Notes

Improved Syntheses of 12-Substituted 5β-Cholanes[1]

Richard C. Ebersole and Frederic C. Chang*

Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tennessee 38103

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The rearrangement of 12-substituted derivatives of various steroidal classes has been investigated[2] for both its synthetic possibilities and mechanistic interest. A study of the rearrangement reactions involving 12α-mesyloxy (**1**), 12β-mesyloxy (**2**), and 12-oxotosylhydrazone (**3**) derivatives of cholane[3] has been carried out,[4] the cholane system being chosen in order that the rearrangement process *per se* could be studied free of complications from other functional groups. To ensure adequate supplies of compounds **1**, **2**, and **3** for the study, practical methods for their preparation were sought.

12α-Cholanol (**4**), the key intermediate to the other compounds of the group, had been obtained as a side product in a previous research[5] which involved an attempt to selectively tosylate 3α,12α,24-cholanetriol (**5**). A direct preparation of **4** is available by $LiAlH_4$ reduction of the 24-mesylate[6] (**6**) of 12α,24-cholanediol (**7**). However the only currently feasible routes[5,7] to **7**, and in fact to any 12-hydroxycholane derivative, originate with the readily available deoxycholic acid as starting material; so a satisfactory overall method for obtaining **4** was already manifest in the reaction[5] which first yielded **4**. In that reaction **4** must have been formed from the triol **5** *via* an intermediary 3α,24-ditosylate derivative **8**, so that our first efforts were directed toward finding suitable conditions for obtaining **8** in reasonable yield. An obstacle to the satisfactory preparation of **8** was recognized in reviewing earlier tosylations[8] of 24-cholanols; invariably the desired tosylate would be contaminated with the chloro analog. The chloro compound was shown to be formed by a replacement of the tosyloxy group in a facile reaction by chloride ion of pyridinium chloride, which is formed as the tosylation proceeds.

An obvious way of minimizing this side reaction was to decrease the contact time between the sulfonate and pyridinium chloride. After careful experimentation, a satisfactory procedure, depending on precise temperature control, the use of a high ratio of mesyl chloride[9] to alcohol, and quick work-up, was found whereby the desired triol dimesylate[10] **9** can be obtained in crystalline form and good yield. Reduction of **9** with lithium aluminum hydride to **4** proceeded smoothly;[11] the overall yield of **4** from methyl deoxycholate[12] was 61%.

With the alcohol **4** available, direct mesylation to **1** is the method of choice, but **1** has been prepared also by selective reduction of the 12,24-diol dimesylate **11**. The $LiAlH_4$ reduction[13] was easily controlled to stop at the desired stage.

Oxidation of **4** to 12-oxocholane **15** by K_2CrO_4 in acetic acid proceeds smoothly when carried to completion, but incomplete oxidations are misleading, as crystalline products are obtained which consist of mixed (1:1) crystals of alcohol and ketone.

Raney nickel reduction[14a] of **15** (without additional base[14b]) gave 81% of the 12β isomer, a method representing an improvement over previous procedures.[15] The 12-ol epimers also form a 1:1 molecular compound.

The 12β-mesylate **2** is formed readily from the alcohol **16** but isolation and crystallization were achieved only after much careful experimentation. The compound is markedly unstable in an erratic manner. Our efforts to ascertain the precise conditions which cause decomposition of **2** were unsuccessful. Characterization of the compound is by ir and nmr spectroscopy. In experiments reported in the rearrangement study[4] the ir spectrum of a solution of **2** in anhydrous collidine was found to be unchanged after 4 hr at room temperature; decomposition was observed at higher temperatures.

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(1) (a) Excerpted in part from the Ph.D. dissertation of R. C. E., University of Tennessee Medical Units, 1973. (b) The major portion of this work was reported at the 19th Southeastern Regional Meeting of the American Chemical Society, Nov 1967. (c) This work was supported in part by NIH Grants USPHS CA-05011 and FR-05423.

(2) See ref 6, 11, 13, and 26 cited in ref 4 of this paper.

(3) All cholane derivatives mentioned in this paper are 5β compounds; the designation "5β" will be omitted in referring to them.

(4) R. C. Ebersole and F. C. Chang, *J. Org. Chem.*, **38**, 2579 (1973).

(5) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **81**, 2835 (1959).

(6) F. C. Chang, *J. Pharm. Sci.*, **53**, 1014 (1964).

(7) G. V. Rao and C. C. Price, *J. Org. Chem.*, **27**, 205 (1962).

(8) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958).

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 662.

(10) In an early experiment in which the reaction mixture was allowed to stand for a longer period of time, 24-chloro-3α,12α-cholanediol 3-mesylate **10**, formed from **9** by the chloride replacement reaction, was isolated as a crystalline product (see Experimental Section).

(11) After this procedure was worked out and used as a standard preparation of **4**, a publication [S. Ahmed, M. Alauddin, B. Caddy, M. Martin-Smith, W. T. L. Sidwell, and T. R. Watson, *Aust. J. Chem.*, **24**, 521 (1971)] appeared which included a synthesis of **4** by essentially the same process. However, the dimesylate intermediate **9** was not isolated, and failure to do so might be caused by contamination of the product by the chloro analog **10**, as the reaction was of 16-hr duration and only 2.15 equiv of mesyl chloride was used.

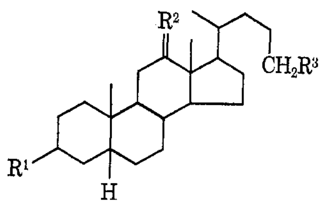
(12) The triol **5** can be prepared from deoxycholic acid, but in our experience the methyl ester is much more conveniently reduced[5] because of a more favorable solubility in the solvents used for $LiAlH_4$ reduction.

(13) Similar preferential $LiAlH_4$ reduction of 3α,24-cholanediol dimesylate **12** gave 3α-cholanol mesylate **13**, in contrast to the difficulty encountered[6] in attempting to selectively mesylate the 3α,24-diol **14**. The 24-carbomethoxy group is also reduced by $LiAlH_4$ in preference to either the 3α- or 12α-mesyloxy group when both (mesyloxy and carbomethoxy) are substituents in cholane. (Unpublished results from this laboratory.)

(14) (a) M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **26**, 2097 (1943); (b) F. C. Chang, N. F. Wood, and W. G. Holton, *J. Org. Chem.*, **30**, 1718 (1965).

(15) (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 269; (b) J. W. Huffman, D. M. Alabran, J. W. Bethea, and A. C. Ruggles, *J. Org. Chem.*, **29**, 2963 (1964).

The 12β-acetate **17** was prepared by conventional room-temperature treatment of the β-ol with acetic anhydride, but the 12α-acetate **18** from **4** required more vigorous acetylating conditions.



Compd	R¹	R²	R³
1	H	H, α-OMs	H
2	H	H, β-OMs	H
3	H	NNHTs	H
4	H	H, α-OH	H
5	OH	H, α-OH	OH
6	H	H, α-OH	OMs
7	H	H, α-OH	OH
8	OTs	H, α-OH	OTs
9	OMs	H, α-OH	OMs
10	OMs	H, α-OH	Cl
11	H	H, α-OMs	OMs
12	OMs	H, H	OMs
13	OMs	H, H	H
14	OH	H, H	OH
15	H	O	H
16	H	H, β-OH	H
17	H	H, β-OAc	H
18	H	H, α-OAc	H

Experimental Section[16]

3α,12α,24-Cholanetriol 3,24-dimesylate (**9**) was prepared by adding a solution of methanesulfonyl chloride (76.1 ml dissolved in 300 ml of freshly distilled pyridine and cooled to 0°) to a solution of 3α,12α,24-cholanetriol[5,17] (76.1 g of triol **5** dried by azeotropic distillation of a benzene solution, dissolved in 740 ml of pyridine and maintained at 0°). The reaction mixture, after 5 min in the ice bath, was allowed to stand at room temperature for an additional 3.5 min, then stirred into ice chips. The total product was promptly extracted into ether. The ethereal solution was washed successively with ice-cold dilute HCl, dilute $NaHCO_3$, and water, then decolorized with Norit and dried over calcium sulfate. Evaporation of the ether gave a viscous oil (99.1 g) which crystallized from a mixture of benzene (560 ml) and petroleum ether (bp 63–70°) (300 ml added under reflux) in the form of fine needles (75 g, 72%): mp 128.5–129.0°; $[\alpha]_D$ +44.3° (*c* 2.07); ir ($CHCl_3$) 2.78, 9.70 (12α-OH), 7.38, 8.53 ($-SO_2-$), 10.86, 11.45 μ (mesylate[6]); nmr τ 9.35 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 6.98 (s, 6, $-OSO_2Me$), 6.02 (m, 1, –CHOH), 5.78 (t, 2, $-CH_2OMs$), 5.33 (br s, 1, CHOMs).

Anal. Calcd for $C_{26}H_{46}O_7S_2$: C, 58.39; H, 8.67. Found: C, 58.25; H, 8.73.

24-Chloro-3α,12α-cholanediol 3-Mesylate (**10**).—In a similar reaction (as the above) which was allowed to stand for 8 hr after addition of the mesyl chloride, after similar processing and rapid column chromatography on a Florisil column, the ether-eluted fractions afforded a residual oil which crystallized in isopropyl ether to give **10** as needles: mp 124.0–127.0°; ir (KBr) 2.73, 9.65 (12α-OH), 7.38, 8.53 ($-SO_2-$), 10.57, 11.40, 11.72 μ (mesylate); nmr τ 9.30 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 7.0 (s, 3, $-OSO_2Me$), 6.47 (t, 2, $-CH_2Cl$), 5.97 (m, 1, –CHOH); 5.32 (br s, 1, –CHOMs).

Cnal. Calcd for $C_{25}H_{43}O_4SCl$: C, 63.19; H, 9.12. Found: *A*, 63.23; H, 8.99.

12α-Cholanol[5] (**4**) was prepared by $LiAlH_4$ (a stirred suspension of 39.4 g of powdered hydride in 640 ml of anhydrous tetrahydrofuran) reduction of **9** (70.0 g dissolved in 400 ml of tetrahydrofuran added dropwise). After 24 hr under reflux, the reaction was processed by addition of aqueous sodium sulfate until formation of a white precipitate was completed. Filtration and evaporation of the organic layer left 44.0 g (97%) of crystalline product. Crystallization from methyl Cellosolve gave colorless, prismatic needles: mp 103.5–104.0°; $[\alpha]_D$ +45.8° (*c* 5.00) (lit.[5] mp 100.9–103.3°; $[\alpha]_D$ +41.0°); nmr τ 9.32 (s, 3, C-18 Me), 9.08 (s, 3, C-19 Me), 6.00 (m, 1, –CHOH–).

12-Oxocholane[15b] (**15**) was prepared by oxidation of **4** (20.0 g) in a stirred suspension of K_2CrO_4 (16.0 g) in acetic acid (600 ml) and water (18 ml). After 24 hr at 23°, the reaction mixture was added to ice chips and the precipitated solid (18.4 g) was washed with water and collected. Recrystallization from methanol gave rectangular plates of **15** (16.9 g), mp 112.0–115.0° (lit. mp 116–117°).

12β-Cholanol[15b] (**16**).—12-Oxocholane (2.00 g) in methanol (250 ml) was hydrogenated in the presence of W-2 Raney nickel (an equal quantity air dried weighed 12 g) at a pressure of 3 atm in a Parr apparatus. After 30 hr, the catalyst was removed by filtration, and the concentrated filtrate was taken up in benzene (200 ml). Evaporation of the benzene gave a colorless oil (1.95 g). Glc analysis indicated that the oil was composed of 81% 12β- and 17% 12α-cholanol. Crystallization from acetone produced 1.12 g of dense rhombic crystals (by glc, 96% pure). Further recrystallization produced a sample, homogeneous by glc and tlc: mp 93.0–94.0°; $[\alpha]_D$ +31.3° (*c* 4.98) (lit.[15b] mp 92–93°, $[\alpha]_D$ +45°); ir (CS_2) 2.73 (OH), 7.29, 9.80, 9.90 μ (CO); nmr τ 9.32 (s, 3, C-18 Me), 9.07 (s, 3, C-19 Me), 6.62 (m, CHOH).

Anal. Calcd for $C_{24}H_{42}O$: C, 83.16; H, 12.22. Found: C, 82.81; H, 12.28.

Further concentration of the mother liquor induced formation of long, prismatic crystals. Tlc showed that these crystals were composed of the 12α- and 12β-ols in equal proportion.

12α-Cholanol Mesylate[6] (**1**). A.—12α-Cholanol **4** was mesylated as previously reported[6] to give **1**.

B.—Two grams of 12α,24-cholanediol dimesylate[6] (**11**), dissolved in 50 ml of ether and 5 ml of tetrahydrofuran, was added dropwise to a stirred suspension of 390 mg of $LiAlH_4$ in 80 ml of ether. Stirring was continued for 4 hr, and after overnight standing the mixture was processed as for the preparation of **9** (above), resulting in a residual oil, which on crystallization in methanol yielded **1** (0.77 g, 47%) as thin rectangular plates, mp 99.5–100.0°, identical with the product of part A according to melting point, ir, and nmr comparisons.

12β-Cholanol mesylate[2b] (**2**) was prepared by adding 12β-cholanol (0.100 g) to a pyridine (2 ml) solution of methanesulfonyl chloride (0.05 ml) chilled to 4°. After 14 hr at 4°, the reaction mixture was poured on 250 ml of ice chips and then covered with cold water. After standing for 2 hr, the semicrystalline material was filtered and washed free of pyridine with cold water. The air-dried material was dissolved in ether, and the solvent was removed under a stream of nitrogen. The residual oil was dissolved in ethanol for crystallization, which yielded colorless, slender needles (0.05 g): mp 56.0–56.5°; $[\alpha]_D$ +27.2° (*c* 2.68); ir (CS_2) 7.33, 7.47, 8.50 ($-SO_2-$), 10.86, 11.04, 11.16, 11.30 μ (–OMs); nmr (CCl_4) τ 9.23 (s, 3, C-18 Me), 9.03 (broad singlet, *ca.* 6, C-19 Me plus contributions from C-21 and C-24), 7.12 (s, 3, $-OSO_2CH_3$), 5.57 (t, 1, J = 7 Hz, CHOMs).

12α-Acetoxycholane[18] (**18**) was obtained by *p*-toluenesulfonic acid (0.03 g) catalyzed acetylation of 12α-cholanol (1.00 g) with acetic anhydride (0.66 ml) in acetic acid (10 ml). After 24 hr at room temperature, conventional work-up yielded a yellowish oil (1.00 g). Crystallization from an acetone–ethanol mixture produced dense cubes: mp 75.0–75.5°; $[\alpha]_D$ + 71.3° (*c* 5.06); ir (CS_2) 5.73 (acetate C=O), 8.03, 9.73, 9.82 (acetate CO–), 7.27, 10.30 μ; nmr τ 9.27, 9.10 (s, 6, 2 Me), 7.93 (s, 3, $-OOCCH_3$), 4.90 (t, 1, J = 3 Hz, CHOAc).

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 79.88; H, 11.33.

12β-Acetoxycholane[18] (**17**) was prepared from **15** in the usual way with acetic anhydride–pyridine. The acetate crystallized

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[16] See Experimental Section of ref 4 for general experimental information.

[17] G. B. Spero, *J. Amer. Chem. Soc.*, **70**, 1907 (1948).

[18] These acetates were mentioned in ref 15b but were neither crystallized nor characterized.

from an ethanol–acetone mixture: mp 74.0–74.5°; $[\alpha]_D$ +16.5° (*c* 5.07); ir (CS_2) 5.75 (C=O), 8.05, 9.78, 9.73 μ (acetate CO–); nmr τ 9.23, 9.08 (s, 6, 2 Me), 7.98 (s, 3, $-OOCCH_3$), 5.33 (m, 1, CHOAc).

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.03; H, 11.25.

Registry No.—**1,** 1251-13-4; **2,** 40429-72-9; **4,** 35649-45-7; **5,** 2603-77-2; **9,** 40429-41-2; **10,** 40429-42-3; **11,** 1259-02-5; **15,** 5916-16-5; **16,** 40429-45-6; **17,** 40429-46-7; **18,** 19684-29-8; methanesulfonyl chloride, 124-63-0; acetic anhydride, 108-24-7.

Synthesis of 3,4,5,10,11,12-Cyclotetradecahexaene-1,8-dione, a Monocyclic Dicumulenedione[1]

PETER J. GARRATT,* KYRIACOS C. NICOLAOU,
AND FRANZ SONDHEIMER

*Department of Chemistry, University College London,
London WC1H OAJ, United Kingdom*

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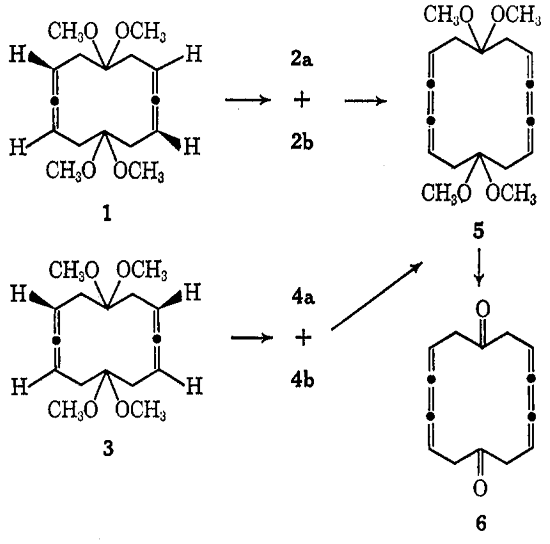
We have recently described the synthesis of 12- and 14-membered monocyclic diallenes containing carbonyl groups,[2] and we have explored this method as a means of preparing monocyclic dicumulenes. We now report the synthesis of 3,4,5,10,11,12-cyclotetradecahexaene-1,8-dione (**6**), and the attempted preparation of 3,4,5,6,11,12,13,14-cyclohexadecaoctaene-1,9-dione (**8b**).

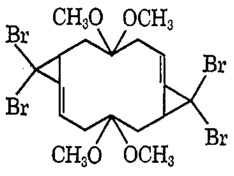
The racemic diallene (**1**), prepared by the previously described method,[2] was treated in pentane at 0° with excess bromoform and potassium *tert*-butoxide. Two isomeric bis(dibromocarbene) adducts were obtained, **2a** (mp 117–118°) and **2b** (mp 95–97° dec). The spectra of **2a** and **2b** (Table I) both showed signals in the olefinic and cyclopropyl regions, but no signals in the allenic region (τ 4.5–5.5), and thus addition to both allene groups of **1** must have occurred. Furthermore, the nmr spectrum of **2a** showed only one type of methoxyl proton, which suggests that **2a** most probably has the symmetric structure shown.[3] By contrast, the nmr spectrum of **2b** showed two methoxyl signals, and the spectrum can be accommodated by a number of isomeric structures.

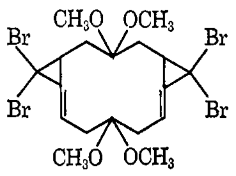
The *meso*-diallene **3**,[2] under the same conditions, gave two further bis(dibromocarbene) adducts, **4a** (mp 79–80° dec) and **4b** (mp 77–78° dec). The nmr spectra (Table I) showed that both allenic groups in **3** had reacted. The spectrum of **4b** had three types of methoxyl signals, suggesting the asymmetric structure shown,[4] whereas that of **4a** showed two methoxyl signals and consequently provided less structural information.

TABLE I
NMR SPECTRA (100 MHz, CCl_4) OF **2a**, **2b**, **4a**, AND **4b** AS τ VALUES RELATIVE TO TMS

2a	3.74	(m, 2 H, olefin)
	6.72	(s, 12 H, OCH_3)
	7.32	(d, *J* = 8 Hz, 4 H, allylic CH_2)
	7.65	(d, *J* = 14 Hz, 2 H, CH_2)
	7.86	(d, *J* = 12 Hz, 2 H, CH_2)
	8.64	(dd, *J* = 12, 14 Hz, 2 H, cyclopropyl)
2b	3.66	(m, 2 H, olefin)
	6.66	(s, 12H, OCH_3)
	6.73	(s,
	7.26–8.00	(m, 8 H, allylic CH_2 + CH_2)
	8.32	(dd, *J* = 7, 14 Hz, 2 H, cyclopropyl)
4a	3.64	(m, *J* = 2, 8, 8 Hz, 2 H, olefin)
	6.70	(s, 6 H, OCH_3)
	6.77	(s, 6 H, OCH_3)
	7.32	(d, *J* = 8 Hz, 4 H, allylic CH_2)
	7.56	(d, *J* = 14 Hz, 2 H, CH_2)
	7.88	(dd, *J* = 2, 10 Hz, 2 H, CH_2)
	8.67	(dd, *J* = 10, 14 Hz, 2 H, cyclopropyl)
4b	3.63	(m, *J* = 2, 8 Hz, 2 H, olefin)
	6.64	(s, 3 H, OCH_3)
	6.74	(s, 9H, OCH_3)
	6.78	(s,
	7.30–7.70	(m, 4 H, allylic CH_2 + CH_2)
	8.38	(dd, *J* = 8, 16 Hz, 2 H, cyclopropyl)




2a


4b

When a mixture of the racemic **1** and *meso*-**3** diallenes were treated with bromoform and potassium *tert*-butoxide, a mixture of the four bis adducts was obtained. These could be separated by chromatography and this is the best method for the preparation of these compounds.

Reaction of either **2a** or **4a**, or a mixture of all four isomers, with methyllithium in ether at −10° gave a solution of the dicumulene **5**, which was stable under these conditions for several days. Removal of the ether below 0° gave **5** as a crystalline compound, which

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[1] For a preliminary communication of part of this work, see P. J. Garratt, K. C. Nicolaou, and F. Sondheimer, *Chem. Commun.*, 1018 (1971).

[2] P. J. Garratt, K. C. Nicolaou, and F. Sondheimer, *J. Amer. Chem. Soc.*, **95**, 4582 (1973).

[3] The cyclopropyl rings in **2a** might be both on the same side of the 12-membered ring or on opposite sides. For either structure, the spectrum is still deceptively simple, since two methoxyl groups in different environments must have fortuitously coincidental chemical shifts. However, the environment of the methoxyl groups in the alternative isomers are even less similar.

[4] The two cyclopropyl rings would have to be on the same side of the 12-membered ring, and the spectrum is again deceptively simple.