SHORT PAPER

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Synthesis and X-ray crystal structure of 5β-cholan-24-yl chloride†

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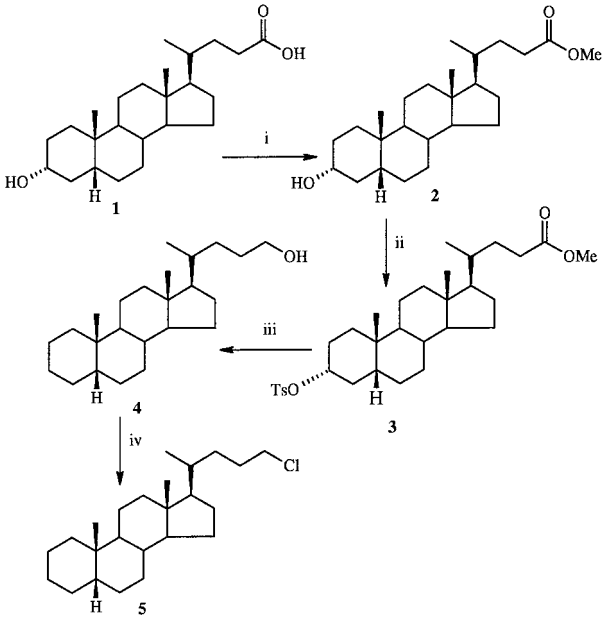
5β-cholan-24-yl chloride (**5**) was prepared from lithocholic acid (**1**) in four steps, and following spectral investigations its crystal and molecular structure was determined by X-ray crystallography.

Keywords: 5b-cholan-24-yl chloride

Introduction

Lithocholic acid (**1**), the simplest of the bile acids, has previously been used as the starting material for the synthesis of several steroid derivatives.[1] For example, during the synthesis of 3β-cholanol from methyl lithocholate, several chloro and unsaturated analogues were produced.[1] 5β-Cholan-24-yl chloride (**5**) was previously prepared from lithocholic acid (**1**) in five steps, using pyridinium chloride in pyridine at room temperature (r.t.) for 40 h in the final step.[1,2] We now report on a simpler and efficient synthetic route for the production of 5β-cholan-24-yl chloride (**5**) from lithocholic acid (**1**) in four steps, using *p*-TsCl in pyridine at r.t. for 24 h, and complete ^{1}H and ^{13}C NMR assignments on the basis of extensive 2D NMR studies.

Synthesis of 5β-cholan-24-yl chloride **(5):** Lithocholic acid (**1**), *p*-toluenesulfonyl chloride (*p*-TsCl) and lithium aluminium hydride (LAH), were purchased from Aldrich and used as received. Most chemicals and solvents were analytical grade and used without further purification. The purity of the products and the reaction time were supported by thin-layer chromatography (TLC) performed on silica gel (Merck type 60) and visualised under UV illumination and/or by I_2 vapour. Silica gel 60G was used for vacuum liquid chromatography (VLC). Melting points of the products were determined on a Gallenkamp melting point apparatus. IR spectra (wavenumbers in cm^{-1}) were recorded on an ATI Mattson Genesis FTIR spectrophotometer as KBr pellets. NMR spectra were recorded on a Varian Unity INOVA 400 MHz spectrometer. Chemical shifts are reported in ppm downfield from TMS, using the middle resonance of $CDCl_3$ (7.25 ppm for ^{1}H and 77.23 ppm for ^{13}C) as an internal standard and coupling constants (*J*) in Hz. All compounds were confirmed by 1D NMR spectroscopic analysis except the target compound (**5**), which was identified unambiguously by 1D and 2D NMR spectroscopic analysis.



Scheme 1 i = MeOH, AcCl, 24 h, r.t. ii = *p*-TsCl, pyridine, 36 h, r.t. iii = LAH, THF, 24 h, r.t. iv = *p*-TsCl, pyridine, 24 h, r.t.

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3a-Hydroxy-5b-cholan-24-oic acid methyl ester **(2):** Esterification of 3α-hydroxy-5β-cholan-24-oic acid (**1**) was performed according to the method described in the literature.[3] 3α-Hydroxy-5β-cholan-24-oic acid methyl ester (**2**) was obtained as white solid (yield: 99 %), m.p.: 115–117 °C (*lit.* m.p. 116–118 °C; IR and ^{1}H NMR; ^{13}C NMR).[2-4]

3a-Tosyloxy-5b-cholan-24-oic acid methyl ester **(3):** Tosylation of 3α-hydroxy-5β-cholan-24-oic acid methyl ester (**2**) (500 mg, 1.28 mmol) was performed following the procedure described in the literature.[5] 3α-Tosyloxy-5β-cholan-24-oic acid methyl ester (**3**) was found as white solid (588 mg, 84%), mp: 106-108 °C (*lit*. m.p. 107–109 °C; IR and ^{1}H NMR; ^{13}C NMR).[4-6]

5β-Cholan-24-ol **(4):** To a stirred suspension of LAH (348 mg, 9.2 mmol, 1:10 equiv.) in dry THF (20 ml), a solution of 3α-tosyloxy-5β-cholan-24-oic acid methyl ester (**3**) (500 mg, 0.92 mmol) in dry THF (20 ml) was added quickly under N_2. After 24 h, the mixture was treated dropwise with a saturated Na_2SO_4 solution until a white precipitate was formed. The solid was filtered off and the solution was concentrated and washed with ether to yield a white solid (307 mg). The compound was purified by VLC using 10% EtOAc in pet-ether. 5β-Cholan-24-ol (**4**) was obtained as white solid (249 mg, 78%), m.p.: 124-125 °C (*lit*. mp 127–129 °C; IR and ^{1}H NMR). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 63.7 (C-24), 56.7 (C-14), 56.3 (C-17), 43.8 (C-5), 42.8 (C-13), 40.6 (C-9), 40.4 (C-12), 37.6 (C-1), 36.0 (C-8), 35.6 (C-10), 35.4 (C-20), 31.9 (C-23), 29.5 (C-22), 28.4 (C-16), 27.6 (C-7), 27.3 (C-4), 27.1 (C-3), 26.6 (C-6), 24.3 (C-15), 24.3 (C-19), 21.4 (C-2), 20.9 (C-11), 18.7 (C-21), 12.1 (C-18).

Synthesis of 5b-cholan-24-yl chloride **(5)** *from* **4:** Tosylation of 5β-cholan-24-ol (**4**) (225 mg, 0.65 mmol) gave a white solid (214 mg). The compounds were separated by VLC using 100% pet-ether as eluent. The pure compound found to be 5β-cholan-24-yl chloride (**5**), a colourless crystal (190 mg, 80%), mp 72 °C (*lit*. m.p. 74–74.5 °C, 74.6 °C). IR

Table 1 ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data, and ^{1}H-^{13}C long-range correlation obtained from HMBC spectrum of **(5)**

No.		δ_H*	δ_C	^{1}H-^{13}C long-range correlation	
				2*J*	3*J*
1	α	1.74	37.6	C-3, C-5	b 1.68
2	α	1.34	21.4	C-1	
b		1.34			
3	α	1.74	27.1	C-4	C-5
	β	1.18			
4	α	1.72	27.3	C-3, C-5	C-6
	β	1.23			
5	β	1.27	43.8	C-4, C-6	C-9
6	α	1.20	26.6	C-5	
	β	1.86			
7	aα	1.08	27.6	C-6, C-8	C-5
	β	1.37			
8		1.39		36.0	C-10
9		1.39	40.6	C-10	
10		–	35.4		
11	α	1.39	20.9	C-10	
	β	1.24			
12	α	1.13	40.3	C-13	C-14, C-17
	β	1.92			
13		–	42.8		
14		1.07	56.7		
15	α	1.04	24.3	C-16	
	β	1.56			
16	α	1.84	28.3	C-17	C-13, C-14
	β	1.25			
17		1.09	56.2	C-13, C-20	C-12, C-21
18		0.61 s, 3H	12.1	C-13	C-12, C-14, C-17
19		0.88 s, 3H	24.3	C-10	C-1, C-5, C-9
20		1.43	35.3		
21		0.89 d, 3H (6.8)	18.7	C-20	C-17, C-22
22	α	1.85	33.3		
	β	1.68			
23	α	1.15	29.5	C-24	
	β	1.50			
24		3.46 m, 2H	45.8	C-23	C-22

*Chemical shift δ in ppm; coupling constant *J* in Hz in parentheses.

(KBr) ν_{max}/cm^{-1}: 2925s (C-H), 2850s (C-H), 1560m, 1449m, 1380m, 1310w, 1251w, 1034m, 790w and 718m (C-Cl). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR data are shown in Table 1.

Table 2 Crystal data and structure refinement

Empirical formula	$C_{24}H_{41}Cl$
Formula weight	365.02
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	*a*=7.4430(2)Å, α=90°
	b=9.8467(2)Å, β=90°
	c=29.4719(9)Å, γ=90°
Volume	2159.97(10)Å^3
Z, Calculated density	4, 1.122 Mg/m^3
Absorption coefficient	0.181 mm^{-1}
F(000)	808
Crystal size	0.46 × 0.04 × 0.02 mm
Theta range for data collection	2.93 to 27.44°
Limiting indices	–9<=*h*<=9,
	–12<=*k*<=12,
	–37<=*l*<=38
Reflections collected/unique	12689/4618(R_{int}=0.0409)
Completeness to theta = 27.44°	96.5%
Max. and min. transmission	0.9964 and 0.9212
Refinement method	Full-matrix LS on F^2
Data / restraints / parameters	4618 / 0 / 231
Goodness-of-fit on F^2	1.018
Final weighting scheme	calc w=1/[σ^2(Fo^2)+(0.051P)^2]
	where P=(Fo^2+2Fc^2)/3
Final R indices [*I*>2σ(*I*)]	R1=0.0423,wR2=0.0889
R indices (all data)	R1=0.0621,wR2=0.0964
Absolute structure parameter	–0.02(5)
Largest diff. peak and hole	0.195 and -0.232 eÅ^{-3}

X-ray crystallography

X-ray diffraction data were collected on an Enraf-Nonius Kappa CCD area-detector diffractometer. The programs DENZO[9] and COLLECT[10] were used in data collection and cell refinement. Details of crystal and structure refinement are shown in Table 2.

The structure was solved using program SIR97[11] and refined with program SHELXL-97.[12] A molecular plot was obtained with program ORTEP-3.[13] A plot of the atomic arrangement in the 5β-steroid is shown in Fig. 1.

The estimated standard deviations for geometrical parameters involving non-H atoms lie within the following ranges: bond lengths, 0.001–002 Å; valency angles, 0.1–0.2°; torsion angles, 0.1–0.3°. The C24–Cl1 bond length is 1.798(2)Å and Csp^3 – Csp^3 bond lengths range from 1.509(3) – 1.558(2) Å.

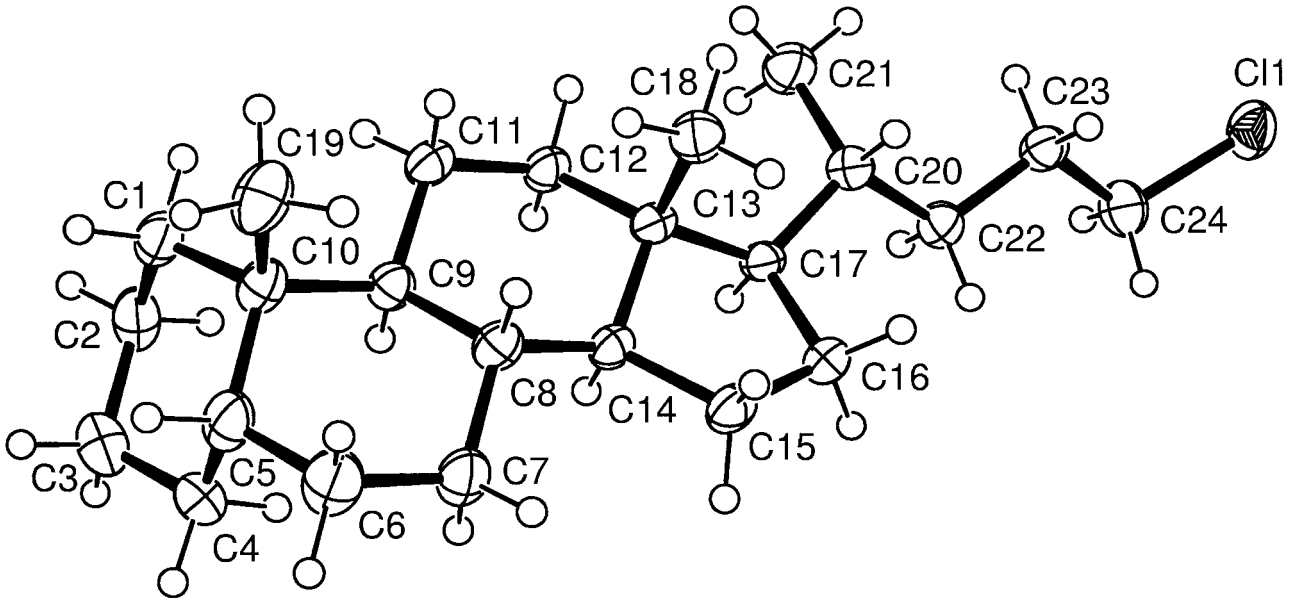

Fig.1 The atomic arrangement in 5β-cholan-24-yl chloride.

Maximum and minimum valency angle distortions are associated with the cyclopentane ring and are at C14-C13–C17 = 100.3(1)° and at C20-C17–C13 = 119.3(1)°.

The absolute stereochemistry has been determined with C5 (S), C8 (R), C9 (R), C10 (R), C13 (S), C14 (S), C17 (R) and C20 (R); ring fusions are: A/B 5β,10β; B/C 8α,9β and C/D 13β,14α. Rings A,B and C adopt chair conformations whilst ring D is twisted on C13-C14 with the best asymmetry parameter[14] ΔC_2 (C16) = 0.0267(8)°.

Full crystallographic data, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Research (S) 2001*, Issue 1. Any request to the CCDC should quote the full literature citation and the reference number 156416.

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