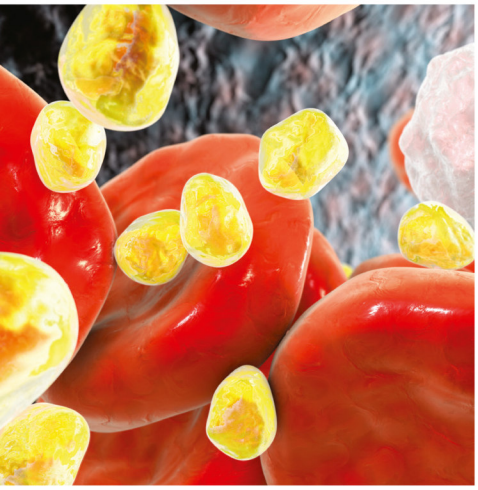
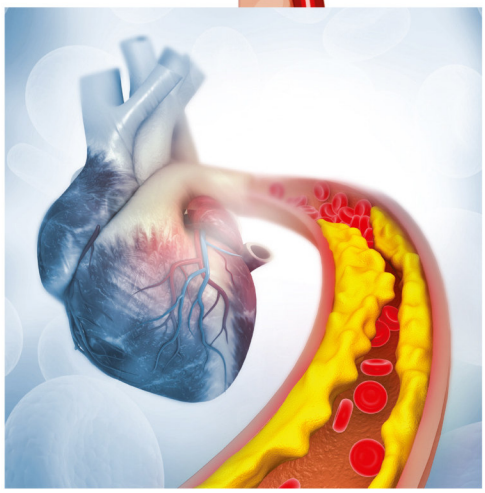
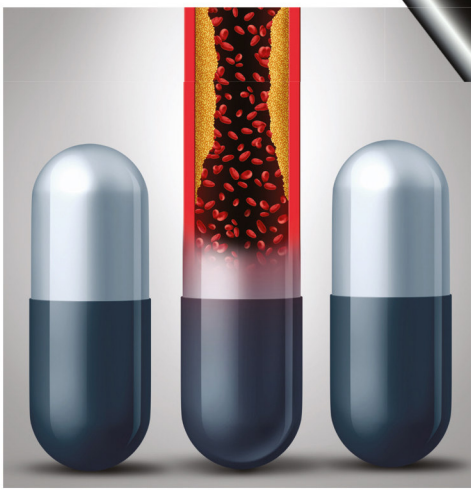
CHOLESTEROL

From Chemistry and Biophysics to the Clinic









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Contents

CHAPTER

1

Cholesterol chemistry and laboratory synthesis

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Abbreviations

Ac	acetyl
ABSA	acetamidobenzenesulfonyl azide
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
COSY	correlation spectroscopy
DEPT	distortionless enhancement by polarization transfer
DMSO	dimethylsulfoxide
DMF	*N,N*-dimethylformamide
DMAP	4-dimethylaminopyridine
Et	ethyl
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
HMPA	hexamethylphosphoramide
IUPAC	International Union of Pure and Applied Chemistry
LDA	lithium diisopropylamide
Me	methyl
MMC	magnesium methyl carbonate
Ms	methanesulfonyl (often shortened to mesyl)
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
p	*para*
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
Ph	phenyl
Py	pyridine
t	*tert*
TBSCl	*tert*-butyldimethylsilyl chloride

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THF tetrahydrofuran
TMS tetramethylsilane
Ts toluenesulfonyl (often shortened to tosyl)

Introduction

The name cholesterol derives from the Ancient Greek chole- (bile) and stereos (solid), followed by the chemical suffix of the functional group alcohol (-ol). Known also by the name cholesterin, cholesteryl alcohol, cholest-5-en-3β-ol, among others, this interesting natural molecule is a type of modified sterol belonging to the heterogeneous group of organic compounds known as lipids. With a bulky, rigid, and asymmetric structure, the cholesterol skeleton possesses four fused rings aligned from A to D, corresponding to three six-membered and one five-membered. As a whole, the four rings comprise the 1,2-cyclopentane perhydrophenanthrene system (Fig. 1A) (Nes, 2011). The rings are *trans*-connected and create an almost planar structure (Fig. 1C). The C-18 and C-19 methyl substituents are linked at C-10 and C-13, in relative *cis* configuration. Due to this structural prolife, the flat face of cholesterol is called the smooth α-face, and all substituents located on this face (in *trans*-conformation relative to C-19) are called α, while the substituents located on the rough β-face (presence of the two methyl substituents) are called β (in *cis*-conformation relative to C-19). The cholesterol moiety bears an additional polar 3β-hydroxy group and a C5=C6 double bond in B-ring (Róg, Pasenkiewicz-Gierula, Vattulainen, & Karttunen, 2009).

From a chemical point of view, the cholesterol molecule comprises four essential domains (Fig. 1B). The 3-hydroxy group of domain I constitutes not only an important active site for hydrogen bond interactions with several biological molecules but also a versatile functional group for derivatization. In domain II, the absence of methyl groups at C-4 and C-14 influences the planarity of the molecule, and the C5=C6 double bond is an attractive carbon center to several addition reactions. The natural (*R*)-configuration at C-20 observed in domain III determines the "right-handed" conformation of the side chain, while in domain IV, the conformation and length of the side chain are of high importance to intermolecular contacts (Cerqueira et al., 2016). The recommended name by the International Union of Pure and Applied Chemistry (IUPAC) for natural cholesterol is (3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-[(*R*)-6-methylheptan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol. In its pure state, it is a white and crystalline powder

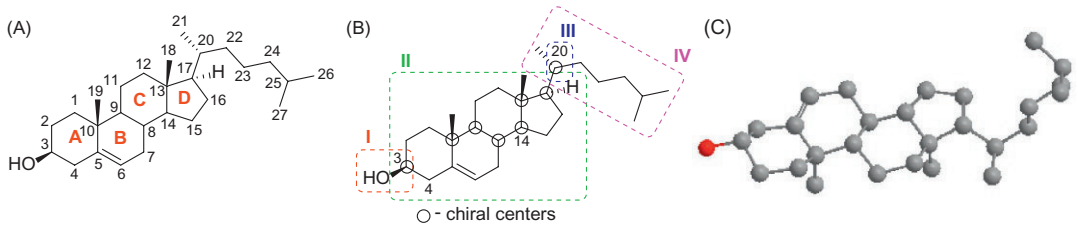


FIG. 1 (A) Cholesterol tetracyclic nucleus with numbering of carbon atoms and rings labelling; (B) cholesterol four structural domains; (C) cholesterol crystal structure obtained from https://www.ccdc.cam.ac.uk/structures/search?id=doi:10.5517/cc66d1t&sid=DataCite.

that is odorless and tasteless, with a melting point of 148–149°C ("[cholesterol],", 2016; Barton, 1976).

Historically, the first identification of cholesterol is attributed to the French chemist François Poulletier de la Salle, who collected it as a crystalline component from human gallstones, in 1769. In 1815, the chemist Michel Eugène Chevreul isolated a crystalline compound of bile stones and named it cholesterine, which was renamed to cholesterol after knowing that the substance was a secondary alcohol. The correct chemical formula of $C_{27}H_{45}O$ was only proposed in 1888 by F. Reinitze, and the first steric representations of the molecule were published by Heinrich Wieland and Adolf Windaus, their efforts leading the two scientists to win the Nobel Prize in Chemistry in 1927 and 1928, respectively (Nes, 2011). The steroid nucleus proposed by Wieland in his Nobel lecture presented some limitations. In 1932, however, his research group corrected it to the skeleton known nowadays (Vaupel, 2007). The research in steroids by Konrad Bloch and Feodor Lynen granted them the Nobel Prize in Physiology or Medicine in 1964, for their discoveries concerning the mechanism and regulation of cholesterol and fatty acid metabolism. Later in 1985, Michael S. Brown and Joseph L. Goldstein were also awarded with the Nobel Prize in Physiology or Medicine for their findings relating to the regulation mechanisms of cholesterol metabolism ("Feodor Lynen—Biographical, 2021," "Joseph L. Goldstein—Biographical, 2021," "Konrad Bloch—Biographical, 2021," "Michael S. Brown—Biographical, 2021").

Cholesterol is synthesized by all animal cells and is an essential structural component of animal cell membranes, where it contributes to the order of phospholipid chains and overall membrane (dis)order, integrity and heterogeneity. It is also used as a precursor for the biosynthesis of steroid hormones, bile acids and vitamin D (Cerqueira et al., 2016; Ercole, Whittaker, Quinn, & Davis, 2015; Róg et al., 2009). Although cholesterol has eight stereocenters (Fig. 1B) that could rise to 256 stereoisomers, only the natural enantiomer with the (3*R*,20*R*)-configurations, is used as a membrane constituent (Xu et al., 2005).

As an amphiphilic molecule, having a hydrophobic hydrocarbon body and a hydrophilic hydroxy headgroup, cholesterol occupies a position at polar-nonpolar interfaces, as observed in cell membranes. The crystal structure of one form of cholesterol monohydrate published by Craven (1976) is based on a local pseudosymmetry arrangement of eight independent molecules in the triclinic cells, similar to the structure reported by Shieh, Hoard, and Nordman (1977) for anhydrous cholesterol crystals at room temperature (25°C). This molecular packing in the crystal structures is in some way in line to the tendency toward double layer structures with an end-for-end arrangement of nearly parallel molecules (Bernal, Crowfoot, & Fankuchen, 1940). On the other hand, cholesterol crystals at 37°C have a remarkably large unit cell containing 16 independent cholesterol molecules, and the transition preserves a closely obeyed pseudosymmetry present in the structure (Hsu & Nordman, 1983). Garti et al. studied phase transitions in cholesterol crystallized from various solvents, characterizing the effect of several solvents (e.g., carbon tetrachloride, acetonitrile, methanol, ethanol) and conditions of crystallization (Garti, Karpuj, & Sarig, 1980). Using differential thermal analysis, infrared spectroscopy and polarization microscopy, Barton had found that the phase transitions of cholesterol and other sterols subjected to heating and cooling in a range of −20°C to +150°C were dependent on the state of hydration and on the structure of the aliphatic side chain (Barton, 1976).

Below, we will review major milestones in characterization of cholesterol structure, cholesterol laboratory synthesis, and synthetic routes for production of enantiomeric cholesterol.

Cholesterol structural characterization

In 1973, Barry et al. used 1D ^{1}H nuclear magnetic resonance (NMR) experiments to assign unequivocally the chemical shifts of the A and B ring protons of cholesterol using deuterated chloroform ($CDCl_3$) as solvent (Table 1) (Barry et al., 1973). Years later, Sawan et al. performed ^{1}H NMR spectrum of cholesterol in pyridine-d_5 to accomplish the same goal (Sawan et al., 1979). Since then, several 1D and 2D NMR techniques have been used to complete ring proton assignment of various steroids by comparison with cholesterol data (Drew, Brisson, Morand, & Szabo, 1987; Zipser et al., 1998).

The latest NMR characterization of cholesterol dates back to 1998, and therefore, with more than 20 years passed by, we were encouraged to get our own 1D (^{1}H, ^{13}C, DEPT 90, and DEPT 135) and 2D NMR (HSQC, HMBC, COSY, and NOESY) data for the commercial cholesterol molecule, presenting the ^{1}H and ^{13}C NMR spectra as standard reference (Figs. 2 and 3). Our own interpretation of NMR data, based on the obtained 1D and 2D NMR, is listed in Tables 1 and 2, with unequivocal assignments of almost all carbons. Carbons C-7, C-11, C-13, C-15, C-16, and C-23 were assigned by analogy with previous reported data (*) (Table 2).

Although the assignment of ^{13}C NMR chemical shifts in a molecule as large as cholesterol is a challenging task, some research groups dedicated their efforts to achieve this goal (ApSimon, Beierbeck, & Saunders, 1973; Mantsch & Smith, 1973; Reich, Jautelat, Messe,

TABLE 1 ^{1}H chemical shifts of cholesterol in several deuterated solvents.[a]

H	$CDCl_3$[b,c]	Pyridine-d_5[b,c]	$CDCl_3$[d]	$CDCl_3$[e]
1α, 1β	–	1.83	–	–
2α	1.90	2.07	1.50	–
2β	1.58	1.80		–
3α	3.47	3.82	3.39	3.47–3.57 (m)
4α, 4β	2.3	2.60	2.13	2.17–2.33 (m)
6	5.30	5.41	5.34	5.34–5.36 (m)
7α, 7β	2.05	2.03	1.95	–
8	–	–	1.5	–
18-CH_3	0.68[c]	–	0.72	0.67 (s)
19-CH_3	1.02[c]	–	1.02	1.00 (s)
21-CH_3	–	–	0.94	0.91 (d, J = 6.5 Hz)
26-CH_3	–	–	0.87	0.862 (d, J = 6.6 Hz) or 0.858 (d, J = 6.6 Hz)
27-CH_3	–	–		

[a] *Chemical shifts in ppm relative to the internal standard, tetramethylsilane (TMS).*
[b] *Barry, Dobson, Sweigart, Ford, and Williams (1973).*
[c] *Sawan, James, Gruenke, and Craig (1979).*
[d] *Zipser, Bradford, and Hollingsworth (1998).*
[e] *Our own data ^{1}H NMR (300 MHz).*

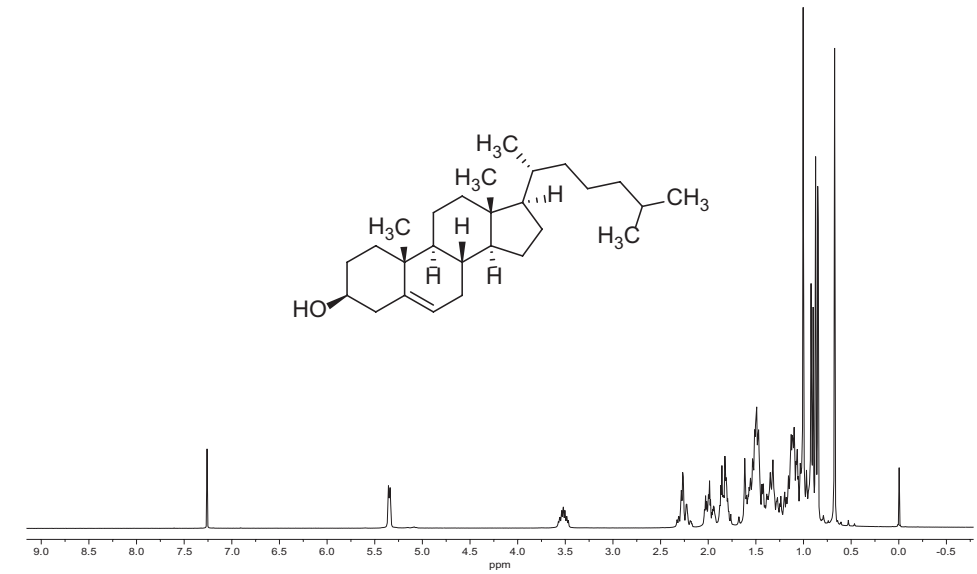


FIG. 2 ^{1}H NMR spectrum of cholesterol ($CDCl_3$, 300 MHz).

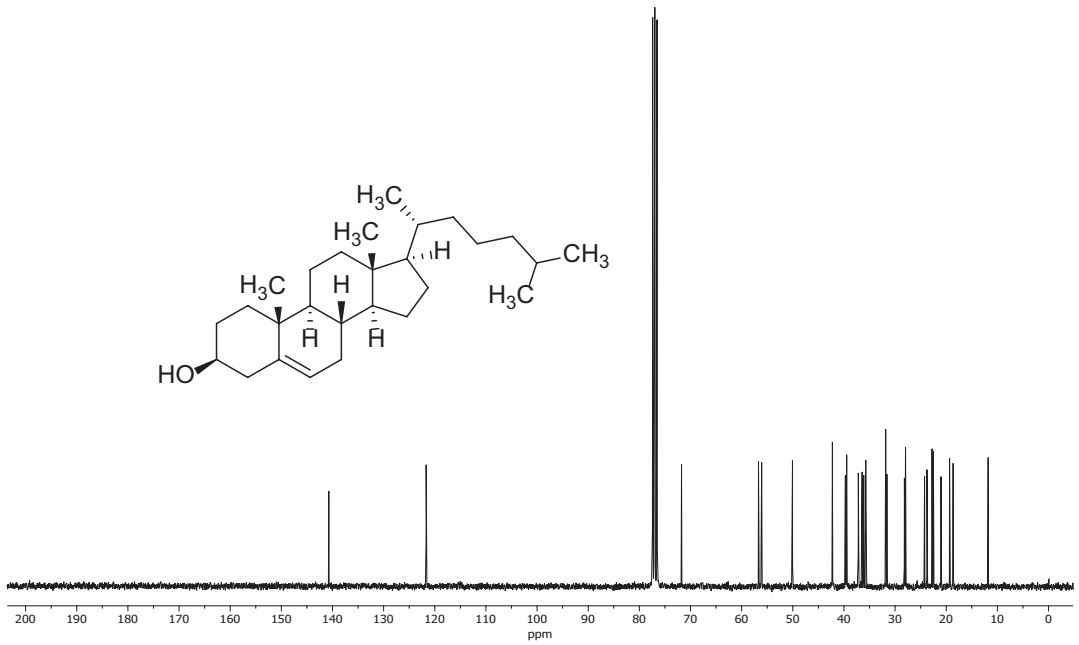


FIG. 3 ^{13}C NMR spectrum of cholesterol ($CDCl_3$, 75 MHz).

TABLE 2 ^{13}C chemical shifts of cholesterol in several deuterated solvents.[a]

C	$CDCl_3$[b,c]	$CDCl_3$[c]	$CDCl_3$[d]	$CDCl_3$[e] (DEPT 135, DEPT 90)	CCl_4[b,c]	Benzene-d_6[b,c]	Pyridine-d_5[b,c]	1,4-Dioxane-d_4[b,c]
1	38.6	37.3	37.2	**37.2** (CH_2)	38.6	38.0	38.4	38.2
2	32.8	31.6	31.6	**31.7** (CH_2)	32.6	32.4	32.7	32.7
3	72.8	71.6	71.8	**71.8** (CH)	72.1	71.9	71.6	71.8
4	43.5	42.2	42.3	**42.3** (CH_2)	43.5	43.2	43.8	43.5
5	142.1	140.6	140.6	**140.7**	142.1	141.6	142.4	142.4
6	122.7	121.4	121.4	**121.7** (CH)	122.3	121.8	121.5	121.7
7	33.1	31.9	31.9	**31.9**[f] (CH_2)	33.1	32.6	32.7	32.7
8	33.1	31.9	31.9	**31.9** (CH)	33.1	32.6	33.0	32.7
9	51.4	50.2	50.2	**50.1** (CH)	51.4	50.9	51.0	51.3
10	37.6	36.5	36.5	**36.5**	37.6	37.0	37.4	37.4
11	22.3	21.1	21.1	**21.1**[f] (CH_2)	22.3	21.7	21.9	21.9
12	41.0	39.8	39.8	**39.8** (CH_2)	41.0	40.4	40.8	40.7
13	43.4	42.3	42.3	**42.3**[f]	43.3	43.0	43.0	43.2
14	58.0	56.8	56.8	**56.8** (CH)	58.0	57.2	57.4	57.8
15	25.5	24.3	24.3	**24.3**[f] (CH_2)	25.4	24.8	25.0	25.0
16	29.4	28.3	28.3	**28.2**[f] (CH_2)	29.4	24.8	29.0	29.0
17	57.4	56.2	56.1	**56.1** (CH)	57.4	56.9	57.0	57.2
18	13.1	11.9	11.9	**11.9** (CH_3)	13.1	12.3	12.5	12.4
19	20.6	19.4	19.4	**19.4** (CH_3)	20.6	19.8	20.1	19.9
20	37.0	36.8	35.8	**35.8** (CH)	37.0	36.5	36.8	36.8
21	20.0	18.8	18.7	**18.7** (CH_3)	20.0	19.3	19.5	19.4
22	37.4	36.2	36.2	**36.2** (CH_2)	37.4	37.0	37.0	37.2
23	25.1	23.9	23.8	**23.8**[f] (CH_2)	25.1	24.6	24.7	24.7
24	40.7	39.5	39.5	**39.5** (CH_2)	40.7	40.2	40.2	40.3
25	29.2	28.0	28.0	**28.0** (CH)	29.1	28.6	28.7	29.0
26	23.9	22.6	22.6	**22.6 or 22.8** (CH_3)	23.9	23.1	23.1	23.1
27	24.1	22.8	22.8	**22.8 or 22.6** (CH_3)	24.1	23.3	23.5	23.3

[a] *Chemical shifts in ppm relative to the internal standard, tetramethylsilane (TMS).*
[b] *Mantsch and Smith (1973).*
[c] *Blunt and Stothers (1977).*
[d] *Smith (1978).*
[e] *Our own data ^{13}C NMR (75 MHz).*
[f] *Assigned by analogy to previous publications.*

Weigert, & Roberts, 1969; Smith, 1978; Smith, Deavenport, Swanzy, & Pate, 1973). Blunt and Stothers covered the ^{13}C NMR assignments of cholesterol in several deuterated solvents (Blunt & Stothers, 1977) and the chemical shifts are presented in Table 2. The 27 carbon atoms of cholesterol are characterized to possess mainly nonpolar atoms (24 out of the 27), a polar atom corresponding to C-3 and the unsaturated carbons corresponding to C5=C6 double bond, in a total range of 130 ppm. From analyzing the data shown in Table 2 we can state that the chemical shifts vary slightly with the solvent used in the acquisition and even using the same solvent, the data can be quite different according to the research group.

Based on a more detailed analyzes on the data provided by Mantsc et al., the most solvent-sensitive positions are the 3-OH and C-6, both of which are shifted by about 1 ppm in $CDCI_3$ and about 0.5 ppm in CCl_4, for higher frequency values, when compared to benzene-d_6, pyridine-d_5, and 1,4-dioxane-d_4 (Table 2).

Cholesterol laboratory synthesis

Cholesterol total synthesis—Historical perspective

The total synthesis of cholesterol was one of the most remarkable achievements of 20th century Chemistry. An upmost historical curiosity is that the laboratory synthesis of cholesterol was some sort of a mental competition between Robinson in Oxford and Woodward at Harvard. The interesting outcome was that both research groups, simultaneously and independently, achieved the cholesterol total synthesis in 1951 (Cardwell, Cornforth, Duff, Holtermann, & Robinson, 1951; Woodward, Sondheimer, & Taub, 1951a). According to chemistry historian Mulheirn (2000), the preliminary notice of Robinson's total synthesis was published in *Chemistry and Industry* in 1951 (Cardwell et al., 1951), only a couple of weeks after Woodward's announcement of his own synthesis at the Chemical Society Centenary Lecture (subsequent preliminary notice of the synthesis was published in the *Journal of the American Chemical Society*) (Woodward, Sondheimer, Taub, Heusler, & McLamore, 1952). Despite Robinson substantial contributions to synthetic organic chemistry (Robinson annulation is perhaps the most well-known), Woodward was able to complete his project in a remarkably short period (around 2 years), which was testimony both to his brilliance and to the pharmaceutical industry financial support.

The Woodward synthesis itself can be described as a C → CD → BCD → ABCD route (Fig. 4), rather than the BC → ABC → ABCD route (Fig. 5) used by Robinson. Woodward was able to gather support of industry to not only fund human resources but also supply key intermediates; Robinson's synthesis in turn had to resort to using relays. Many of chemical intermediates of Robinson's synthesis were already known and available from natural sources, and therefore, Robinson's challenge was to proof that these intermediates could be linked to each other via chemical synthesis, in order to develop a formal cholesterol total synthesis. From a practical point of view, and despite that all steroid intermediates of Robinson's relay approach were already known, his linear cholesterol synthesis requires 68 reaction steps, (Cardwell et al., 1951; Cardwell, Cornforth, Duff, Holtermann, & Robinson, 1953; Cornforth & Robinson, 1946, 1949) in opposition to Woodward's with "only" 35 steps (Woodward et al., 1952; Woodward, Sondheimer, and Taub, 1951a, 1951b; Woodward, Sondheimer, Taub, Heusler, & McLamore, 1951).

Woodward's cholesterol total synthesis

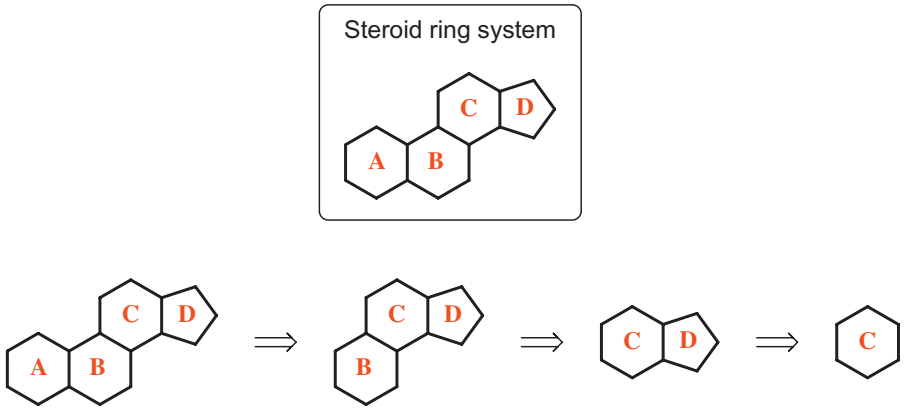


FIG. 4 Retrosynthetic analysis of Woodward's cholesterol total synthesis.

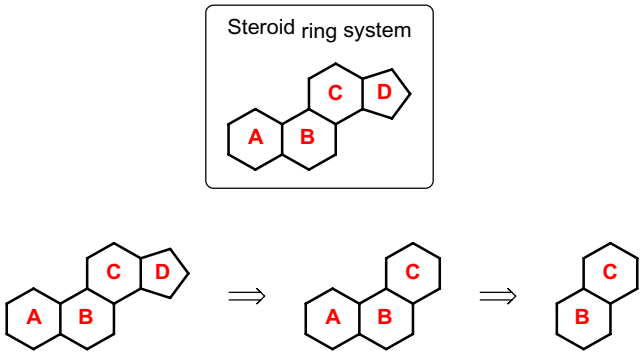
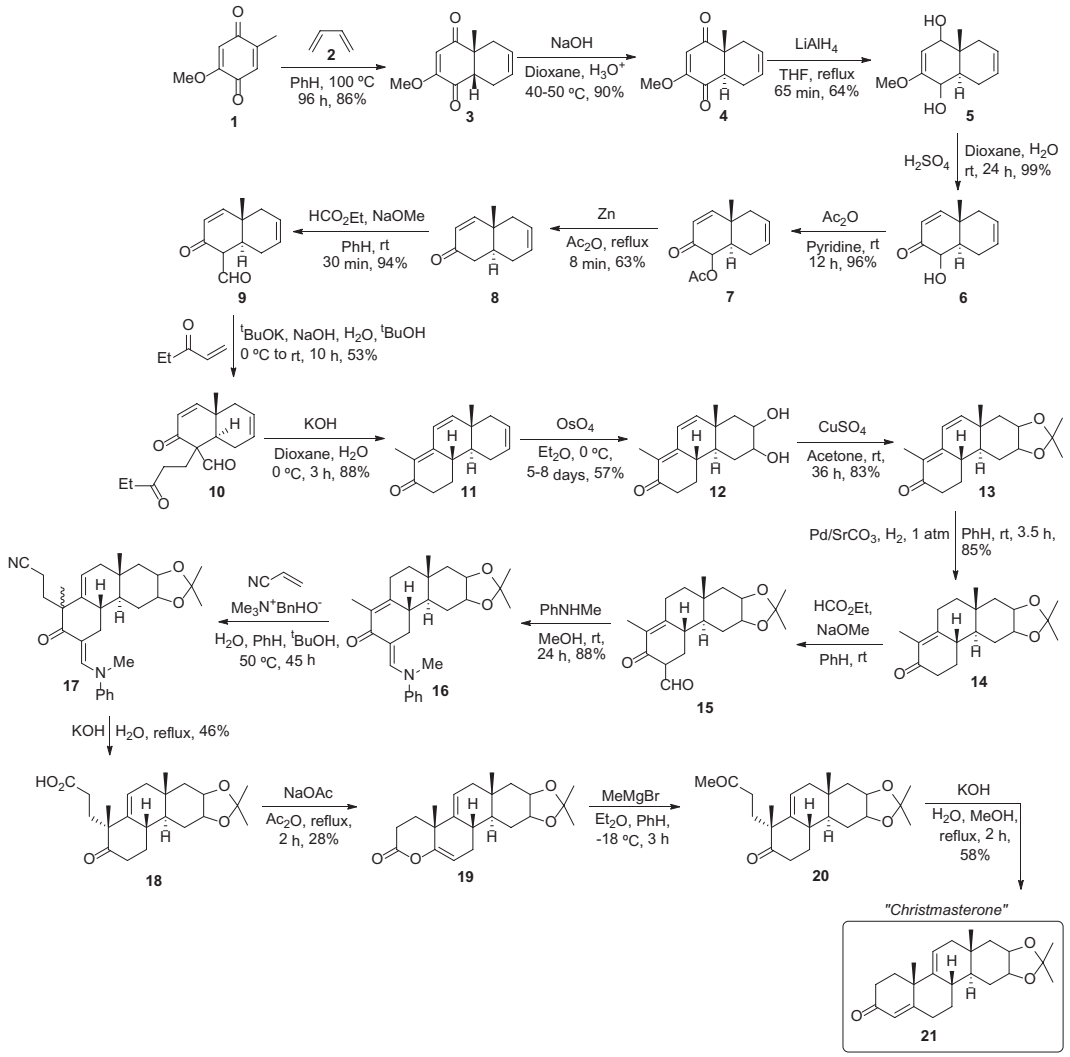


FIG. 5 Retrosynthetic analysis of Robinson's cholesterol total synthesis.

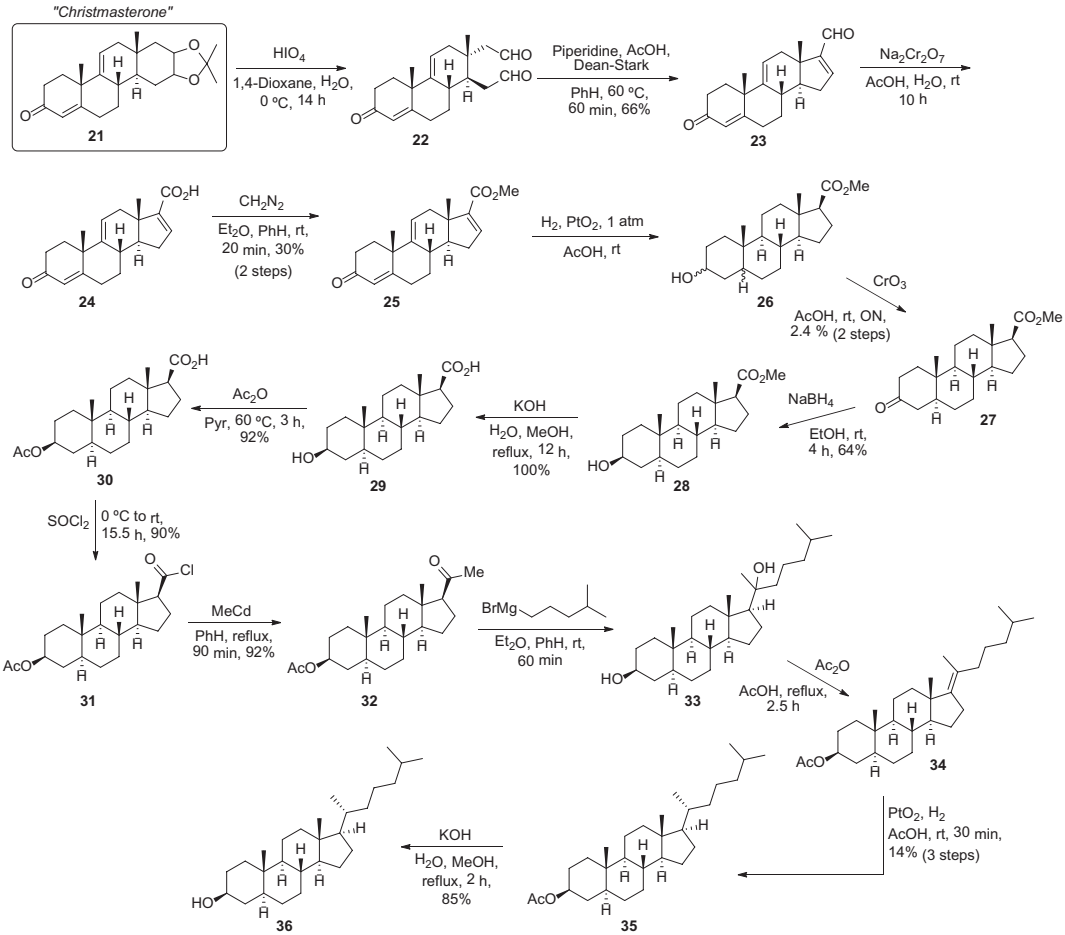
Woodward's cholesterol total synthesis

The retrosynthetic analysis of Woodward's approach could sometimes be misunderstood, since the D ring remains D-homo until the last step of ring construction (Scheme 2) and the required 5-membered ring was obtained only after a ring contraction; it could also be termed as C → BC → ABC → ABCD. Whatever the case, Woodward's starting point was 5-methoxy-2-methyl-1,4-quinone **1**, used to form ring C in the final structure. The Diels-Alder reaction of hydroquinone **1** with butadiene **2** gave the *cis*-bicycle **3**, which was converted to the *trans*-isomer **4** through sodium enolate followed by acidification (Scheme 1). Reduction with lithium aluminum hydride ($LiAlH_4$) followed by dehydration gave ketol **6**, which upon deoxygenation of its acetate with zinc gave enone **8** (Scheme 1). Claisen condensation of enone **9** followed by Michael addition of ethyl vinyl ketone originates dione **10**, which undergoes cyclization with KOH to produce tricycle **11** (Scheme 1). The following steps of Woodward's synthesis involve the diol **12** formation with osmium tetroxide (OsO_4), subsequent diol protection with acetone and copper(II) sulfate ($CuSO_4$), hydrogenation and Claisen condensation to give **15**



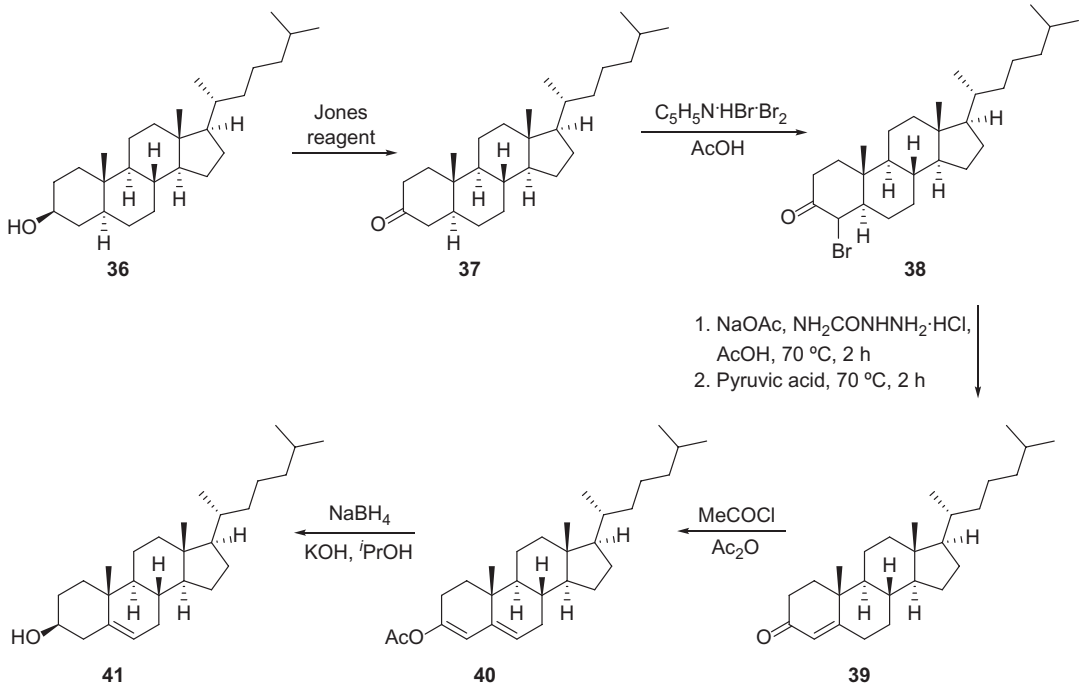
SCHEME 1 Woodward's cholesterol total synthesis: preparation of Christmasterone **21**.

(Scheme 1). The enamine protection followed by Michael addition of cyanoethylene and subsequent nitrile hydrolysis gave the carboxylic acid **18** (Scheme 1). Lactonization of carboxylic acid **19**, followed by Grignard reaction with methylmagnesium bromide (MeMgBr), and subsequent aldol condensation gave the tetracyclic ketone **21** (Scheme 1), which completes the four-ring structure required for cholesterol synthesis. Tetracyclic ketone **21** (nicknamed "*Christmasterone*") was obtained on Christmas Day in 1950 by Sondheimer, and it was a topmost example of Woodward's high-pressure style of leadership combined with the sense of success being just around the corner. At this point, the final hurdle was the contraction of ring D from a six-membered to a five-membered ring.



SCHEME 2 Woodward's cholesterol total synthesis: preparation of cholestanol **36**.

Treatment of Christmasterone **21** with periodic acid (HIO_4) in 1,4-dioxane followed by heating the product **22** in the presence of a catalytic amount of piperidine acetate gave DL-$\Delta^{9(11),16}$-bisdehydro-20-norprogesterone **23** (Scheme 2), from which a route to cholesterol was known. The sodium dichromate ($Na_2Cr_2O_7$) oxidation of the aldehyde function of **23** gave carboxylic acid **24**, which upon diazomethane esterification, hydrogenation and oxidation gave ketone **27** (Scheme 2). The sodium borohydride ($NaBH_4$) ketone reduction, ester hydrolysis, and secondary alcohol acetylation with acetic anhydride gave carboxylic acid **30** (Scheme 2). The final stages of Woodward's synthesis were focused on the preparation of C-17 aliphatic side chain. The thionyl chloride ($SOCl_2$) treatment of carboxylic acid **30** gave the corresponding acyl chloride **31**, which upon methyl cadmium (MeCd) and Grignard reaction with isohexylmagnesium bromide afforded diol **33** (Scheme 2). Three reaction steps later, involving dehydration, hydrogenation and ester hydrolysis, cholestanol **36** was obtained (Scheme 2). The conversion of cholestanol **36** into cholesterol **41** was already demonstrated, involving five additional



SCHEME 3 Cholestanol **36** conversion into cholesterol **41** following Dauben and Eastham method.

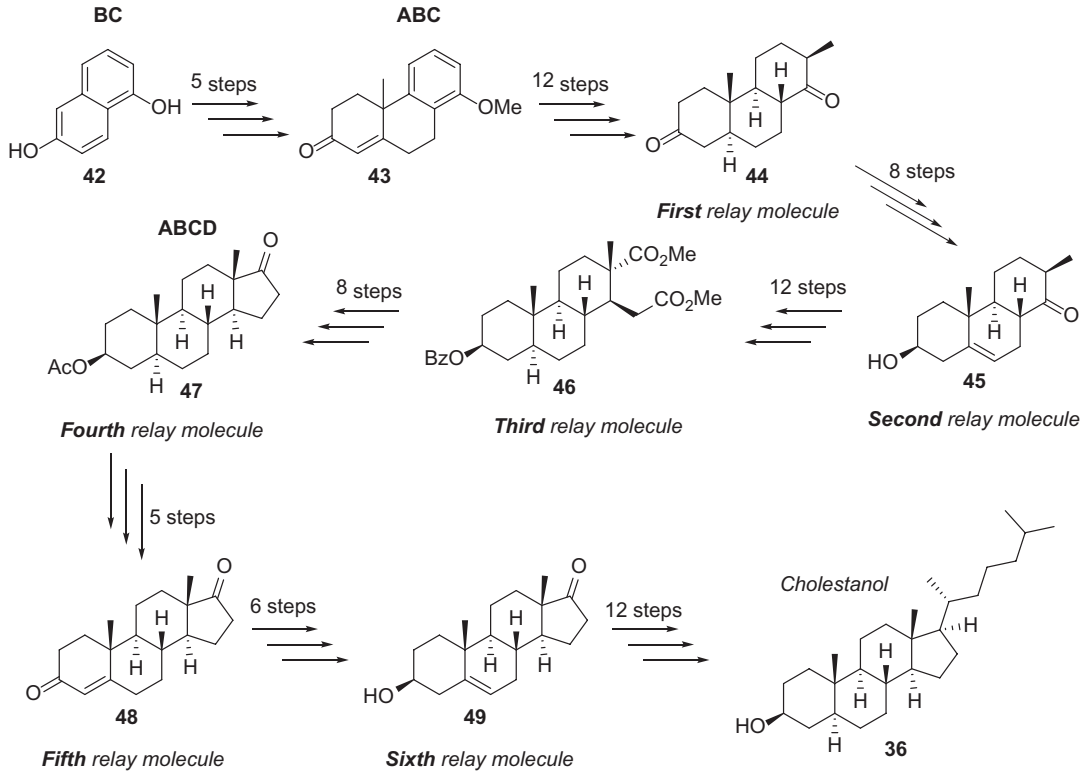
reaction steps (Scheme 3). The oxidation of cholestanol **36** to the corresponding ketone **37** and further selective C-4 bromination and elimination gave cholestenone **39** (Scheme 3).

The conversion of cholestenone **39** into cholesterol **41** was accomplished by the method of Dauben and Eastham reported in 1950 (Dauben & Eastham, 1950). The treatment of cholestenone **39** with acetyl chloride in acetic anhydride gave the enol acetate **40** which, without purification, was reduced by sodium borohydride and potassium hydroxide to yield natural cholesterol **41**, upon fractionation with digitonin for the isolation of the correct isomer (Scheme 3) (Birch, 1950; Dauben & Eastham, 1950; Djerassi & Scholz, 1948; Kritchevsky, Garmaise, & Gallagher, 1952; Ruzicka, Plattner, & Aeschbacher, 1938).

Robinson's cholesterol total synthesis

As Robinson used a BC → ABC → ABCD synthetic approach (Fig. 5), his starting material was 1,6-dihydroxynaphthalene **42** (corresponding to B and C rings in the final cholesterol structure), which was converted in the tricyclic structure **43** in a five reaction steps protocol (addition of A ring) (Scheme 4).

The synthesis of the first relay molecule **44** (also known as Reich diketone) (Reich, 1945) was completed 12 steps later (Scheme 4). The second relay molecule **45** was prepared resorting to eight additional reaction steps. Interestingly, this differed from the first one in "only" a double bond in ring B and the 3-hydroxy group replacing the original carbonyl group (Scheme 4). Resorting to another 12 reaction steps, Robinson prepared his third relay molecule **46**, *en route* to the fourth relay **47**, which has already ring D of the final cholesterol structure (Scheme 4).



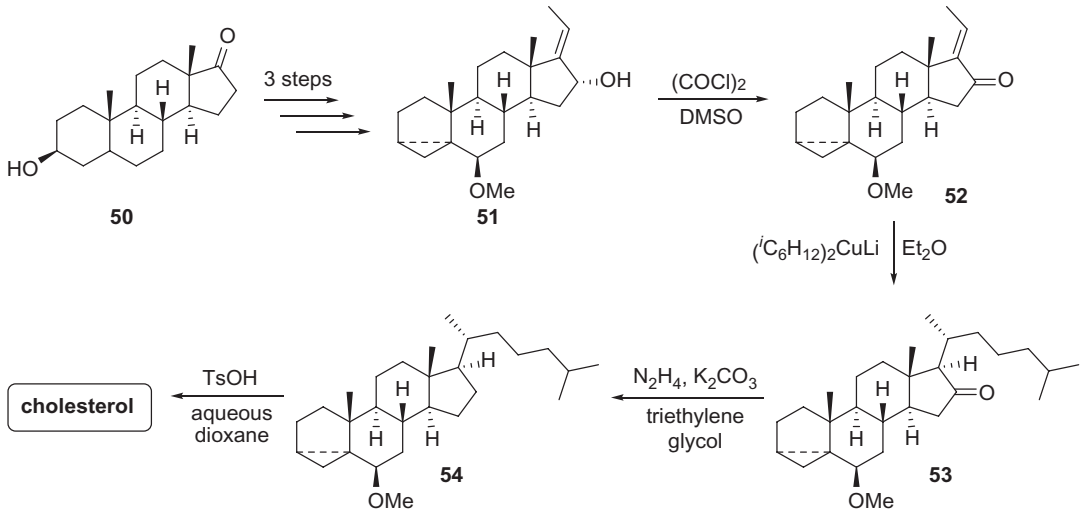
SCHEME 4 Robinson's cholestanol **36** total synthesis, based on a relay approach.

Two more relays were synthesized, molecules **48** and **49**, being the final 12 reaction steps used to add the cholesterol tail. Thus, he resorted to a similar strategy to that used by Woodward (Scheme 4).[a] The conversion of cholestanol **36** into cholesterol **41**, followed the same already known methodology depicted in Scheme 3.

Cholesterol hemisynthesis

The introduction of cholesterol side chain at C-20 is quite a challenge, as can be understood either from Woodward's or Robinson's total syntheses. An interesting approach, however, was developed by Schmuff and Trost (1983), based on organocuprate-mediated methods. This strategy started from the natural dehydroepiandrosterone **50** which was further converted in alcohol **51** in three reaction steps (Scheme 5). Then, the Moffatt-type oxidation gave the (*E*)-enone **52**, which upon reaction with lithium diisohexylcuprate gave cholestanone **53**

[a] A relay molecule can be defined as a compound which needs to be synthesized for the first time in total synthesis methodologies, but once synthesized, it is necessary to have it available in larger quantities from natural sources. This strategy saves many valuable man-hours synthesizing the relay substrates in the laboratory, because for every experiment that is successful, there are many that are not, and so a large amount of substrate is needed at each stage in the synthesis.



SCHEME 5 Alkylcuprate-mediated synthetic route to cholesterol from dehydroepiandrosterone **50**.

as the only detectable C-20 isomer (Scheme 5). Subsequent Wolff-Kishner reduction gave the isocholesterol methyl ether **54**, which was further converted into cholesterol (Scheme 5).

Synthesis of *ent*-cholesterol: The unnatural enantiomer

All known natural sterols have the same absolute configuration at the C-10 and C-13 quaternary centers, and so there is no simple way to convert readily available natural sterols into their enantiomeric series. Therefore, the preparation of *ent*-cholesterol (the unnatural enantiomer of cholesterol) (Fig. 6) is only possible through enantioselective total synthesis.

The *ent*-cholesterol **55** total synthesis was reported for the first time in 1992 by Rychnovsky and Mickus (1992). They took as inspiration an elegant stereoselective synthesis of 19-nor steroids by a group at Hoffmann-La Roche, and prepared *ent*-testosterone **64** as chemical intermediate for the synthesis of *ent*-cholesterol (Scheme 6). The achiral triketone **56** was used as starting material for the enantioselective intramolecular aldol reaction followed by acid-catalyzed elimination to give the chiral enedione **57** (Scheme 6). The stereogenic center in dione **57** was employed to control the remaining stereocenters in the final *ent*-cholesterol. The $NaBH_4$ reduction of the saturated ketone followed by protection with isobutylene gave enone **58**, which upon treatment with Stile's reagent delivers the carboxylic acid **59** (Scheme 6). Hydrogenation and reaction with

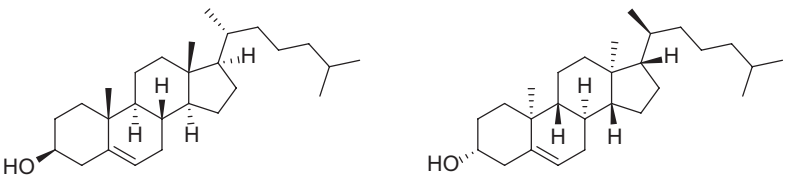
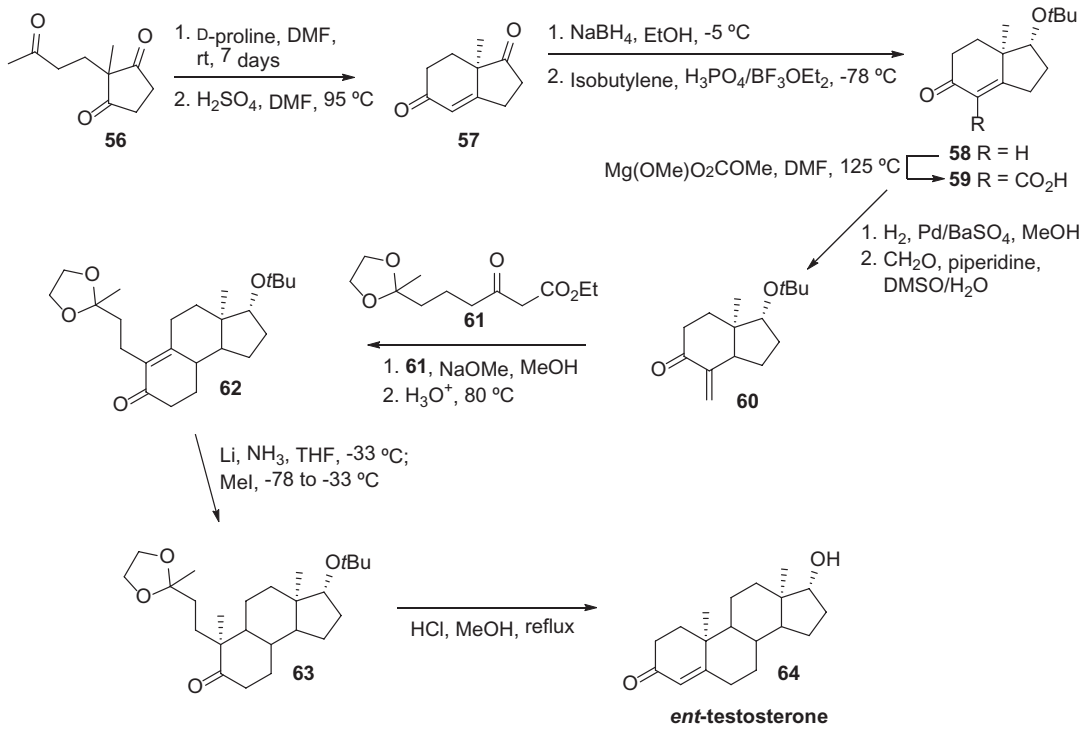


FIG. 6 Structures of cholesterol and *ent*-cholesterol.



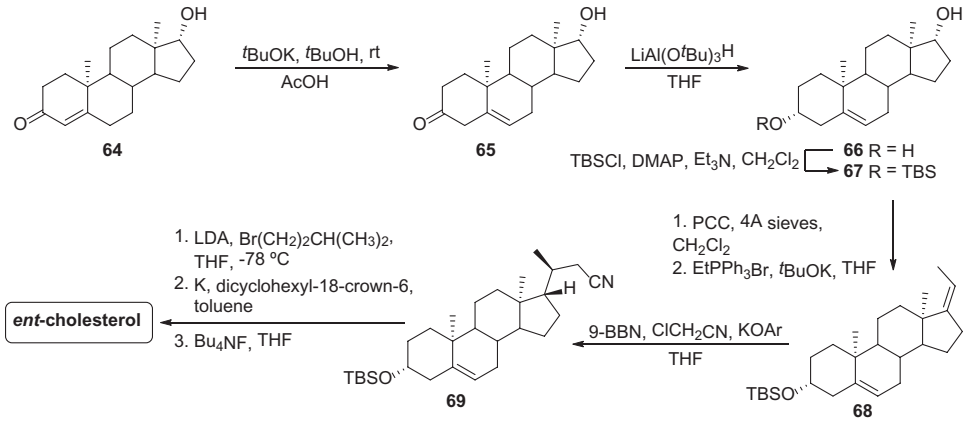
SCHEME 6 Synthesis of *ent*-testosterone **64**, intermediate in the synthesis of *ent*-cholesterol **55**.

aqueous formaldehyde gave the enone **60**, which upon Robinson annulation with β-keto ester **61** gave the tricyclic intermediate **62** (Scheme 6). The 19-methyl group was introduced through enone reduction followed by treatment with iodomethane to give ketone **63** (Scheme 6). The acid catalyzed cyclization of ketone **63** gave the required *ent*-testosterone **64** (Scheme 6).

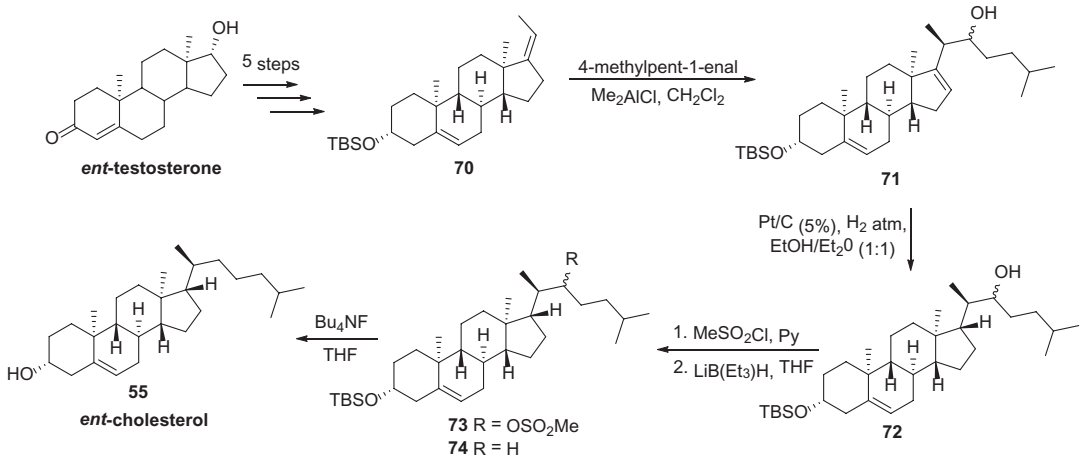
Once *ent*-testosterone **64** was obtained, Rychnovsky and Mickus were able to reach *ent*-cholesterol in a few reaction steps (Scheme 7). They obtained the β,γ-unsaturated ketone **65** in acidic media, which upon reduction with $LiAl(OtBu)_3H$ followed by OH-protection with *tert*-butyldimethylsilyl chloride (TBSCl) gave the monosilyl diol **67** (Scheme 7). The stereochemistry at C-17 and C-20 was set by hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) which enters from the top face of the alkene. Coupling the resulting hindered trialkylborane with chloroacetonitrile in the presence of a hindered base gave nitrile **69** as a single isomer (Scheme 7). The side chain was completed by nitrile alkylation with 1-bromo-3-methylbutane and reductive decyanation followed by desilylation to afford *ent*-cholesterol (Scheme 7).

An alternative methodology to convert *ent*-testosterone into *ent*-cholesterol was reported later in 1999 by Kumar and Covey (1999). To do so, Kumar and Covey used the previously reported methodology to prepare steroid **67** from *ent*-testosterone **64** (Scheme 7). However, they faced successive experimental failures building up the side chain of *ent*-cholesterol, and therefore they were forced to consider an alternative strategy to complete the synthesis (Scheme 8).

The Kumar and Covey strategy relied on the ene reaction of (*Z*)-olefin **70** with 4-methylpent-1-enal which gave the epimeric alcohol **71** (Scheme 8). The selective reduction



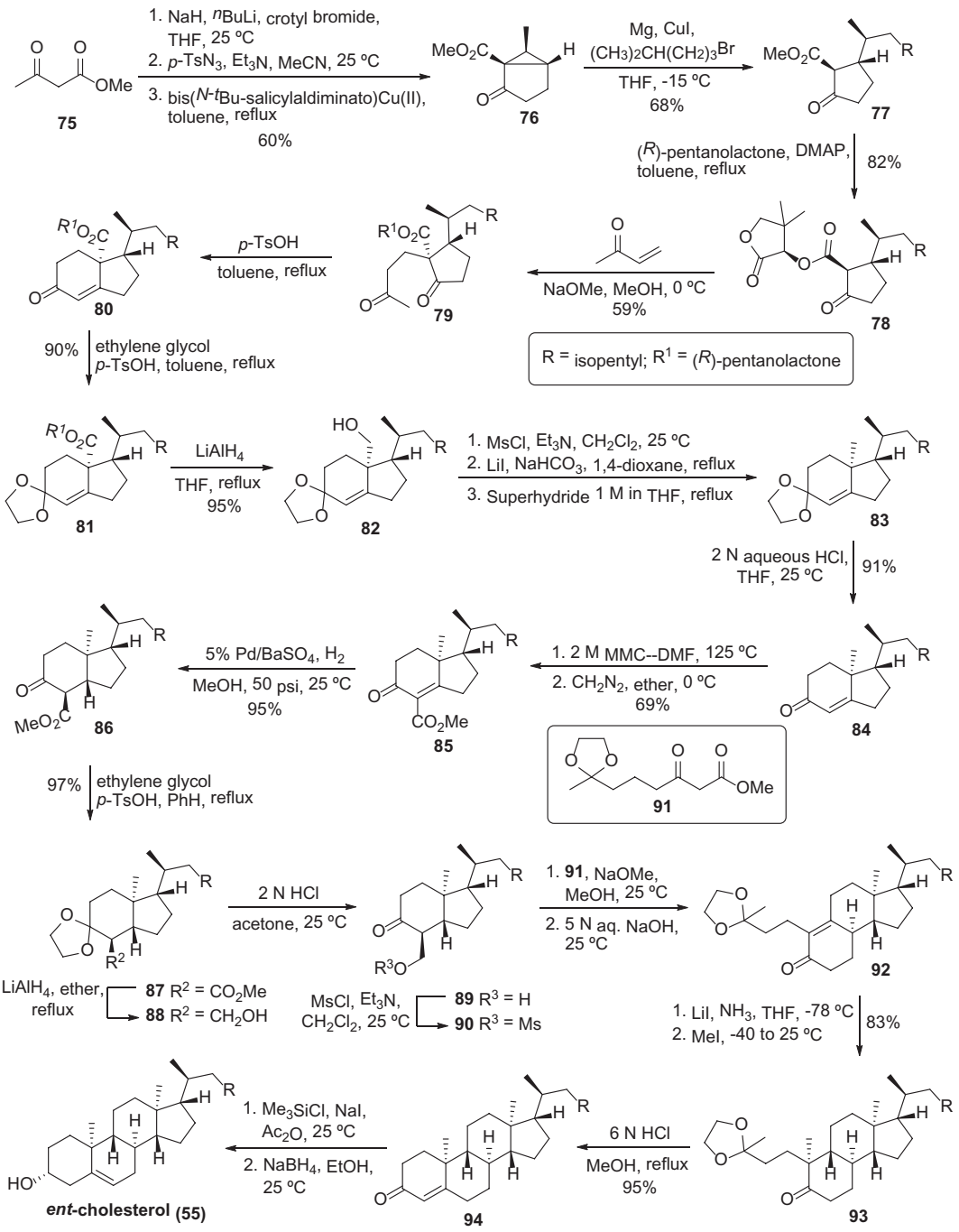
SCHEME 7 Synthesis of *ent*-cholesterol from *ent*-testosterone **64** precursor.



SCHEME 8 Alternative method for the preparation of *ent*-cholesterol from *ent*-testosterone.

of Δ^{16}-double bond of **71** gave the C-22 epimers of steroid **72**, which upon a tosylation/detosylation method gave steroid **74** (Scheme 8). The final removal of TBS protecting group with Bu_4NF gave *ent*-cholesterol **55** (Scheme 8).

As demonstrated earlier in this chapter, the common synthetic strategies for the synthesis of either cholesterol or *ent*-cholesterol proceed via the initial construction of the steroid ring system followed by the subsequent introduction of the C-17 side chain. This type of synthetic strategies is not suitable for preparing ^{13}C-labeled *ent*-cholesterols because the isotopic labels have to be incorporated before the multiple steps involved in construction of the side chain are initiated. In this sense, Jiang and Covey proposed in 2002 the total synthesis of *ent*-cholesterol by a route which starts with construction of the sterol D-ring containing the cholesterol side chain and then proceeds via elaboration of the sterol C, B, and A rings, respectively (Jiang & Covey, 2002). Accordingly, they started with methyl acetoacetate **75** which was converted in three steps into racemic compound **76** (Scheme 9). The addition of 4-methylpentylmagnesium



SCHEME 9 *ent*-Cholesterol total synthesis reported by Jiang and Covey.

bromide to β-keto ester **76** gave racemic product **77**, which upon transesterification with (*R*)-pantolactone gave a diastereomeric mixture from which diastereomer **78** was easily separated (Scheme 9). At this point, the side chain of *ent*-cholesterol was already incorporated, and subsequent reaction with methyl vinyl ketone gave the intermediate compound **79**, thus setting the proper chemical features of what will become the C-ring, and also formation of the 18-methyl group (Scheme 9). *p*-Toluenesulfonic acid (*p*-TsOH) catalyzes the cyclization of intermediate **79** to give enone **80**, which upon reaction with ethylene glycol was converted into ketal **81** (Scheme 9). The (*R*)-pantolactone group of compound **81** was then reduced using $LiAlH_4$ and upon three additional reaction steps, the 18-methyl group with proper stereochemistry was established in compound **83** (Scheme 9). The removal of the ketal protecting group from **83** yielded the desired C,D ring-side chain fragment, indenone **84** (Scheme 9). The reaction between indenone **84** and magnesium methyl carbonate (MMC) in DMF, followed by COOH methylation gave the keto ester **85**, used to stabilize the keto acid obtained from reaction with MMC (Scheme 9). Hydrogenation using 5% $Pd/BaSO_4$ gave saturated keto ester **86**, which was subsequently converted in compound **90**, in four steps so that the remaining rings of *ent*-cholesterol could be built (Scheme 9). Next, displacement of the mesylate group of compound **90** by the anion formed from methyl 6-(2-methyl-1,3-dioxolan-2-yl)-3-oxohexanoate **91**, followed by cyclization gave compound **92** (Scheme 9). The introduction of the 19-methyl group of *ent*-cholesterol into precursor enone **92** was made by reduction followed by lithium enolate intermediate reaction with excess iodomethane to give compound **93**, which upon cyclization rendered *ent*-cholestenone **94** (Scheme 9). The conversion of *ent*-cholestenone **94** to *ent*-cholesterol **55** was achieved via the dienol acetate, which was then reduced with $NaBH_4$ to give *ent*-cholesterol **55** (Scheme 9).

Sixteen years later from Rychnovsky first synthesis of *ent*-cholesterol **55**, his group reported a new concise and scalable synthesis of the unnatural enantiomer of cholesterol, starting from (*S*)-citronellol (Fig. 7) (Belani & Rychnovsky, 2008). The Rychnovsky new synthesis of *ent*-cholesterol **55** is based on a ring D to C to B to A approach and incorporates the cholesterol side chain early in the synthetic procedure, as in the strategy reported in 2002 by Jiang and Covey.

The first key intermediates **C** and **B** were synthesized following a C–H insertion strategy (Fig. 7 and Scheme 10). Commercially available (*S*)-citronellol was converted to the corresponding benzenesulfonate and subsequently alkylated with the dianion of methyl

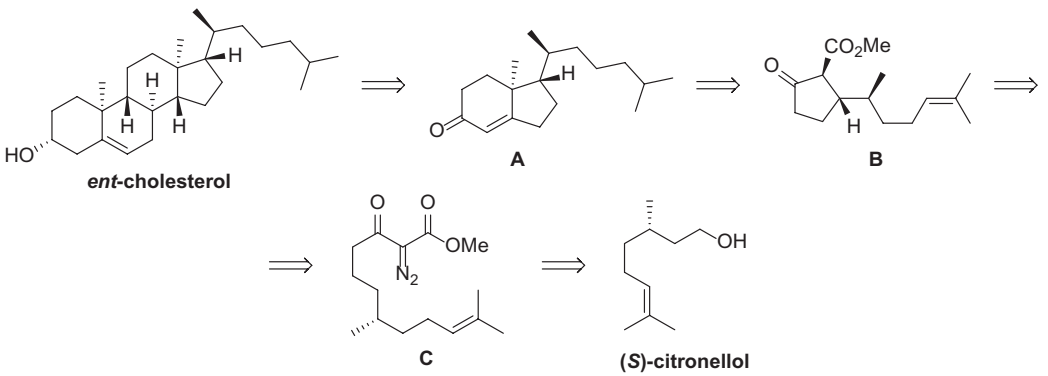
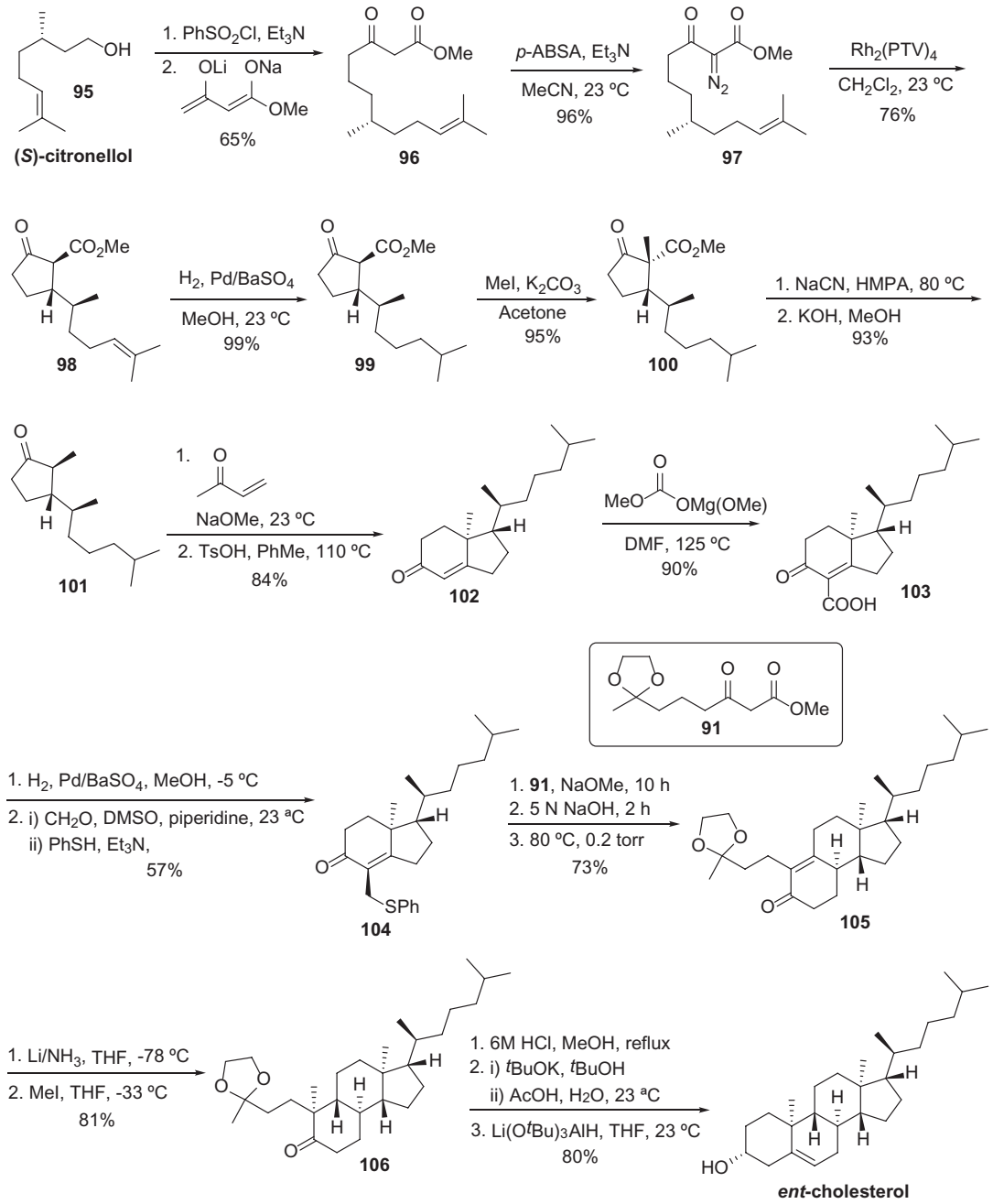


FIG. 7 Retrosynthetic analysis of *ent*-cholesterol starting from (*S*)-citronellol.



SCHEME 10 Synthesis of *ent*-cholesterol from (*S*)-citronellol.

acetoacetate to give β-keto ester **96** (Scheme 10). A diazo transfer reaction allowed the conversion of β-keto ester **96** into α-diazo-β-keto ester **97**, which upon diastereoselective C–H insertion reaction gave the keto ester **98** (Scheme 10). The C–H insertion strategy drastically shortens the synthesis of the sterol side chain and allows the C-20 stereogenic center to be introduced from a chiral pool source. Hydrogenation of keto ester **98** using palladium on carbon (Pd/C) provided compound **99** with a saturated side chain, which subsequently underwent methylation followed by decarbomethoxylation to give α-methyl ketone **101** as a single diastereomer (Scheme 10). The Robinson annulation of ketone **101** with methyl vinyl ketone gave the corresponding Michael adduct which, upon treatment with *p*-TsOH, provided the enone **102** (CD rings completed) (Scheme 10). The strategy for the conversion of enone **102** to *ent*-cholesterol was the same double annulation strategy developed by Hoffmann La Roche, similar to that used by Rychnovsky in his first *ent*-cholesterol synthesis (Rychnovsky & Mickus, 1992). Therefore, the treatment of enone **102** with Stile's reagent gave the carboxylic acid **103**, which upon hydrogenation and subsequent reaction with formaldehyde followed by the addition of thiophenol gave thioether **104** (Scheme 10). The annulation of thioether **104** with β-keto ester **91** provided the tricyclic enone **105**, which upon reduction and alkylation installed the C-19 methyl group stereoselectively (Scheme 10). Acid-catalyzed deprotection of the ketal followed by aldol condensation provided the A ring of *ent*-cholestenone. The AB ring functionality was modified by deprotonation using *t*BuOK, followed by kinetic protonation to provide the deconjugated ketone and diastereoselective reduction of the ketone with $Li(OtBu)_3AlH$ gave *ent*-cholesterol (Scheme 10) (Belani & Rychnovsky, 2008).

Concluding remarks

Cholesterol is an essential component of animal cell membranes and the precursor for the synthesis of steroid hormones and bile acids. The interest of scientist and industry in steroids, particularly cholesterol, dates back to the 1930s as these compounds were widely used in medicine. Steroids were big business in the pharmaceutical industry and a company that discovered viable ways to produce them stood to make huge profits. At that time, steroids were exclusively obtained through chemical conversion of steroid precursors extracted from natural sources in very expensive and unproductive processes. As a consequence, a general belief that completes synthesis might provide a cheaper and quicker method of production of steroids started to grow, even though complete synthesis might require over 30 stages. It is no coincidence, though, that one of the most significant chemical problems of that time drew the attention of two of the greatest chemists of the 20th century: Sir Robert Robinson at Oxford and R.B. Woodward at Harvard. Cholesterol was the most complex organic molecule synthesized up to that time, and its total synthesis paved the way for the synthesis of many related steroid hormones. Since 1951, there was no significant developments in cholesterol synthesis, with only one example of hemisynthesis from dehydroepiandrosterone through organocuprate-mediated methods. Interestingly enough, in recent years, cholesterol unnatural enantiomer—*ent*-cholesterol, has drawn much more attention than cholesterol itself. In fact, the scientific applications of *ent*-cholesterol as a tool to study the enantioselectivity of cholesterol interactions or the molecular recognition of cholesterol stereoisomers by monoclonal antibodies, for example, drove the development of three total synthetic routes to it within 18 years' time lapse. Noteworthy is the synthesis of

Jiang and Covey which allows the preparation of ^{13}C- and ^{2}H-labeled forms of *ent*-cholesterol, introduced near the end of the reaction sequence. This route is of particular importance for NMR studies of *ent*-cholesterol interactions. Apart from that, cholesterol has more interest in Chemistry as synthon to create cholesterol-based new molecules for a wide range of applications ranging from drug delivery or bioimaging applications to cholesterol-based liquid crystals and gelators (Albuquerque, Santos, & Silva, 2019).

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CHOLESTEROL

From Chemistry and Biophysics to the Clinic

Edited by
Anna N. Bukiya, PhD, and Alex M. Dopico, MD, PhD

With ***CHOLESTEROL: From Chemistry and Biophysics to the Clinic***, Professors Anna Bukiya and Alex Dopico have compiled a comprehensive resource on both biological and clinical aspects of cholesterol, spanning the biophysics and biochemistry of this very special lipid, as well as the latest pharmacological discoveries used to tackle human disorders associated with abnormal cholesterol levels. Early chapters on basic sciences offer insights on the fundamental role of cholesterol in biological membranes, lab chemistry, cholesterol metabolism and synthesis, molecular evolution of cholesterol and sterols, and cholesterol modulation of membrane-spanning peptides, ion channels and receptors. Chapters on cellular and organismal development discuss blood cholesterol levels, cholesterol transport by lipoproteins and cholesterol metabolism, the role of cholesterol in early human development, and the contribution of genetics and nutrition to hypercholesterolemia. Pathophysiology specialists review familial hypobetalipoproteinemia, critical illness and cholesterol levels, coronary artery disease, cholesteryl ester storage disease, Niemann-Pick disease type C, cholesterol and viral pathology, cholesterol and neuro-degenerative disorders, and the links of cholesterol to substance use disorders, using alcohol as an example. The final section examines the pharmacology of cholesterol-containing drug delivery systems, the impact of cholesterol on the effect of anesthetics and drug receptors in the cardiovascular system, and clinical strategies for reducing cholesterol levels. The section also introduces the reader to the future of cholesterol-lowering drugs based on cyclodextrins and highlights several examples when clinical management of cholesterol levels faces challenges in specific patient populations, such as patients who have rheumatoid arthritis and HIV.

Key Features

- Ties basic biology to clinical application and drug discovery
- Provides a one-stop source of information from bench to bedside
- Examines the latest pharmacological advances used to tackle cholesterol-related disorders
- Includes chapters contributed by a wide range of specialists, uniting various disciplines

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