Remote functionalization by tandem radical chain reactions

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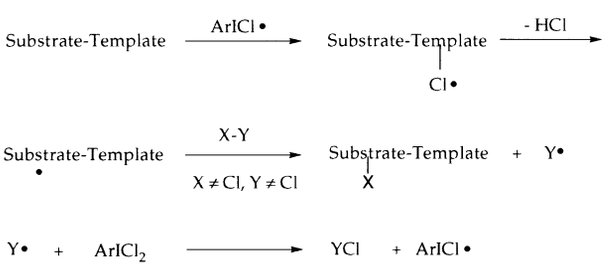
Normal radical relay chlorination of cholestan-3α-ol directed by an attached *m*-iodobenzoate ester group affords a 9α-chloro steroid, but when the same reaction is conducted in the presence of an excess of CBr_4 the product is a 9α-bromo steroid. Similarly, when the same radical relay reaction is carried out in the presence of an excess of $(SCN)_2$ rather than CBr_4, the product is a 9α-thiocyano steroid. Several other examples of these reactions have been developed. These tandem remote functionalization reactions succeed because an intramolecular hydrogen abstraction by a complexed-chlorine atom generates a specific substrate radical in each case.

Some years ago the remote radical chlorination of steroids and of linear alkanols directed by attached templates was described.[1] These template-directed reactions differed from those of the traditional synthetic style as geometric constraints, rather than just intrinsic chemical reactivity, were a dominant factor in product formation. Furthermore, without template control a low yield of a complex product mixture would have resulted in each case. The novel steroid products were also of potential medicinal interest and would be difficult to prepare by the traditional synthetic approach. Therefore, it was of interest to generalize the remote chlorination chemistry to other functional groups. Recently the extension of this chemistry to the formation of carbon–bromine and carbon–sulfur bonds by tandem radical chain reactions on one substrate was communicated.[2] This report describes how general the latter reactions were with more of the previously developed[1] radical relay systems.

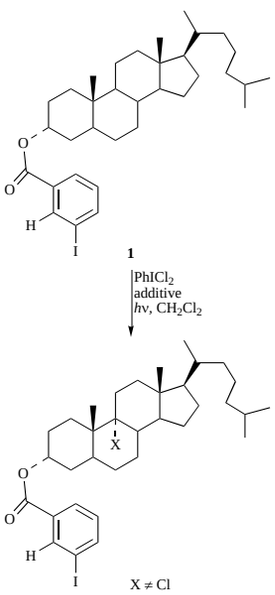
Results and discussion

A general strategy for introducing remote functional groups other than chlorine has been developed (Scheme 1). The template-complexed chlorine atom would be produced as in normal remote radical chlorination chemistry. In the first radical chain propagation step, an intramolecular HCl elimination reaction would take place. In the second step, an additive X–Y (X,Y ≠ Cl) would react with the substrate radical to give the functionalized product as well as a free radical that was capable of propagating the chain reaction. Implicit in this strategy was the necessity to identify additives which reacted with the substrate radical at a rate similar to that at which the chlorine sources did. This strategy towards remote functionalization was of the tandem type; one reagent was responsible for substrate radical formation, while a second was responsible for the substrate radical functionalization.



Scheme 1

The initial substrate chosen to test the tandem strategy was cholestan-3α-yl *m*-iodobenzoate **1** (Scheme 2). This ester was



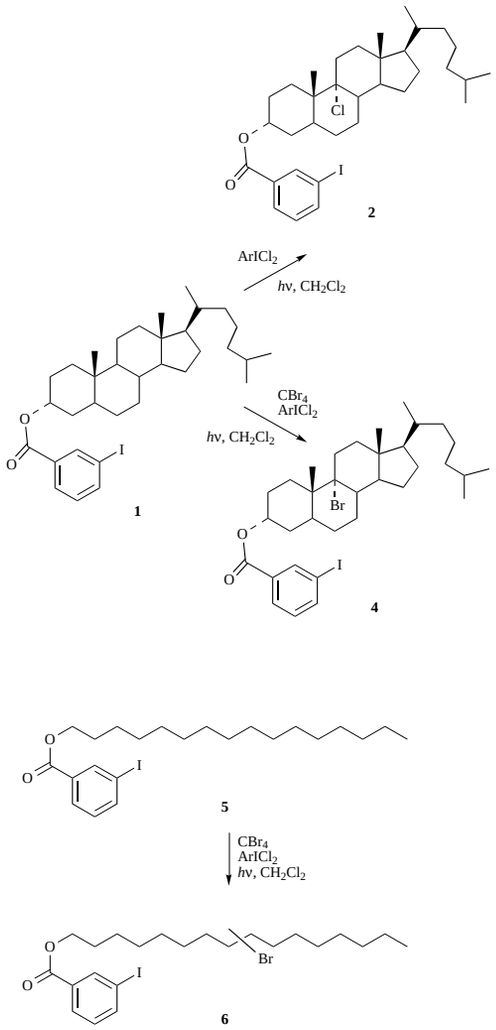
Scheme 2

reported to afford 9α-chloride **2** upon reaction with phenyliodine dichloride (PID) under radical relay conditions (Scheme 3).[3] Chloride **2** was found to be a robust material at room temperature and treatment with base or Ag^+ was necessary to effect elimination.[3] The initial additive tried in the tandem scheme was Br_2, since this material has long been known to react with alkyl radicals to produce alkyl bromides (Scheme 1).[4] However, photolysis of 2 equiv. of Br_2 along with 1 equiv. of PID and 1 equiv. of ester **1** in CH_2Cl_2 led only to the 9-chloride **2** (20%) and recovered starting material **1** (80%). Increasing the number of equivalents of Br_2 led to even lower conversions into products.

A possible explanation was that the second radical chain propagation step (X, Y = Br in Scheme 1) was operational to some extent, as envisioned, but that the formed bromine radical then failed to propagate the chain.

Remote bromination

$CBrCl_3$ and CBr_4[5,6] have been reported to brominate various hydrocarbons *via* a free radical mechanism. Elevated temperatures have occasionally been used for these reactions, but the radical chain propagation step that involved bromine abstraction from $CBrCl_3$ by an alkyl radical appeared to be exothermic



Scheme 3

and facile.[7] This seemed likely to be true for CBr_4 also. Thus, it seemed possible that the second chain propagation step might be competitive with the normal substrate radical reaction with the chlorine source if either of these reagents were used as X–Y in Scheme 1. With either of these reagents, the third propagation step in Scheme 1 would also be facile based on known reactions and reported bond strengths.[8,9] The work described below focused arbitrarily on the use of CBr_4 as an additive to the remote radical reaction rather than $CBrCl_3$.

Photolysis of 2 equiv. of CBr_4 with 1 equiv. of PID and 1 equiv. of ester **1** led to a significant conversion into products. A new product was assigned by ^{1}H NMR spectroscopy to be the desired 9-bromide **4** (Scheme 3) and the isolated reaction mixture consisted mainly of the bromide and corresponding olefin formed upon HBr elimination. Integration of the 18-methyl and aromatic regions[10] gave estimates of the amounts of the new material **4** (20%), the $\Delta^{9(11)}$ olefin **3** (25%), the 9-chloride **2** (25%) and **1** (30%).

The bromide **4** decomposed to olefin **3** with gentle warming and even when kept at room temperature. This elimination

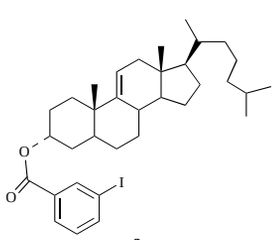


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Table 1 Functionalization of cholestan-3α-yl *m*-iodobenzoate **1** with NPID and added CBr_4[a]

CBr_4 equiv.	NPID equiv.	Product distribution (%)[b,c] 9α-Br	$\Delta^{9(11)}$	9α-Cl	SM*	9α-Br+$\Delta^{9(11)}$
5	—	—	—	—	100	—
—	1.00	—	—	88	12	—
—	1.50	—	—	>90	—	—
—	1.50	—	—	86[d]	—	—
2	1.25	31	15	32	22	46
4	1.25	35	27	17	21	62
6	1.30	20	48	16	16	68
8	1.30	21	47	11	21	68
10	1.10	40	19	9	32	59
20	1.10	51	14	3	32	65
10	1.50	26	49	15	10	75
20	1.50	32	49	7	12	81
20[e]	1.50	58	19	7	16	77
10	1.75	17	56	14	13	73
20	1.75	25	52	9	14	77

* SM = Starting material. [a] [**1**] = 12.5 mM; all reactions were conducted in CH_2Cl_2 at room temperature under purified nitrogen with sunlamp photolysis for 15–20 min. Complete consumption of the oxidant was always confirmed at the end of the photolysis with KI–starch test paper. [b] Analysed by ^{1}H NMR spectroscopy of the crude product mixture. [c] Abbreviations used in this table: 9α-Br = 9α-Br **4**, $\Delta^{9(11)} = \Delta^{9(11)}$ **3**, 9α-Cl = 9α-Cl **2**, SM = **1**. [d] Isolated yield after silica chromatography. [e] Reaction conditions as before except [**1**] = 5 mM and irradiation time = 30 min.

product indicated that the initial functionalization was at C-9. The initial amount of olefin **3** detected was the result of HBr elimination which resulted from the work-up and delay before analysis. Photolysis of ester **1** with 5 equiv. of CBr_4 but no chlorine source, under radical relay conditions as above, led to no functionalization of the steroid. These observations supported the tandem sequence outlined in Scheme 1 with PID as the chlorine source and Br–CBr_3 as X–Y.

In the bromination of ester **1** with PID and CBr_4, a lower conversion into products was observed than in the normal radical relay chlorination reaction. The low conversions noted when Br_2 was an additive were rationalized as a failure of radical chain propagation step three in Scheme 1. It seemed possible that the lower than expected conversion in the CBr_4 reaction could also have been due to some sluggishness in this step and so a different chlorine source was used.

p-Nitrophenyliodine dichloride (NPID)[11,12] led to the normal chlorination product of **1** in the absence of any special additive. When this reagent was substituted for PID in the bromination reaction, a higher conversion into products was observed. It was not certain whether the increased conversion was entirely fortuitous or if the above rationalization about radical chain propagation step three was correct. The apparent usefulness of introducing bromine as opposed to chlorine at C-9 was to provide a milder entry to the $\Delta^{9(11)}$ olefin. Accordingly, no precautions were taken to try to optimize the yield of the bromide **4** itself when the stoichiometry of the reagents was varied (Table 1). The best yield, >75% of bromide **4** plus olefin **3**, was obtained when 20 equiv. of CBr_4 were used along with 1.5 equiv. of NPID (5 mM steroid).

The isolated yield for the bromination reaction was found to be in reasonable agreement with the ^{1}H NMR yield. For example, when the amount of material from bromination had been estimated to be 76% the actual yield, after processing steps, was found to be 68%.

It has been previously demonstrated that templates could direct chlorination at secondary centres on long alkyl chains.[10e,13] Although mixtures of products were produced due to the flexibility of the long alkyl chains, these reactions were demonstrated to be template driven. In the ^{1}H NMR spectrum of such a chlorination, a broad resonance at δ 3.80–3.95 due to

the methine protons α to the chloride was observed. The yield was estimated by comparison of the integration of this broad resonance with that of the methylene group α to the ester.[10e,13]

Since it was known that secondary bromides were considerably more stable than tertiary, one of the previously described[10e,13] long alkyl chain iodobenzoate esters was studied under the conditions used to brominate **1**. Photolysis of hexadecyl *m*-iodobenzoate **5** with 2.5 equiv. of NPID and 10 equiv. of CBr_4 (Scheme 3) produced a new compound as shown by ^{1}H NMR spectroscopy; a resonance at δ 3.80–3.95 was barely visible and instead a broad resonance at δ 3.95–4.10 was observed. Integration of this resonance and comparison with that of the methylene group α to the ester indicated a 65% yield of the new product(s). However, the new product(s) could not be separated by silica gel chromatography from residual 1-iodo-4-nitrobenzene which was also produced in the reaction.

Therefore, the reaction was repeated with PID as the chlorine source. The predominant product was again that with a resonance at δ 3.95–4.10. The crude yield was estimated to be 40% and the product(s) were isolated by silica gel chromatography in 23% yield. Mass spectrometry (MS) indicated the product(s) were the monobromide(s) **6**.

Formation of the isolable bromide(s) **6** under the identical conditions used for reaction of compound **1** with NPID supported the assignment of unstable **4** as a bromide. Furthermore, since the same template complexed chlorine atom is responsible for substrate radical formation in both the chlorination and bromination of **5**, the latter reaction was template driven by analogy with the former.[10e,13]

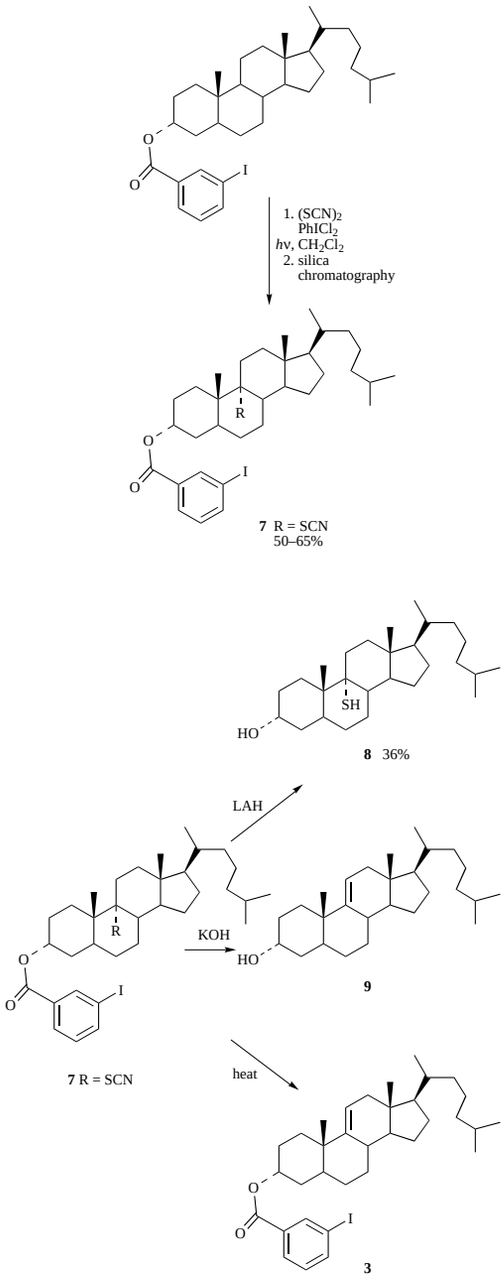
Remote thiocyanation

Thiocyanogen, $(SCN)_2$, has been used to functionalize carbons with activated hydrogens, such as benzylic carbons, *via* a free-radical mechanism to give thiocyanates.[14] Therefore, the reaction of ester **1** (5 mM) with 1.4 equiv. of PID and 5.7 equiv. of $(SCN)_2$ in CH_2Cl_2 was conducted under radical relay conditions. The $(SCN)_2$ was prepared by the oxidation of $Pb(SCN)_2$ with Br_2.[14,15]

Analysis by ^{1}H NMR spectroscopy and thin layer chromatography (TLC) revealed a new steroid as the major reaction product. Integration indicated that the reaction mixture contained 68% of the new compound **7** along with 32% of a 2:1 mixture of normal 9-chloride **2** and unfunctionalized material **1**. The new compound **7** was isolated in 56% yield by silica gel chromatography. When the same reaction was repeated, except with 11.4 equiv. of $(SCN)_2$, the isolated yield of the new material **7** increased to 64%. Mass spectral analysis was consistent with **7** being a thiocyanate or isothiocyanate.

The ^{13}C NMR spectrum had one more line than that of the starting material **1**. Examination in the region where thiocyanates and isothiocyanates resonate showed a line at δ 113.4 which indicated **7** was a thiocyanate.[16] The IR spectrum also indicated that **7** was a thiocyanate as an absorbance was observed at 2137 cm^{-1}.[14,16] As reductions of thiocyanates have been reported to yield thiols whereas those of isothiocyanates yield amines,[14] **7** was reduced with lithium aluminium hydride (LAH) in tetrahydrofuran (THF). The major steroidal product from the reduction was isolated by silica gel chromatography and MS analysis was consistent with thiol **8** (Scheme 4). The reduction reaction provided further evidence in favour of the assignment of **7** as a thiocyanate.

Thiocyanate **7** was stable at room temperature. However, concentration of solutions of this material had to be carried out without heating or the $\Delta^{9(11)}$ olefin **3** was formed. Treatment of the *purified thiocyanate* **7** with a hot KOH solution led to $\Delta^{9(11)}$ olefin **9**. These observations were consistent with the known reactivity of thiocyanates.[14] The formation of this olefin also confirmed that the thiocyanate was located at C-9. Therefore, the major product of the $(SCN)_2$/PID reaction was 9α-thiocyanocholestan-3α-yl *m*-iodobenzoate **7** (Scheme 4).



Scheme 4

When ester **1** was photolysed with $(SCN)_2$ under radical relay conditions in the absence of a chlorinating reagent, no functionalization of the steroid took place. These observations taken together supported the tandem reaction sequence outlined in Scheme 1 with PID as the chlorine source and $(SCN)_2$ as X–Y.

Similar results were obtained in the reaction with **1** when PID itself was used to oxidize the $Pb(SCN)_2$ salt.[17] However, generation of $(SCN)_2$ solutions with Br_2 was preferable to the use of PID for these reactions. Br_2 acted as a colour indicator for when the $(SCN)_2$ solution was ready. If the $(SCN)_2$ solution had not decolourised (*i.e.* if the colour of Br_2 was still evident), then the thiocyanation led to only low conversions into products. This is consistent with the inhibitory effect that Br_2 has as an additive. On the other hand, some difficulty was experienced when PID was used as the oxidant of the $Pb(SCN)_2$, since it was not trivial to know when $(SCN)_2$ generation was complete. When $(SCN)_2$ generation had not gone to completion, extensive multiple functionalization of the steroid occurred.

It has been reported that $(SCN)_2$ reacts sluggishly with PID to give ClSCN and iodobenzene in $CHCl_3$.[18] Therefore, an NMR experiment was conducted to determine if these compounds

reacted under the conditions used to functionalize **1**. PID (1 equiv., *ca*. 40 mM) was added to 6 equiv. of $(SCN)_2$ in CD_2Cl_2. The ^{1}H NMR spectrum of the resulting solution was monitored for PID disappearance and iodobenzene formation. After 30 min, >95% of the PID (relative to iodobenzene) was still present. A second spectrum was taken 30 min later which indicated >90% of the PID was still present. The amount of PID did not change markedly after an additional 30 min. Similar results were obtained in $CDCl_3$ solution. These results indicated that a direct reaction between the tandem partners was probably not important under the reaction conditions used in the thiocyanation, which is consistent with the proposed mechanism.

Steroids with templates that led to functionalization at positions other than C-9 were also subjected to thiocyanation, due to interest in the remote introduction of non-halogen functionality. The template-directed chlorination at C-17 with cholestan-3α-yl 4′-iodobiphenyl-3-carboxylate **10** has been extensively studied (Scheme 5).[3,10a,10c,20–22] In the original studies,[3,10a,20] the solvent of choice for chlorination of ester **10** was CCl_4 (37% chlorination) rather than CH_2Cl_2 (15% chlorination). Consistent with the literature reports, reaction of **10** with 1.5 equiv. of PID in CCl_4 led to a 30–40% crude yield of 17-chloride **11** as estimated by ^{1}H NMR spectroscopy. A repeat of the reaction in the presence of 9 equiv. of $(SCN)_2$, followed by silica gel chromatography, led to a new product **12** in 41% yield.

The mass, IR and ^{13}C NMR spectra of **12** all indicated that it was a monothiocyanate. Reduction of this new compound **12** with LAH in THF afforded a product that gave a MS consistent with thiol **13** (Scheme 5). The reduction product supported the assignment of **12** as a thiocyanate.

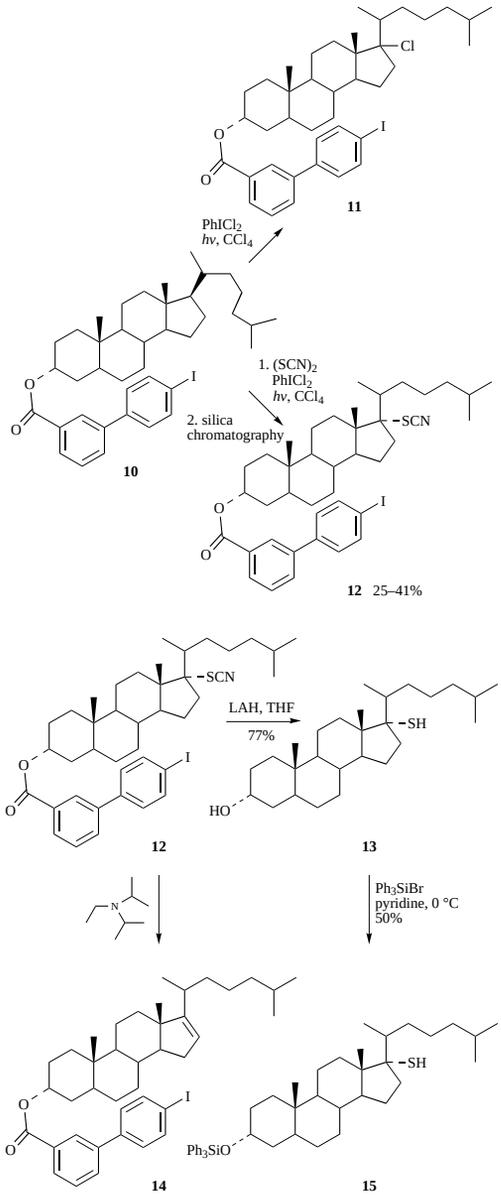
Treatment of the 17-thiocyanate **12** with *N*,*N*-diisopropylethylamine in refluxing dioxane or heating it in $CDCl_3$ without base led to the endocyclic Δ^{16} olefin **14**. Therefore the location of the thiocyanate was at C-17 and **12** was 17-thiocyanocholestan-3α-yl 4′-iodobiphenyl-3-carboxylate (Scheme 5).

In principle, the side chain could have epimerized during the radical reaction and so the stereochemistry of **12** was not known. From the ^{13}C NMR spectrum, it was clear that only one epimer was present. Crystals suitable for an X-ray diffraction study were obtained with the triphenylsilyl ether derivative **15** of thiol **13** (Scheme 5). The crystal structure (Fig. 1) showed that the sulfur was α for ether **15** and, by analogy, the stereochemistry of **12** and **13** was the same. Also by analogy the normal chloride product **11** was α. In principle, knowing the stereochemistry of the chloride should facilitate a molecular modelling study of the elimination which could lead to a better understanding of the partitioning between the possible endocyclic and exocyclic olefins.

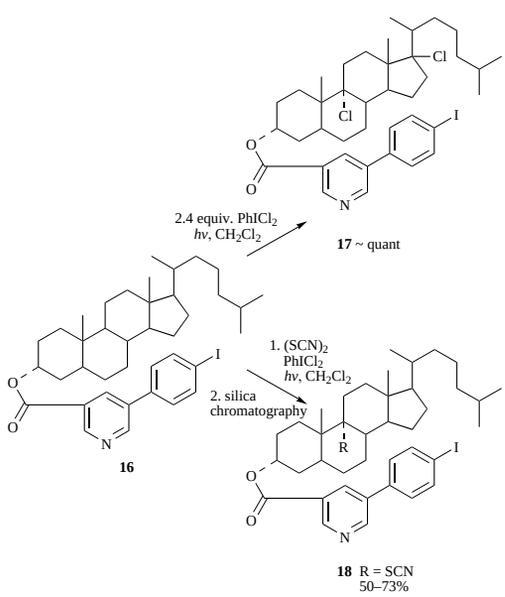
Cholestan-3α-yl 5-(4-iodophenyl) nicotinate **16** has been reported to yield the 9,17-dichloro derivative **17** under normal radical relay chlorination conditions (Scheme 6).[23] By analogy to **11**, it seemed likely that the chloride at C-17 was α; however, it was shown that the C-9 position was functionalized first in this case[23] and that could have affected the radical that was formed later at C-17.

Consistent with the literature report,[23] treatment of the mixed iodophenyl nicotinate ester with 2.4 equiv. of PID led to a roughly quantitative yield of the dichloride **17**. However, when this reaction was repeated in the presence of 23 equiv. of $(SCN)_2$, a major product was isolated in 73% yield which bore a striking resemblance to the previously prepared 9-thiocyanate **7**; the main difference in the ^{1}H NMR spectrum was in the aromatic (*i.e.* template) region. The mass, IR, and ^{13}C NMR spectra all indicated monothiocyanation. Heating, or treatment with KOH, led to the $\Delta^{9(11)}$ olefin. Hence, with the mixed bifunctional steroid ester **16**, the major product formed in the thiocyanation was 9-thiocyanate **18** (Scheme 6).

One explanation for these results is that the bulky thiocyanate group of **18** blocked further template-induced attack at C-17. That initial attack is at C-9 was consistent with the earlier



Scheme 5



Scheme 6

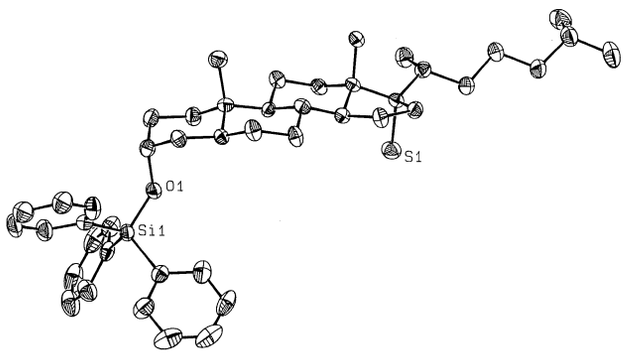
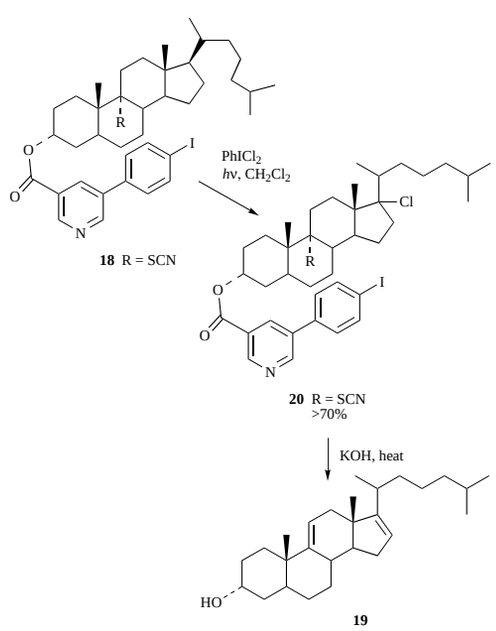


Fig. 1 Crystallographic structure of **15**. X-ray data were collected on a Siemens P4 diffractometer with Mo-Kα radiation at 158 K and the structure solved by direct methods. Crystal data: colourless plates, monoclinic $P2_1$, $a = 18.774(2)$, $b = 7.565(1)$, $c = 28.061(3)$ Å, $\beta = 93.12(1)°$, $V = 3980(1)$ Å^3, $Z = 4$. Full-matrix least-squares refinement of 875 parameters converged at $R = 5.18\%$, $\omega R_2 = 10.97\%$, GOF = 1.123 for all data (6719 unique reflections, $4° < 2\theta < 45°$).

studies which showed that the ester **16** formed exclusively the 9-chloride when treated with 1 equiv. of PID.[23] Since formation of the template hydrochloride may have made the template sterically more demanding than when it existed as the free base, the $(SCN)_2$ tandem reaction was run as before except in the presence of 3 equiv. of the acid scavenger[23] phenyliodine diacetate; however, primarily starting material **16** was recovered in this reaction.

An alternative explanation for the lack of functionalization at C-17 was that the $(SCN)_2$ interfered with further attack at C-17. Therefore, the 9-thiocyanate **18** was subjected to reaction with PID alone and also with $(SCN)_2$ –PID mixtures.

Photolysis of the 9-thiocyanate **18** with 1.25 equiv. of PID led to a product which resembled (by ^{1}H NMR) the known 9, 17-dichloride **17** in greater than 70% yield. MS analysis of the new material gave the expected mass for monochlorination of thiocyanate **18**. Furthermore, this material yielded the known $\Delta^{9(11)}$,Δ^{16} di-olefin **19** upon treatment with base. Therefore, the new material produced in the chlorination of the thiocyanate **18** was the 9-thiocyano-17-chlorosteroid **20** (Scheme 7). However,



Scheme 7

primarily 9-thiocyanate **18** was recovered when subjected to reaction with PID in the presence of $(SCN)_2$.

Previous studies showed that solvent effects on these reactions can be subtle (*e.g.* compare reactions of **10** in CH_2Cl_2 *versus* CCl_4, *vide supra*).[3,10a] Perhaps the excess of $(SCN)_2$ changed the effective relative permittivity of the reaction mixture which, in turn, affected the packing of the template underneath the steroid preventing formation of the C-17 steroid radical.

Significantly, the $(SCN)_2$–PID reaction with steroid ester **16** demonstrated that the tandem scheme also worked with pyridine-based templates. Furthermore, the monothiocyanated *and* monochlorinated derivative **20** was the first case of a steroid derivative formed by sequential and different remote functionalization reactions.

Summary

Through the use of a new tandem scheme, the remote radical chlorination reaction was extended to remote thiocyanation and remote bromination. In successful cases, comparable yields and the same specificity observed in the original chlorination were obtained. The novel products would be very challenging targets if one used traditional organic synthetic methods. These results further demonstrated the utility of template-directed reactions for selective synthetic transformations. Without template control, a low yield of a mixture of products would instead have been obtained in each case.

Experimental

General

(A) Chemicals and procedures. Most starting reagents were obtained from Aldrich. THF was dried by distillation under Ar from K–benzophenone or Na–benzophenone and CH_2Cl_2 was dried by distillation under Ar from CaH_2. Anhydrous CCl_4 and pyridine were obtained in Sure/Seal™ bottles from Aldrich. KI-starch test paper was obtained from Beckman Instruments. Ar was obtained from Matheson. Steroid esters and compound **5** were either already present in house or were prepared as described previously.[3,10,13,23]

Unless specified otherwise, reactions were carried out under Ar in flame-dried round-bottom flasks which were equipped with magnetic stirrer bars. PID was recrystallized from CCl_4 before use. NPID was recrystallized from either CCl_4 or CCl_4–light petroleum before use. In all photoinitiated reactions, a General Electric RSM-6 sunlamp (275 W) placed *ca.* 15 cm from the reaction vessel was used.

(B) Physical measurements. Except as noted, ^{1}H NMR spectra were recorded on Varian VXR 200, 300 or 400 MHz instruments and ^{13}C NMR spectra were recorded on a Varian VXR 75 MHz instrument. Residual solvent peaks were used for reference signals and *J* values are reported in Hz. IR Spectra were recorded with either a Perkin-Elmer 983 or a Perkin-Elmer 1600 Fourier transform spectrometer as KBr pellets. Mass spectra were recorded with a Nermag R-10-10 instrument [for chemical ionization (CI) with NH_3 or CH_4 ionization gas] or a JEOL JMS-DX-303 HF instrument (for FAB spectra with 3-nitrobenzyl alcohol matrix and Xe ionization gas). Reversible melting points were not observed in those cases examined; presumably this was due to the known decomposition pathways.

(C) Chromatography. EM Science pre-coated 0.25 mm thickness silica gel (60 F254) plates, which contained a fluorescent indicator, were used for analytical TLC. Compounds were visualized under shortwave UV light and/or by use of a phosphomolybdic acid strain. Flash silica gel chromatography[24] was normally carried out with 32–60 μm Universal Scientific silica gel. Except where noted, preparatory plate chromatography utilized EM Science plates (0.25, 0.50 or 1.00 mm).

9α-Bromocholestan-3α-yl *m*-iodobenzoate 4

Small scale reaction. Ester **1** (31 mg, 0.050 mmol) and CBr_4 (336 mg, 1.01 mmol) were dissolved in dry CH_2Cl_2 (10 cm^3) ([steroid] = 5 mM). NPID (24 mg, 0.76 mmol) was then added to

the solution after which it was irradiated at room temperature (water bath) for 30 min. At this time, the solution gave a negative KI-starch test. The solution was then transferred to a separatory funnel and washed with 5% aq $Na_2S_2O_3$ (1×) and sat. aq $NaHCO_3$ (1×). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (2×). The combined organic extracts were dried (Na_2SO_4) and concentrated. The ^{1}H NMR of the crude material showed 58% 9-bromide **4**, 20% $\Delta^{9(11)}$ olefin **3**, 7% 9-chloride **2**, 13% starting material **1**, and an unknown impurity (*ca.* 2%, 18-methyl at δ 0.75).

The 18-methyl region was assigned as follows: $\Delta^{9(11)}$ olefin **3**: δ 0.59 (s), ester **1**: δ 0.65 (s), 9-chloride **2** and 9-bromide **4**: δ 0.67 (s) (the last two singlets are only partially resolved at 200 MHz resolution). The aromatic proton *ortho* to the iodide and ester group (H′ in Scheme 2) region was assigned as follows: starting material **1** and olefin **3**: δ 8.34 (s), 9-chloride **2**: δ 8.44 (s), 9-bromide **4**: δ 8.54 (s).[25]

This solution was heated in the ^{1}H NMR tube at 45 °C for 20 min after which the spectrum was re-recorded. The spectrum showed 51% 9-bromide **4**, 32% $\Delta^{9(11)}$ olefin **3**, 4% 9-chloride **2**, 11% starting material **1** and 2% of the unknown impurity. The solution was kept at room temperature overnight and the spectrum was recorded once more. Analysis as before showed 29% 9-bromide **4**, 55% $\Delta^{9(11)}$ olefin **3**, 6% 9-chloride **2**, 4% of the starting material **1** and 5% of an unknown impurity.

Large-scale reaction. Ester **1** (102 mg, 0.165 mmol), CBr_4 (1.094 g, 2.298 mmol) and NPID (79 mg, 0.25 mmol) were dissolved in dry CH_2Cl_2 (13 cm^3, [steroid] = 13 mM). The colourless solution was degassed by bubbling purified N_2 (99.98%, Matheson) through it for 30 min. After 75 min irradiation, the solution was green and gave a negative KI–starch paper test. The solvent was then removed *in vacuo* and the crude reaction mixture was analysed by ^{1}H NMR spectroscopy. Integration indicated that the mixture contained 39% 9-bromide **4**, 37% of the $\Delta^{9(11)}$ olefin **3**, 5% of the 9-chloride **2**, 16% starting material **1** and 3% of an unknown compound (18-methyl at δ 0.75).

The reaction mixture was then impregnated on silica gel with CH_2Cl_2 and chromatographed with 5% diethyl ether–hexanes. The CBr_4 was separated from the steroidal material and two fractions of steroidal material were recovered. The first was a mixture of the starting material **1**, the $\Delta^{9(11)}$ olefin **3** and 1-iodo-4-nitrobenzene. The second contained more polar steroidal material which, in the original ^{1}H HMR assay, would have been assigned to be *ca.* 1:1 9-chloride **2**:starting material **1**.

The fraction containing the starting material **1** and $\Delta^{9(11)}$ olefin **3** was dissolved in 1:1 dioxane–10% KOH in methanol solution (15 cm^3) and stirred overnight. The solvents were removed *in vacuo* and the resulting residue was partitioned between CH_2Cl_2 and water. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried ($MgSO_4$) and concentrated. This material was filtered through silica gel (5% diethyl ether–hexanes→diethyl ether) and the steroidal alcohols were easily separated from residual 1-iodo-4-nitrobenzene. Since a ^{1}H NMR spectrum of the collected material showed that some of the crude benzoates had not been hydrolysed, the hydrolysis procedure was repeated with refluxing KOH solution (15 cm^3) for 2 h. This reaction was worked up in the same manner (but, without filtration through silica) and 64 mg of a steroidal alcohol mixture was recovered. This material was refluxed overnight with dry benzene (20 cm^3), pyridine (2 cm^3) and acetic anhydride (2 cm^3). The solvents were then removed and the crude material was taken up in diethyl ether and washed with 10% aq. HCl (4×), 10% aq. $NaHCO_3$ (2×) and brine (1×). The organic layer was then dried (Na_2SO_4) and concentrated.

The resulting yellow oil was chromatographed with 2.5% diethyl ether–hexanes as eluent on $AgNO_3$-impregnated silica gel.[3,10a] Five fractions were collected and analysed by ^{1}H NMR and TLC (30% aq. H_2SO_4 stain). The first (4 mg) was cholestan-3α-yl acetate (*e.g.* unfunctionalized steroid) contaminated by an unknown impurity. The second (26 mg) contained a *ca.* 9:1 mixture of cholest-Δ9(11)-3-en-3α-yl acetate and cholestan-3α-yl acetate. The third fraction (25 mg) was pure $\Delta^{9(11)}$ acetate. The fourth fraction (5 mg) contained unknown, polar steroidal material. The final fraction (8 mg) was collected with diethyl ether as eluent and was also unknown, polar steroidal material. The yields of the collected products were calculated to be 68% of cholest-Δ9(11)-en-3α-yl acetate and 9% of cholestan-3α-ol acetate (*i.e.* unfunctionalized material). Additionally, *ca.* 6% of polar materials were collected after the photoreaction and an additional *ca.* 18% polar materials were collected after the processing steps. The yields of these latter materials were estimated with the assumptions that the weights of the initially collected polar materials were similar to that of the starting material **1**, while those of the second batch of polar materials were similar to that of cholestan-3α-ol acetate. ^{1}H NMR spectral data for 9α-bromocholestan-3α-yl *m*-iodobenzoate **4** ($CDCl_3$): δ 0.67 (3 H, s, 18-Me), 1.14 (s, 19-Me), 0.80–2.10 (steroid envelope), 2.3–2.5 (1 H, br m), 2.6–2.8 (1 H, br m), 5.2–5.3 (1 H, br s, 3β-H), 7.18 (1 H, t, *J* 7.6), 7.86 (1 H, d, *J* 7.6), 8.06 (1 H, d, *J* 7.6) and 8.55 (1 H, s).

CBr_4–Aryliodine dichloride functionalization of hexadecyl *m*-iodobenzoate 5

Hexadecyl *m*-iodobenzoate **5** (40 mg, 0.085 mmol) and CBr_4 (281 mg, 0.847 mmol) were dissolved in dry CH_2Cl_2 (14 cm^3, [**5**] = 6.1 mM). PID (0.070 g, 0.25 mmol) was then added to the solution after which it was irradiated at *ca.* room temperature (controlled with a water bath) for 1 h. The solution was then transferred to a separatory funnel and washed with 5% aq. $Na_2S_2O_3$ (1×). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The organic layers were combined, dried ($MgSO_4$) and concentrated. The ^{1}H NMR spectrum of the crude material showed a new peak centred at δ 3.95–4.10 which had the same line shape as the methine peak associated with the chloro compound(s) which appeared at δ 3.80–3.95.[10e,13] Assuming that the new peak represented the desired bromide(s) **6** integration *versus* the protons α to the ester linkage at δ 4.2–4.4 indicated *ca.* 40% of the new material had been formed in the reaction.

The crude mixture was subjected to preparatory plate chromatography (0.50 mm plate, 5% EtOAc–hexanes, 2 elutions) and three fractions were recovered. The first contained residual CBr_4 and starting material **5** (unweighed). The second contained *ca.* 80% of the starting material **5** and *ca.* 20% of the new compound (^{1}H NMR analysis, 17 mg).

The third fraction was assigned to be the mixture of bromides **6** (11 mg, 23%). In the ^{1}H NMR spectrum, the integral of the peak at δ 4.02 was close to half that of the protons α to the ester linkage (53 *versus* 119). The remainder of the spectrum was quite similar to that of the starting material except that four of the methylene groups had been shifted from δ 1.2–1.4 to δ 1.6–1.9. MS analysis (CI, NH_3) of this material showed peaks at 551 and 553 which corresponded to those expected for **6** (*i.e.* M + 1 with the bromine isotopic distribution). In addition, the corresponding M + NH_4^+ peaks were observed at *m/z* 568 and 570.

9α-Thiocyanocholestan-3α-yl *m*-iodobenzoate 7

To prepare the necessary $(SCN)_2$ solution, a reaction flask was charged with $Pb(SCN)_2$ (500 mg, 1.55 mmol) and then CH_2Cl_2 (15 cm^3). The Ar line was replaced with a ground glass joint bearing a stopper which had a Teflon sleeve and Br_2 (0.028 cm^3, 0.028 cm^3, and finally 0.014 cm^3, 1.4 mmol total) was added at 1 h intervals using a Drummond autopipette. Throughout this period the reaction suspension was stirred vigorously. After the last Br_2 addition, a second portion of $Pb(SCN)_2$ (250 mg, 0.78 mmol) was added and stirring was continued until a virtually colourless suspension was obtained after several hours. More CH_2Cl_2 (10 cm^3) was added and the suspension was filtered

through a Pasteur pipette which contained a small cotton plug into a round-bottom flask. The flask was then equipped with an Ar balloon and a magnetic stirrer bar. The resulting nearly colourless solution of $(SCN)_2$ gave a positive KI–starch paper test.

Ester **1** (75 mg, 0.12 mmol) and PID (48 mg, 0.18 mmol) were then added to the solution which was cooled with an ice–water bath. The mixture was irradiated for 1 h. The reaction mixture was then transferred to a separatory funnel and quenched with sat. aqueous $Na_2S_2O_3$. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were dried (Na_2SO_4) and concentrated at room temperature. Silica gel chromatography (5% EtOAc–hexanes) and concentration of the desired fractions at room temperature gave the 9α-thiocyanate **7** as a colourless foam (53 mg, 64%). Concentration of the early fractions (only higher R_f material was visible in the TLC of the crude reaction mixture) gave 18 mg of a mixture which was assigned by ^{1}H NMR to be 15% 9-SCN **7**, 74% (*ca.* 4:1) 9-Cl **2**:starting material **1** and 11% $\Delta^{9(11)}$ **3**. $\delta_H(CDCl_3)$ 0.720 (3 H, s, 18-Me), 1.143 (s, 19-Me), 0.8–2.3 (steroid envelope), 2.3–2.6 (1 H, br m), 5.2–5.4 (1 H, br s, 3β-H), 7.21 (1 H, t, *J* 7.8), 7.89 (1 H, d, *J* 7.0), 8.04 (1 H, d, *J* 6.8) and 8.48 (1 H, s); $\delta_C(CDCl_3)$ 12.20, 14.49, 18.52, 22.54, 22.80, 23.64, 23.68, 26.08, 26.32, 26.70, 27.93, 28.00, 28.47, 33.10, 33.67, 35.73, 35.92, 36.00, 38.62, 39.46, 42.71, 43.57, 49.53, 55.80, 70.03, 77.20, 78.78, 93.93, 113.44 (SCN), 128.61, 130.15, 132.71, 138.69, 141.64 and 164.12 (C=O); ν_{max}(KBr)/cm^{-1} 2927s, 2873m, 2137w (ν_{SCN}), 1720s ($\nu_{C=O}$), 1654m, 1556m, 1458m, 1382m, 1258s, 1109s, 1071m, 1022m, 744w and 586w; *m/z* (FAB-MS) 676 (MH^+); R_f (10% EtOAc–hexanes) 0.18 (UV+, PMA+).

Purified thiocyanate **7** (13.4 mg, 0.020 mmol) was treated with 1:1 dioxane–10% KOH in methanol (20 cm^3) at reflux for 2.5 h. After the solution had been allowed to cool to room temperature it was evaporated *in vacuo* and the resulting residue was partitioned between EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc (2 ×). The combined organic layers were dried ($MgSO_4$) and concentrated. ^{1}H NMR analysis of the collected organic material (8 mg) showed the known $\Delta^{9(11)}$ olefin **9** as the only formed steroidal product.

9α-Mercaptocholestan-3α-ol 8

A solution of thiocyanate **7** (13 mg, 0.019 mmol) in dry THF (5 cm^3) was cooled with an ice–water bath and LAH (20 mg, excess) was added to it in one portion. The ice bath was removed and stirring was continued overnight. The suspension was then quenched with water (0.1 cm^3) followed by 0.2 M aq. NaOH (0.1 cm^3). The mixture was dissolved in CH_2Cl_2 (50 cm^3), dried ($MgSO_4$) and concentrated without heating. Preparatory plate chromatography (0.25 mm plate, 5% *tert*-butyl methyl ether–$CHCl_3$ eluent) furnished the thiol (3 mg, 36%); $\delta_H(CDCl_3)$ 0.672 (3 H, s, 18-Me), 1.032 (s, 19-Me), 0.8–2.0 (steroid envelope), 2.25–2.45 (1 H, br m) and 3.95–4.05 (1 H, br s, 3β-H); *m/z* (CI-MS; NH_3 matrix) 438 ($MH^+ + NH_3$); R_f (5% *tert*-butyl methyl ether–$CHCl_3$) 0.37 (UV−, PMA+).

Examination of the stability of PID in the presence of $(SCN)_2$

A $(SCN)_2$ solution was generated in CD_2Cl_2, using a similar procedure to that used in the preparation of the solution used to make the thiocyanate **7** with $Pb(SCN)_2$ (0.50 g, 1.5 mmol), Br_2 (0.056 cm^3, 1.1 mmol), and CD_2Cl_2 (4.4 cm^3). After removal of the residual lead salts, PID (0.050 g, 0.18 mmol, [PID] = 41 mM) was added to the $(SCN)_2$ solution. The ^{1}H NMR spectrum was recorded within 5 min and only PID was visible (*i.e.* no iodobenzene was apparent). After 30 min, the spectrum was recorded again and a small amount, relative to PID, of iodobenzene was apparent (*ca.* 2%). After an additional 30 min the amount of iodobenzene, relative to PID, had increased somewhat (6 ± 3%). The spectrum was recorded once more, after an additional 30 min, and the ratio of iodobenzene to PID was similar to that observed after 1 h.

17α-Thiocyanocholestan-3α-yl 4′-iodobiphenyl-3-carboxylate 12

A procedure similar to that used for 9-thiocyanate **7** was followed. Thus, $Pb(SCN)_2$ (0.40 g, 1.2 mmol) was suspended in dry CCl_4 (20 cm^3) and Br_2 (0.056 cm^3, 1.1 mmol) was added to it in one portion; the argon line was then replaced with a ground glass joint bearing a stopper which had a Teflon sleeve. The suspension was stirred vigorously for 30 min, after which a second portion of $Pb(SCN)_2$ (100 mg, 0.309 mmol) was added to it. Stirring was then continued until a clear suspension was obtained (*ca.* 1 h). Filtration as performed previously gave a clear solution of $(SCN)_2$.

Ester **10** (144 mg, 0.207 mmol) and PID (84 mg, 0.31 mmol) were added to the solution which was then irradiated at *ca.* room temperature (controlled by a water bath) for 1 h. Work-up as previously (except using 5% aq. $Na_2S_2O_3$) and silica gel chromatography (5% EtOAc–hexanes) gave the 17-thiocyanate as a colourless foam (64 mg, 41%). Concentration of the earlier fractions gave 82 mg of a *ca.* 4:1 mixture of starting material:17-chloride **11** (^{1}H NMR analysis). When this reaction was conducted with the same procedure on a larger scale (500–700 mg of steroid **10**), the yield of recovered thiocyanate was lower (*ca.* 25%) presumably due to some exposure to air during filtration of the $(SCN)_2$ solution; $\delta_H(CDCl_3)$ 0.84, 0.88 and 0.91 (methyl region not well resolved, 18-Me, 19-Me, 26-Me and 27-Me), 1.02 (d, *J* 6.4, 21-Me), 1.1–2.1 (steroid envelope), 2.4–2.6 (1 H, m), 5.25–5.35 (1 H, br s, 3β-H), 7.36 (2 H, d, *J* 8.2), 7.55 (1 H, t, *J* 7.6), 7.62–7.78 (1 H, m), 7.80 (2 H, d, *J* 8.2), 8.05 (1 H, d, *J* 7.7) and 8.23 (1 H, s); $\delta_C(CDCl_3)$ 11.40, 15.21, 15.43, 20.72, 22.47, 22.72, 23.63, 25.46, 26.24, 27.95, 28.19, 31.77, 32.89, 33.15, 34.09, 34.61, 35.82, 35.98, 37.39, 39.04, 40.32, 42.89, 49.84, 51.52, 53.50, 70.82, 77.20, 81.13, 93.62, 114.47 (SCN), 127.98, 128.63, 128.87, 128.98, 130.57, 131.09, 131.76, 138.01, 139.71, 140.30 and 165.76 (C=O); ν_{max}(KBr)/cm^{-1}, 2931s, 2858m, 2142w (ν_{SCN}), 1714s ($\nu_{C=O}$), 1463m, 1383m, 1299m, 1238s, 1108m, 1001m and 753s; *m/z* (FAB-MS) 752 (MH^+); R_f (10% EtOAc–hexanes) 0.37 (UV+, PMA+).

A solution of the 17-thiocyanate **12** (18 mg, 0.024 mmol) in dioxane (5 cm^3) was treated with *N*,*N*-diisopropylethylamine (0.5 cm^3) and the resulting mixture was first heated to reflux for 5 h and then stirred at room temperature overnight. After the mixture had been evaporated *in vacuo*, the resulting material was partitioned between EtOAc and 5% aq. HCl. The layers were separated and the organic layer was extracted with 5% aq. HCl (2×) and water (1×), dried ($MgSO_4$) and concentrated. ^{1}H NMR analysis of the crude mixture showed only the known Δ^{16} olefin **14**. A similar result was observed when a solution of the 17-thiocyanate **12** was heated in $CDCl_3$ overnight at 50 °C.

17α-Mercaptocholestan-3α-ol 13

A solution of thiocyanate **12** (325 mg, 0.432 mmol) in dry THF (*ca.* 150 cm^3) was cooled with an ice–water bath and LAH (150 mg, excess) was added to it. The ice bath was removed and the solution stirred overnight. It was then quenched with water (0.15 cm^3), followed by 0.2 M aq. NaOH (0.15 cm^3) and finally water (0.45 cm^3). The mixture was dried (Na_2SO_4) and concentrated without heating. Chromatography (10% EtOAc–hexanes eluent) gave the thiol (140 mg, 77%); $\delta_H(CDCl_3)$ 0.77 (3 H, s, 18-Me or 19-Me), 0.79 (3 H, s, 18-Me or 19-Me), 0.84 (6 H, overlapping d, *J* 6.6, 26-Me and 27-Me), 0.91 (3 H, d, *J* 6.4, 21-Me), 1.0–2.1 (steroid envelope) and 3.95–4.05 (1 H, br s, 3β-H); $\delta_C(CDCl_3)$ 11.18, 14.16, 15.50, 20.83, 22.53, 22.76, 23.67, 25.78, 27.98, 28.55, 29.00, 31.98, 32.12, 34.55, 35.15, 35.87, 36.05, 39.07, 39.33, 40.00, 41.16, 41.85, 48.04, 51.01, 53.67, 66.56 and 67.88; *m/z* (CI-MS; NH_3 matrix) 420 (M) and 438 ($MH^+ + NH_3$); R_f (25% EtOAc–hexanes) 0.41 (UV−, PMA+).

17α-Mercaptocholestan-3α-yloxy(triphenyl)silane 15

Triphenylsilyl bromide[26] was prepared by treating Br_2 (0.1 cm^3) with triphenylsilane (0.53 g, 2.0 mmol, 1.1 equiv.) in anhydrous

CCl_4 (40 cm^3) for 1 h. Since residual Br_2 in the mixture was evident as judged by the reaction mixture colour, a second portion of triphenylsilane (0.08 g) was added to it and stirring continued for a further 1 h. At this point, a final portion of triphenylsilane was added (0.03 g, 1.25 total equiv.) to the mixture and stirring was continued for 1.5 h. The solvents were removed on a vacuum line and the resulting colourless solid dried *in vacuo* for several hours and then used.

Triphenylsilyl bromide (65 mg, 0.19 mmol, 4.0 equiv., uncorrected for excess of triphenylsilane) was added to a pre-weighed round-bottom flask under argon. The weight of reagent was determined and hydroxy thiol **13** (20 mg, 0.048 mmol) was then added to the flask. It was then cooled with an ice–water bath and anhydrous pyridine (5 cm^3) added to it. After the reaction mixture had been allowed to warm to room temperature it was stirred overnight. The solvent was then removed without heating on a vacuum line and the crude mixture dissolved in CH_2Cl_2 (75 cm^3) and extracted with water (5 × 50 cm^3). The CH_2Cl_2 layer was dried (Na_2SO_4), filtered and concentrated. The crude material was dissolved in CH_2Cl_2 and filtered through a silica gel plug (Baker 40 μm flash chromatography packing) to give the desired product contaminated by a triphenylsilyl impurity. Preparatory plate chromatography (2 elutions, 0.50 mm Whatman 150 A silica gel plate, hexanes eluent) furnished the silated hydroxy thiol as a colourless oil. Dropwise addition of water to a concentrated acetone solution of the crude oil afforded purified silylated hydroxy thiol (17 mg) as microcrystalline white flakes in 50% yield. Transparent tabular single crystals were obtained for a diffraction study by slow vapour diffusion of acetone–water at 4 °C; δ_H($CDCl_3$, recorded with GE QE-300 MHz instrument) 0.71 (3 H, s, 18-Me or 19-Me), 0.79 (3 H, s, 18 Me or 19 Me), 0.85 (6 H, overlapping d, *J* 6.3, 26-Me and 27-Me), 0.92 (3 H, d, *J* 6.3, 21-Me), 1.0–2.2 (steroid envelope), 4.15–4.22 (1 H, br s, 3β-H), 7.30–7.44 (9 H, m) and 7.55–7.66 (6 H, m); δ_C($CDCl_3$, recorded with Bruker AM-125 MHz instrument) 11.39, 14.18, 15.52, 20.89, 22.52, 22.75, 23.71, 25.78, 27.99, 28.54, 29.32, 32.08, 32.59, 34.59, 35.22, 35.97, 36.13, 36.17, 39.22, 39.34, 41.19, 41.87, 48.11, 51.08, 53.75, 67.98, 68.45, 127.74, 129.76, 135.24 and 135.41 [Found (CI-HRMS; NH_3 matrix): *m/z* 678.4288. Calc. for $C_{45}H_{62}OSSi$: 678.4291]; X-ray structure: see Fig. 1; R_f (10% EtOAc–hexanes) 0.58 (UV+, PMA+).

9α-Thiocyanocholestan-3α-yl 5-(4-iodophenyl)nicotinate 18

A solution of $(SCN)_2$ was prepared using $Pb(SCN)_2$ (300 mg, 0.928 mmol), Br_2 (0.028 cm^3, 0.54 mmol) and dry CH_2Cl_2 (10 cm^3) as described in the experimental for **7**. Ester **16** (17 mg, 0.024 mmol) and PID (20 mg, 0.072 mmol) were added to the $(SCN)_2$ solution and the resulting reaction mixture was photolysed with ice bath cooling for 1 h.

Work-up as for the 9-thiocyanate **7** followed by silica gel chromatography (eluent: 2.5% *tert*-butyl methyl ether–$CHCl_3$) gave thiocyanate **18** (13 mg, 73%); δ_H($CDCl_3$) 0.72 (3 H, s, 18-Me), 0.93 (d, *J* 5.6, 21-Me), 1.16 (s, 19-Me), 0.8–2.4 (steroid envelope), 2.4–2.6 (1 H, br m), 5.30–5.42 (1 H, br s, 3β-H), 7.40 (2 H, d, *J* 8.4), 7.86 (2 H, d, *J* 8.4), 8.5–8.6 (1 H, br s), 8.9–9.1 (1 H, br s) and 9.2–9.4 (1 H, br s); δ_C($CDCl_3$) 12.23, 14.49, 18.53, 22.55, 22.82, 23.64, 23.71, 26.11, 26.35, 26.70, 27.94, 28.01, 28.52, 29.68, 33.18, 33.77, 35.76, 35.87, 36.00, 38.65, 39.48, 42.73, 43.60, 49.50, 55.75, 70.39, 79.02, 94.87, 113.36, 128.85, 135.00, 136.08, 138.48, 149.67, 151.17 and 164.15; ν_{max}(KBr)/cm^{-1} 3409m, 2948s, 2930s, 2866m, 2143w (ν_{SCN}), 1723s ($\nu_{C=O}$), 1300m, 1251m, 1235m and 1104m; *m/z* (FAB-MS) 753 (MH^+) and 694 (MH^+ − HSCN).

The elimination of the 9-thiocyanate **18** was examined. An NMR sample of purified **18** (13 mg, 0.017 mmol) in $CDCl_3$ was heated at 50 °C for 2.5 h after which the ^{1}H NMR spectrum was recorded again. The spectrum showed that *ca*. 10% decomposition to the $\Delta^{9(11)}$ olefin (with the template intact) had occurred. The sample was then heated at the same temperature overnight. A second ^{1}H NMR spectrum was recorded and it showed that the mixture now contained *ca*. 30% of the $\Delta^{9(11)}$ olefin (with the template intact) and *ca*. 70% of the thiocyanate **18**.

The mixture was then transferred to a round-bottom flask and the solvent was removed. The residue was then treated with 1:1 dioxane–10% KOH in methanol at reflux for 2 h. The reaction mixture was worked up as described for the corresponding reaction for the thiocyanate **7**. ^{1}H NMR analysis showed the known $\Delta^{9(11)}$ olefin **9** to be the only steroidal product (4.1 mg).

9α-Thiocyano-17-chlorocholestan-3α-yl 5-(4-iodophenyl)-nicotinate 20

A solution of thiocyanate **18** (11 mg, 0.015 mmol) and PID (5 mg, 0.018 mmol) in CH_2Cl_2 (5 cm^3, [steroid] = 3 mM) was irradiated at *ca*. room temperature (controlled by a water bath) for 45 min. The solution was transferred to a separatory funnel and extracted with 5% aq. $Na_2S_2O_3$ (1×). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1×). The organic layers were combined, dried ($MgSO_4$) and concentrated without heating. ^{1}H NMR analysis of the crude material showed that one major product was formed in the reaction. It was characterized by a 21-Me shift at δ 1.02 (d, *J* 6.2) and more of the methine resonances shifted downfield of the steroidal envelope than observed in the spectrum of the starting material **18**. In addition, the 18-Me group was shifted downfield, with respect to that of the starting material **18**, to δ 0.85–0.89 (several unresolved methyl groups). Clean integration against the starting material was not possible. However, the resonances associated with the starting material **18** (18-Me and 21-Me groups) were visible but indicated that not much starting material was still present. An estimate of the yield of **20** was >70%. Steroid **20** can be isolated by preparatory plate chromatography (2.5% *tert*-butyl methyl ether–$CHCl_3$); δ_H($CDCl_3$) 0.85 and 0.88 (methyl region not well resolved, 18-Me, 26-Me and 27-Me), 1.02 (d, *J* 6.2, 21-Me), 1.1–1.9 (steroid envelope), 2.1–2.9 (3 H, multiplets, downfield shifted methines), 5.30–5.42 (1 H, br s, 3β-H), 7.3–7.6 (2 H, m), 7.6–7.9 (2 H, m), 8.5–8.6 (1 H, m), 8.9–9.1 (1 H, br s) and 9.20–9.35 (1 H, br s); *m/z* (FAB-MS) 787 (MH^+).

The crude material was treated with 1:1 dioxane–10% KOH in methanol (10 cm^3) at reflux overnight. The reaction mixture was worked up in the same fashion as for the similar elimination reaction of 9-thiocyanate **7**. The ^{1}H NMR spectrum of the crude recovered material showed that the known cholestan-9(11),16-dien-3α-ol **19** was the major steroidal product as indicated by the shifts of the 18-methyl, 21-methyl and vinyl protons.[10e,23]

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Supplementary material available

The X-ray structural data for compound **15** have been deposited with the Cambridge Crystallographic Data Centre.† Any request for this material should be accompanied by a full bibliographic citation together with the reference number CCDC 207/63.

† For details, see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

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