A User-Friendly Procedure for the Preparation of Secondary Alkyl Chlorides

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Received: 19.11.2012; Accepted: 26.11.2012

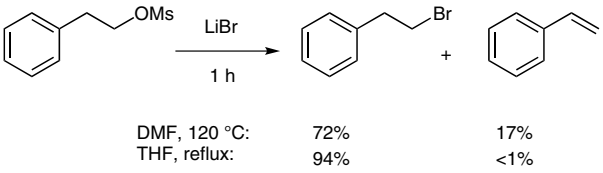
Abstract: Secondary alkyl chlorides have been efficiently prepared from secondary alkyl sulfonates under mild and user-friendly conditions. The exchange reaction was generally performed by using benzyltributylammonium chloride in acetone (reflux, 30 min). Yields are excellent from functionalized, base-sensitive and hindered secondary alkyl sulfonates.

Key words: nucleophilic substitution, sulfonates, secondary alkyl chlorides, quaternary ammonium halides, sulfonate–halogen exchange

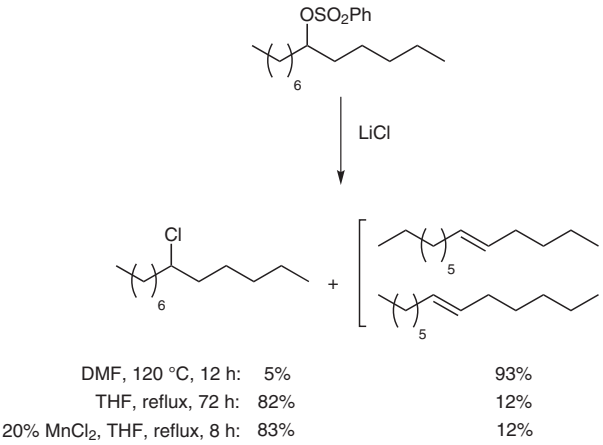
In recent years, we have reported new alkyl–alkyl, alkyl–aryl and alkyl–alkenyl coupling procedures involving the reaction of Grignard reagents with secondary alkyl halides[1] under iron[2] or cobalt[3] catalysis. To perform our research in this field, we needed an efficient large-scale preparative procedure to synthesize secondary alkyl halides. One of the classical ways to prepare alkyl halides is to convert an alcohol into the corresponding alkyl sulfonate which is then reacted with a metal halide such as LiX, MgX_2, KX or NaX (sulfonate–halogen exchange reaction).[4] These reactions, generally performed in polar solvents like acetone, DMF or DMSO, are very inexpensive and very easy to carry out; however, the synthetic scope of these procedures suffers from some limitations, particularly for preparing secondary alkyl halides and especially chlorides. Recently, we reported that the sulfonate–halide exchange reaction is advantageously achieved in tetrahydrofuran.[5] Primary alkyl iodides, bromides or chlorides can thus be prepared in excellent yields under mild conditions since the formation of elimination products is not observed, or very limited, even in the case of highly sensitive substrates such as homobenzylic sulfonates (Scheme 1).

The procedure is also efficient for preparing secondary alkyl bromides. On the other hand, the preparation of secondary alkyl chlorides is not as easy. Indeed, we showed that, in tetrahydrofuran, LiCl reacts with secondary alkyl sulfonates to give only a limited amount of olefins; however, the reaction is very slow. Fortunately, we discovered that the exchange is clearly accelerated in the presence of a catalytic amount of $MnCl_2$ (Scheme 2).

Nevertheless, the preparation of secondary alkyl chlorides could still be improved since the $MnCl_2$-catalyzed exchange reaction lasts many hours under reflux and the yields are good, but not quantitative. Moreover, in the case of base-sensitive (Table 1, entries 1 and 2) or hindered (Table 1, entry 3) secondary alkyl sulfonates, the yields are unsatisfactory.



Scheme 1



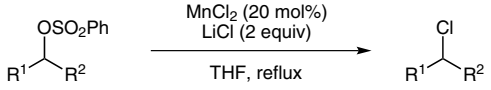
Scheme 2

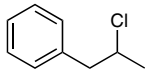
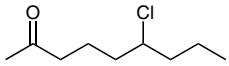
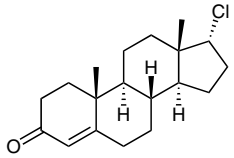
We thus decided to continue our investigations to find a faster and more efficient large-scale preparative procedure to synthesize secondary alkyl chlorides.

It is well known that the rate of nucleophilic substitution (S_N2) by a chloride anion, in a polar aprotic solvent like acetone, clearly depends on the degree of dissociation; thus, Bu_4NCl (TBACl) is more efficient than LiCl.[6] Despite this, the use of quaternary ammonium chlorides for preparing secondary alkyl chlorides has not been frequently reported. Only a few isolated examples have been described and all involve an excess of Bu_4NCl, an expensive reagent compared to LiCl.[7] We thought that quaternary ammonium chlorides could be interesting candidates to prepare secondary alkyl chlorides and we decided to start a more detailed study.

SYNTHESIS 2013, 45, 0231–0236
Advanced online publication: 19.12.2012
DOI: 10.1055/s-0032-1317927; Art ID: SS-2012-Z0894-OP

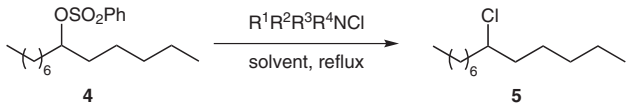
Table 1 Challenging Secondary Alkyl Chloride Targets



Entry	Product	Time (h)	Yield (%)
1	 **1**	4	60
2	 **2**	4	48
3	 **3**	48	traces

Our first results were very encouraging since the reaction of tridec-6-yl benzenesulfonate (**4**) with Bu_4NCl (2 equiv) in refluxing tetrahydrofuran afforded quantitative yields of 6-chlorotridecane (**5**) in one hour (Table 2, entry 1);[8] however, the price of Bu_4NCl limits the interest of this reaction for a large-scale preparative use. Accordingly, we tried to replace Bu_4NCl by a less expensive quaternary ammonium chloride.[7] We were able to show that

Table 2 Reaction of the Secondary Alkyl Sulfonate **4** with Quaternary Ammonium Chlorides: Influence of Various Parameters



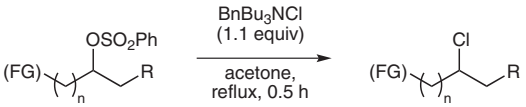
4 **5**

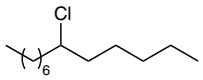
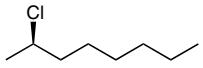
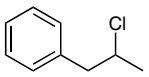
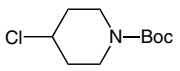
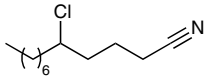
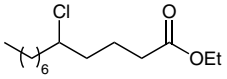
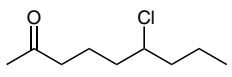
Entry	$R^1R^2R^3R^4NCl$	Solvent	Time (h)	Yield[a] (%)
1	Bu_4NCl (2 equiv)	THF	1	98
2	$BnEt_3NCl$ (2 equiv)	THF	20	99
3	$BnBu_3NCl$ (2 equiv)	THF	1	99
4	$BnBu_3NCl$ (2 equiv)	THF	72[b]	99
5	$BnBu_3NCl$ (1.1 equiv)	THF	1	94
6	$BnEt_3NCl$ (2 equiv)	acetone[c]	2	97
7	$BnBu_3NCl$ (2 equiv)	acetone[c]	0.5	97
8	$BnBu_3NCl$ (1.1 equiv)	acetone[c]	0.5	97
9	py·HCl (2 equiv)	acetone[c]	1	22[d]
10	Me_2NH·HCl (2 equiv)	acetone[c]	1	7[d]
11	NH_4Cl (2 equiv)	acetone[c]	1	traces

[a] GC yield using decane as an internal standard.
[b] Reaction was performed at room temperature.
[c] Technical grade acetone (up to 2% H_2O) was used.
[d] Reaction mainly gives elimination products.

$BnEt_3NCl$, an industrial product which is 10 times less expensive than Bu_4NCl and available on a large scale, also afforded a quantitative yield of **5** under similar reaction conditions (Table 2, entry 2); however, the reaction was slower (20 h instead of 1 h) as $BnEt_3NCl$ is not very soluble in tetrahydrofuran. This can be circumvented by using $BnBu_3NCl$ which is slightly more expensive but also more soluble; a quantitative yield of **5** was then obtained in one hour (Table 2, entry 3). The reaction can even be performed at room temperature, however, in this case, a reaction time of 72 hours is required (Table 2, entry 4). Interestingly, excellent results were obtained when only 1.1 equivalents of $BnBu_3NCl$ was used (Table 2, entry 5). It should be emphasized that $BnBu_3NCl$ is more user-friendly than lithium halides[6] since it is much less hygroscopic.

Table 3 Scope of the Reaction



Entry	Product	Yield[a] (%)
1	 **6**	97
2	 **5**	96
3	 **7**	92[b]
4	 **1**	82
5	 **8**	89
6	 **9**	99
7	 **10**	88
8	 **2**	92

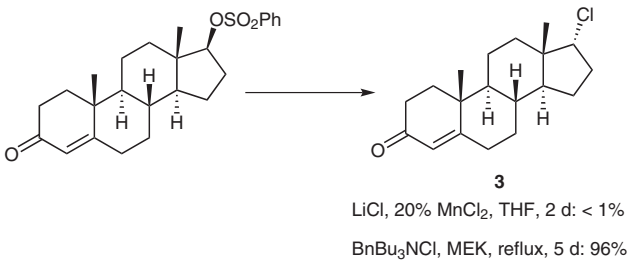
[a] Isolated yield.
[b] From the sulfonate of (*S*)-(+)-octan-2-ol; (*R*)-**7**: $[\alpha]_D^{20}$ –37.4 (neat) [Lit.[10] $[\alpha]_D^{20}$ –37.3 (neat)].

The reaction can also be performed successfully in acetone (Table 2, entries 6 and 7), since the formation of elimination products was not observed.[9] The yields are similar to those obtained in tetrahydrofuran but, interestingly, the reaction is much faster (10 times faster in the case of $BnEt_3NCl$; Table 2, entry 6). It should be emphasized that anhydrous acetone is not required to perform the reaction. Excellent results were achieved by using commercial technical grade acetone ($H_2O \leq 2\%$). This is interesting for a large-scale procedure since this solvent is less expensive than tetrahydrofuran. Finally, some attempts of this reaction with various amine hydrochlorides led to failure (Table 2, entries 9–11).

In the light of these promising results, we decided to study the scope of the reaction. The results presented in Table 3 show that many functional groups (FG), a Boc-protected amine, a nitrile, an ester or a ketone, are tolerated under our reaction conditions (Table 3, entries 5–8). Excellent yields were also obtained from challenging base-sensitive sulfonates (Table 3, entries 4 and 8; cf. Table 1, entries 1 and 2). Noteworthy, as in the case of the manganese-catalyzed reaction,[5] the reaction proceeds with complete inversion of configuration (Table 3, entry 3). It should be noted that the crude product is generally pure enough to be used directly for further synthetic uses.

As expected, the procedure described herein is superior to the $MnCl_2$-catalyzed procedure for the challenging preparation of 17α-chloroandrost-4-en-3-one (**3**) from the corresponding hindered 17β-sulfonate (Scheme 3).

We have also tried to prepare 3α-chlorocholest-5-ene (**12**) from the 3β-sulfonate **11**. It is challenging[11] since it has been described that, according to the conditions, the sulfonate–chloride exchange reaction gives either the 3β-chlorocholest-5-ene epimer in good yield according to an

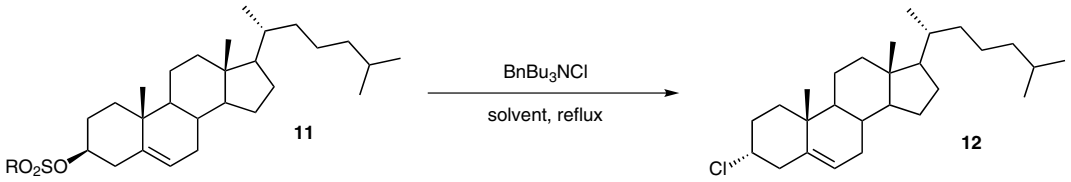


Scheme 3 Synthesis of 17α-chloroandrost-4-en-3-one

S_N1 substitution (94%; LiCl, MeCN, reflux) or the 3α-epimer **12** (S_N2 substitution) but only in moderate yield (42%; Bu_4NCl, TMU, acetone).[11c] Thus, it should be noted that the synthesis of **12** generally involves multistep procedures.[12] Under our conditions and after complete consumption of the 3β-tosylate derivative **11** (R = 4-Tol), we obtained only 57% yield of **12** contaminated with large amounts of elimination products (Table 4, entry 1).

In methyl ethyl ketone, it is possible to operate at a higher temperature and the reaction is faster, but the yield was not improved (Table 4, entry 2). It is commonly accepted that mesylate derivatives are slightly more reactive than the corresponding tosylates;[13] accordingly, we decided to use the 3β-mesylate **11** (R = Me). Our first attempt, in methyl ethyl ketone at reflux, mainly led to elimination products (Table 4, entry 4). As it is well established that polar solvents can favor elimination reactions,[14] we then tried to perform the reaction in toluene in place of acetone. To our delight, the reaction proceeded with an excellent yield in only two hours (Table 4, entry 5). Noteworthy, only two equivalents of $BnBu_3NCl$ are enough to perform the reaction efficiently (Table 4, entry 6).

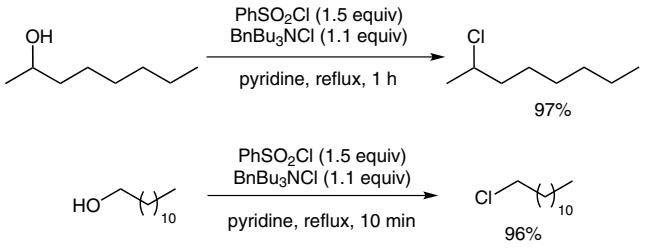
Table 4 Synthesis of 3α-Chlorocholest-5-ene



Entry	R	$BnBu_3NCl$ (equiv)	Solvent[b]	Time (h)	Yield[a] (%)
1	4-Tol	10	acetone	24	57
2	4-Tol	10	MEK	1	53
3	4-Tol	5	MEK	2	52
4	Me	5	MEK	6	39
5	Me	5	toluene	2	95
6	Me	2	toluene	4	89

[a] NMR yield using 1,3,5-trimethoxybenzene as an internal standard.
[b] MEK = methyl ethyl ketone.

In conclusion, we have described herein a fast and efficient method to prepare secondary alkyl chlorides from the corresponding sulfonate derivatives and $BnBu_3NCl$. To the best of our knowledge, this is the first use of $BnBu_3NCl$ for this purpose. Functionalized or hindered alkyl sulfonates afford excellent yields. This method is especially interesting for preparative purposes since high yields can be obtained by using commercial non-anhydrous acetone and inexpensive $BnBu_3NCl$. Moreover, the latter can be used and stored without special precautions, in contrast to the very hygroscopic lithium halides. It should be emphasized that, in simple cases, it is possible to synthesize the alkyl chloride in high yield directly from the corresponding primary or secondary alkanol in a one-pot reaction (Scheme 4).



Scheme 4 One-pot procedure

We are confident that this method is a reliable and economical large-scale preparative procedure for the synthesis of secondary alkyl chlorides.

LiCl and LiBr were purchased from Acros and were dried for 8 h at 150 °C under vacuum. Anhydrous THF (H_2O <5 ppm) was directly obtained from a commercial source and stored under a nitrogen atmosphere. All other solvents (analytical grade) were used without further purification. All reactions were carried out with mechanical stirring under a nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, with a Jeol ECX-400 NMR spectrometer using $CDCl_3$ as a solvent. Mass spectra were recorded on a Hewlett Packard HP 5973 mass spectrometer via GC/MS coupling with a Hewlett Packard HP 6890 gas chromatograph equipped with a capillary column (HP-5MS, 50 m × 0.25 mm × 0.25 μm). Ionization was performed by electron impact (EI, 70 eV). Yields refer to isolated compounds; purity was >96%, as determined by GC analysis (Hewlett Packard HP 6890 gas chromatograph equipped with a HP-5 column). The analytical data for all compounds match the literature data.

Tridec-6-yl Benzenesulfonate (4); Typical Procedure
Tridecan-6-ol (2 g, 10 mmol) and CH_2Cl_2 (10 mL) were introduced into a 100-mL flask. Pyridine (1.58 g, 20 mmol) was added at r.t., then benzenesulfonyl chloride (2.65 g, 15 mmol) was added at 0 °C and the reaction mixture was stirred at r.t. for 24 h. The reaction mixture was quenched with H_2O (20 mL) and the organic layer was washed with 1 M HCl soln (20 mL), sat. Na_2CO_3 soln (20 mL) and finally with H_2O (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography on a silica gel column (cyclohexane–EtOAc, 95:5) to give **4** as a yellowish oil; yield: 3.17 g (93%).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04–8.00 (m, 2 H), 7.76–7.60 (m, 3 H), 4.72–4.63 (m, 1 H), 1.68–1.62 (m, 4 H), 1.37–1.27 (m, 16 H), 0.99–0.90 (m, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6, 133.26, 128.9, 127.5, 84.8, 34.0, 31.5, 31.3, 29.1, 28.9, 24.6, 24.2, 22.5, 22.3, 13.9, 13.8.

Sulfonate–Halide Exchange Reaction (Tables 2 and 3); General Procedure
Solvent (5 mL), an alkyl sulfonate (5 mmol) and a tertiary ammonium halide (5.5 mmol, 1.1 equiv) were introduced into a 20-mL flask under a nitrogen atmosphere and the reaction mixture was refluxed for 0.5 h. Then, the reaction was quenched with H_2O (20 mL) and the product was extracted with petroleum ether (2 × 40 mL). The combined extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure; the product was distilled or purified by chromatography on a silica gel column.

One-Pot Reaction (Scheme 4); General Procedure
Pyridine (5 mL), an alkanol (5 mmol), benzenesulfonyl chloride (7.5 mmol) and $BnBu_3NCl$ (5 mmol, 1.1 equiv) were introduced into a 20-mL flask under a nitrogen atmosphere and the reaction mixture was refluxed for the specified time. Then, the reaction was quenched with H_2O (20 mL) and the product was extracted with petroleum ether (2 × 40 mL). The combined extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure; the product was distilled or purified by chromatography on a silica gel column.

(2-Chloropropyl)benzene (1)
Solvents were distilled under atmospheric pressure, then the trace solvents were carefully eliminated by evaporation under 8 mmHg (purity of the crude product ≥ 97% by GC); yield: 634 mg (82%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.10 (m, 5 H), 4.19 (sept, *J* = 6.7 Hz, 1 H), 3.05 (dd, *J* = 13.9, 7.0 Hz, 1 H), 2.93 (dd, *J* = 13.9, 6.9 Hz, 1 H), 1.51–1.40 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 129.7 (2 C), 128.7 (2 C), 127.1, 58.8, 47.0, 25.0.

6-Chlorononan-2-one (2)
Purification by chromatography on silica gel (PE–EtOAc, 96:4); yield: 856 mg (92%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.97–3.84 (m, 1 H), 2.46 (td, *J* = 6.8, 1.7 Hz, 2 H), 2.14 (s, 3 H), 1.90–1.33 (m, 8 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.6, 63.5, 43.1, 40.6, 37.9, 30.0, 20.9, 19.8, 13.7.

HRMS (ESI): *m*/*z* calcd for $C_9H_{17}ClO$: 176.0968; found: 176.0966.

17α-Chloroandrost-4-en-3-one (3)
Purification by chromatography on silica gel (PE–CH_2Cl_2–EtOAc, 7:1:2); yield: 1.472 g (96%); white solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.73 (d, *J* = 1.7 Hz, 1 H), 4.10–4.03 (m, 1 H), 2.52–2.20 (m, 5 H), 2.09–0.91 (m, 14 H), 1.45 (s, 3 H), 0.84 (d, *J* = 0.5 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.6, 171.1, 124.1, 70.9, 53.3, 47.9, 46.2, 38.7, 36.1, 35.8, 34.3, 34.1, 33.6, 32.9, 32.3, 24.7, 20.9, 18.0, 17.6.

6-Chlorotridecane (5)
Purification by distillation (bp 124 °C/2 mmHg); yield: 1.050 g (96%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.95–3.83 (m, 1 H), 1.78–1.62 (m, 4 H), 1.59–1.46 (m, 2 H), 1.46–1.20 (m, 14 H), 0.88 (t, *J* = 6.6 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 64.6, 38.7, 31.9, 29.0, 26.6, 22.7, 14.2.

2-Chlorotridecane (6)
Solvents were carefully evaporated under 20 mmHg (purity ≥ 97% by GC); yield: 1.061 g (97%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88–3.75 (m, 1 H), 1.86–1.58 (m, 4 H), 1.52–1.33 (m, 2 H), 1.33–1.18 (m, 14 H), 1.01 (t, *J* = 7.3 Hz, 3 H), 0.92–0.80 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 66.1, 38.3, 32.1, 31.6, 29.8, 29.7, 29.7, 29.5, 29.4, 26.7, 22.8, 14.3, 11.1.

(*R*)-2-Chlorooctane (7)
Due to high volatility of the product, the solvent was carefully evaporated under 150 mmHg; yield: 683 mg (92%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.04 (sept, *J* = 6.5 Hz, 1 H), 1.79–1.62 (m, 2 H), 1.51 (d, *J* = 6.5 Hz, 3 H), 1.44–1.22 (m, 8 H), 0.96–0.86 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 59.1, 40.5, 31.9, 28.9, 26.8, 25.5, 22.7, 14.2.

***tert*-Butyl 4-Chloropiperidine-1-carboxylate (8)**
Purification by chromatography on silica gel (PE–EtOAc, 98:2); yield: 977 mg (89%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (tt, *J* = 7.6, 3.7 Hz, 1 H), 3.69 (ddd, *J* = 13.2, 7.2, 3.7 Hz, 2 H), 3.28 (ddd, *J* = 13.6, 7.7, 3.6 Hz, 2 H), 2.07–1.95 (m, 2 H), 1.79 (ddt, *J* = 15.7, 11.7, 5.6 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.7, 79.9, 57.1, 35.0, 28.6, 9.2.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}ClNO_2$: 219.1026; found: 219.1022.

5-Chlorododecanenitrile (9)
Purification by chromatography on silica gel (PE–EtOAc, 98:2); yield: 1.068 g (99%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96–3.83 (m, 1 H), 2.40 (t, *J* = 6.3 Hz, 2 H), 2.06–1.64 (m, 6 H), 1.60–1.18 (m, 10 H), 0.88 (sept, *J* = 4.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 119.4, 62.8, 38.7, 37.2, 31.9, 29.3, 29.2, 26.6, 22.8, 22.6, 16.9, 14.2.

Ethyl 5-Chlorododecanoate (10)
Purification by chromatography on silica gel (PE–EtOAc, 98:2); yield: 1.156 g (88%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.1 Hz, 2 H), 3.89 (dq, *J* = 5.4, 2.4 Hz, 1 H), 2.32 (t, *J* = 6.8 Hz, 2 H), 1.93–1.63 (m, 6 H), 1.57–1.35 (m, 2 H), 1.35–1.20 (m, 11 H), 0.91–0.84 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.5, 63.7, 60.5, 38.6, 37.8, 33.8, 31.9, 29.3, 29.2, 26.6, 22.8, 22.1, 14.4, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{27}ClO_2$: 262.1700; found: 262.1705.

3α-Chlorocholest-5-ene (12)
Purification by chromatography on silica gel (PE); yield: 1.944 g (95%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.42–5.33 (m, 1 H), 4.53–4.41 (m, 1 H), 2.87–2.66 (m, 1 H), 2.27 (dt, *J* = 15.2, 2.5 Hz, 1 H), 2.06–1.79 (m, 5 H), 1.70–1.00 (m, 21 H), 1.00 (s, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.87 (dd, *J* = 6.6, 1.9 Hz, 6 H), 0.68 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.5, 123.7, 60.7, 56.8, 56.3, 49.9, 42.5, 40.5, 39.9, 39.7, 37.1, 36.3, 36.0, 33.1, 31.9, 31.9, 30.1, 28.4, 28.2, 24.4, 24.0, 23.0, 22.7, 20.9, 19.3, 18.9, 12.0.

Acknowledgment

The authors thank the CNRS for financial support and the Ministère de l'Education Nationale et de la Recherche for financial support and a grant to M.P.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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