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An Improved Synthesis of 1α-hydroxy Vitamin D3

W. Nerinckx, P.J. De Clercq*

State University of Gent, Department of Organic Chemistry,
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

and

C. Couwenhoven, W.R.M. Overbeek, S.J. Halkes*
Duphar B.V., Weesp (The Netherlands)

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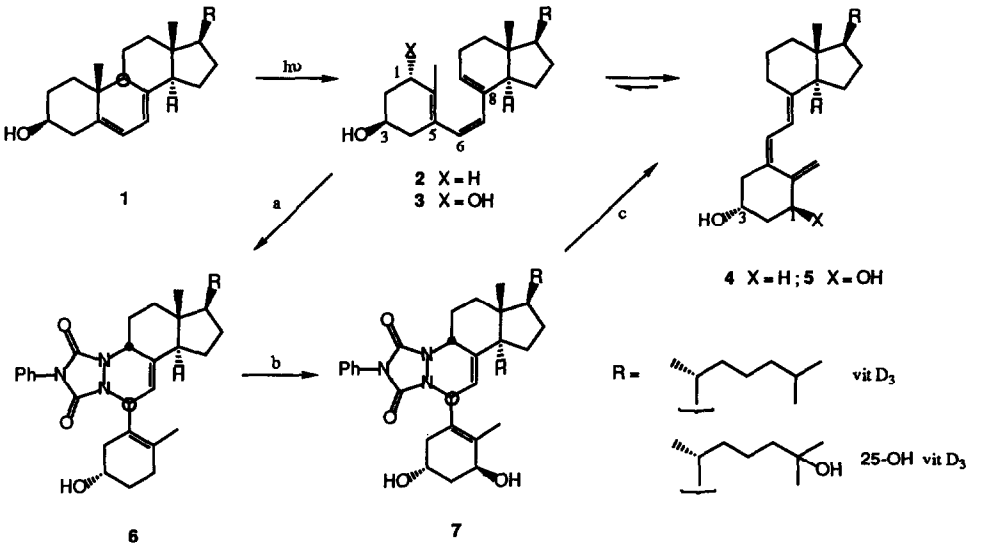
***Abstract** : The efficient and stereoselective introduction of the 1α-OH function in vitamin D_3 is described starting from the known previtamin D_3 adduct **6**. The sequence involves the stereoselective allylic bromination to **9**, followed by substitution with mercuric(II)acetate which occurs with retention of configuration to yield acetate **22**. Basic hydrolysis gives diol **7**, a known precursor of 1α-OH vitamin D_3.*

INTRODUCTION

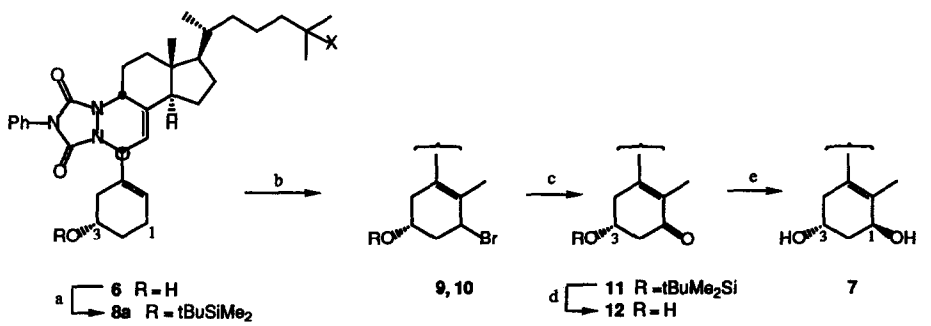
In view of the biological importance of 1α-hydroxylated vitamin D_3 metabolites and analogues[1], a general and efficient approach for the stereoselective introduction of the 1(S)-hydroxy function remains an important synthetic challenge[2]. In this context we have reported syntheses of 1α-OH[3] and 1α,25-diOH[4] vitamin D_3 (**5**) which involved three distinct stages (scheme 1) : (a) the generation of the previtamin triene system **2**, via low temperature irradiation of the provitamin **1**[5] or via equilibration from the vitamin **4**, followed by protection of its 6,8-diene part under the form of the triazoline Diels-Alder adduct **6**; (b) the regio- and stereoselective introduction of the 1(S)-hydroxy group to **7** via a multistep sequence (vide infra); (c) the eventual conversion of the substituted adduct **7** to 1α-hydroxylated vitamin D_3 (**5**) in basic medium.[6] In the present paper we wish to focus on a few steps that were involved in sequence b and will also disclose a more efficient way for the selective transformation of **6** into diol **7**.

The regio- and stereoselective introduction of the 1(S)-hydroxy group starting from **6** was originally performed as shown in scheme 2. Of crucial importance is the stereoselective reduction of hydroxy ketone **12** with aluminum hydride, which involves prior formation of an alkoxyaluminum hydride complex with the hydroxyl group at C-3, followed by intramolecular hydride transfer to the carbonyl group which leads to the preponderant formation (9:1) of the desired isomer **7**. The introduction of the carbonyl group at C-1 proceeds via allylic bromination of the protected derivative **8a**, followed by direct oxidation of what was originally thought to be a diastereomeric mixture of bromides **9** and **10**. We will now essentially focus on two different aspects : (1) the allylic bromination step; (2) the possibility for a more direct conversion of the allylic bromide into diol **7** without having to proceed via an oxidation-reduction sequence.



[a] 4-phenyl-1,2,4-triazoline-3,5-dione, CH_2Cl_2, 0°C, N_2, 2 min; recryst. from acetone; [b] see scheme 2; [c] 80°C, 15 N KOH-MeOH, 24 h; recryst. from hexane.

Scheme 1



[a] t-$BuMe_2SiCl$, imidazole, DMF; [b] see text; [c] silicagel, H_2O, collidine, hexane, 24 h, rt; PDC, CH_2Cl_2, 4 hr (ref. 3) or $(n\text{-}Bu_4N)_2Cr_2O_7$, $CHCl_3$, reflux, 3 h (ref. 4); [d] $n\text{-}C_3H_7COOH$, $n\text{-}Bu_4NF$, THF, 20°C, 2 h; [e] AlH_3, THF, -70°C.

Scheme 2

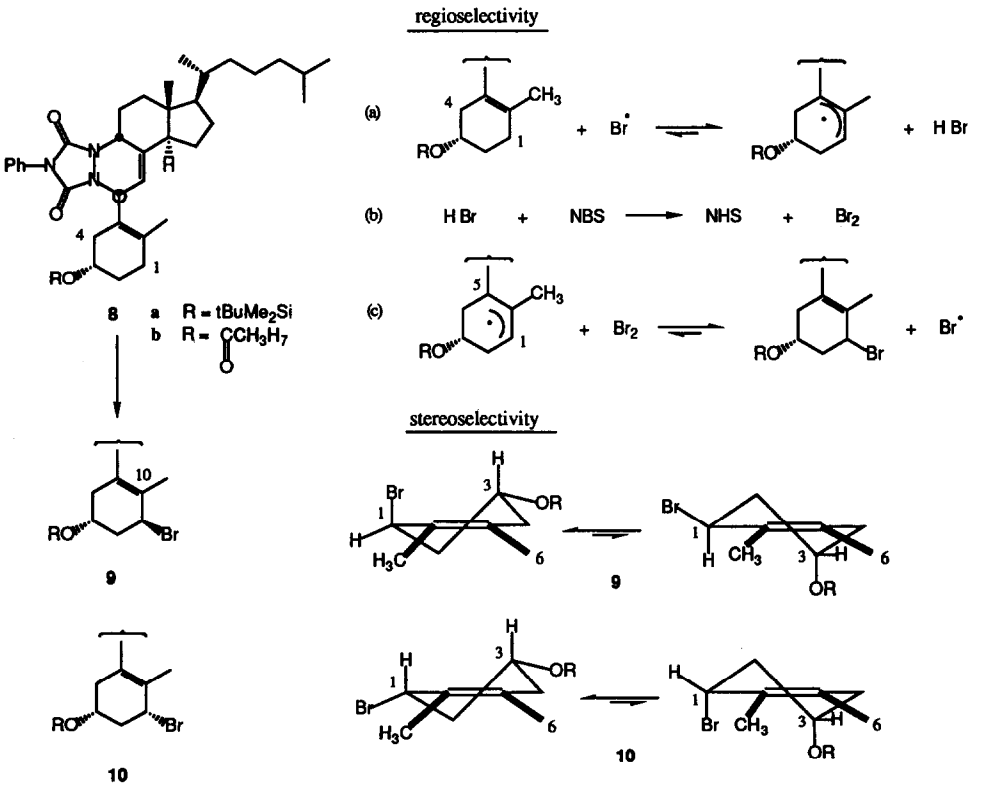
The allylic bromination of 8

Revisiting the original procedures. Originally, the allylic bromination was performed using the classical experimental conditions :[7] heating a solution of **8a** in CCl_4 with N-bromosuccinimide (NBS) in the presence of AIBN (20 min)[3]. A later modification involved the use of 1,3-dibromo-5,5-dimethylhydantoin (DDH) as the brominating agent in a refluxing mixture of n-hexane-CH_2Cl_2 (7:1) as solvent in the presence of one equivalent of collidine[8] and AIBN as initiator (20 min). Since the latter was found to hydrolyze on silica gel, in

practice the crude bromide was not purified, but directly further oxidized. Typically, an overall yield of ca 55 % of enone **11** is obtained starting from protected **8a**.

For the study of the direct conversion of the allylic bromide into diol **7** the knowledge of the exact composition of the bromide is obviously necessary. The need to isolate the bromide in pure form led us to follow the bromination reaction by ^1H NMR. Under the last-mentioned conditions (DDH) it appeared that, already after 2 min, all starting material had disappeared and that, upon further heating, many side products were formed. Evidently, the used conditions were too drastic. A further systematic search to optimize the required conditions eventually revealed that, in the solvent system n-hexane-CH_2Cl_2, high yield (>90 %) bromination could be effected with NBS or DDH, at room temperature instead of reflux (45 min), in the absence of any added collidine and radical initiator. Under these conditions pure bromide precipitates and can be recrystallized from n-hexane if desired. Alternatively, crude bromide can be oxidized directly to enone **11** in high yield (95 %) using bis-tetrabutylammoniumdichromate in refluxing 1,2-dichloropropane (1 h).

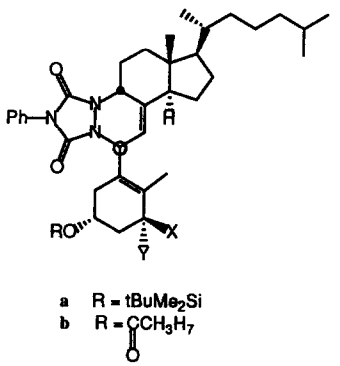
Pure allylic bromide 9. Somewhat to our surprise ^1H NMR analysis showed the presence of a single diastereomeric bromide with the 1(S)-configuration. In the preferred half-chair conformation the bromine is axial (cf. allylic strain), as revealed by the small vicinal coupling constant values observed for H-1 (Table 1). The very high regio- and stereoselectivity of this substitution deserves further comment (scheme 3).



Scheme 3

It is now well established that the allylic bromination with NBS, as originally observed by Ziegler[10], proceeds via a bromine atom chain reaction as shown in scheme 3 (the so-called Goldfinger mechanism)[11]. Here the bromine atom is the hydrogen acceptor (step a). The N-bromoimide serves as a scavenger of hydrogen bromide and as a source of further bromine (step b). The latter is about 10^3 times more reactive than N-bromoimides in trapping free radicals (step c). The rate determining propagating step a involves dissociation of the weakest C-H bond provided the bond is not too sterically hindered. Therefore one usually observes the preferred formation of a secondary radical centre rather than a tertiary or a primary. From the 6 different allylic positions in **8**, two positions, i.e., at C-1 and C-4, are of the secondary type. The hydrogen abstraction at C-4 is retarded, however, both on steric and electronic grounds.[12] The subsequent formation of the C-Br bond in step c will lead preferentially to the formation of the stronger secondary bond at C-1 (rather than the weaker tertiary bond at C-5) without allylic rearrangement. The observed stereoselectivity in favor of the 1(S)-derivative **9** is a consequence of stereoelectronic control : the axial introduction of the bromine on the preferred half-chair conformation with the equatorial RO at C-3 permits the maintainance of maximum π-overlap in the allylic radical during the reaction.

Table 1. ^{1}H NMR Spectral Data of H-1 and H-3 in **9**, **18**, **22** and **23** ($CDCl_3$)



product	X	Y	H-1 δ(ppm)	H-1 $^3J^a$	H-3 δ(ppm)	H-3 Σ^3J
9a	Br	H	4.80	2.5, 2.5	4.38	30
9b	Br	H	4.77	3.2, 3.2	5.32	30.5
18a	Cl	H	4.60	br d[b]	4.17	30
18b	Cl	H	4.59	3.0, 3.3	5.24	29.5
22a	OAc	H	5.37	1.8, 4.2	3.89	29.5
22b	OAc	H	5.41	3.8, 3.8	5.02	29.0
23a	H	OAc	5.44	br t[c]	3.75	30

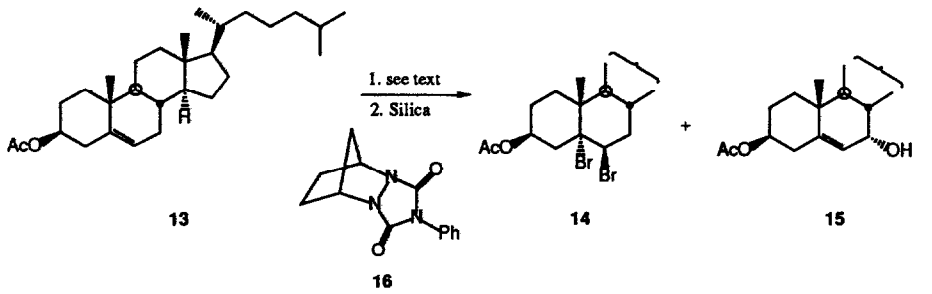
[a] J(H-1,H-2), J(H-1,H-2); [b] Σ^3J ~6 Hz; [c] Σ^3J ~15 Hz

Solvent, radical initiator. It is interesting to note that our revisited conditions are very similar to Ziegler's original[19] conditions for allylic bromination with NBS, which involved refluxing CCl_4 without irradiation or addition of initiators. In CCl_4 NBS is sparingly soluble. The very fast capture of any HBr by NBS under these conditions secures a steady and low concentration of bromine throughout the reaction. This is a well known requisite for the success of the allylic bromination reaction since high concentrations of bromine are known to promote the electrophilic addition to the alkene in apolar solvents.[13] This aspect was kept in mind when alkane-CH_2Cl_2 (7:1) was proposed as an alternative solvent for the carcinogenic CCl_4 : CH_2Cl_2 ensures partial solution of the substrate, while the n-pentane or n-hexane prevents the dissolution of NBS or DDH.

Ziegler's original conditions seemingly do not require an initiatior. This aspect, however, has been thoroughly studied by Dauben and McCoy,[14] who showed that allylic brominations do not proceed unless a trace of initiator is present. In the absence of added initiator, the initiating role is performed by alkene hydroperoxides which are almost invariably formed from an alkene in the presence of oxygen.

The self-initiating capacity of **8a** was further unambiguously proven by using **8a** as initiator in an allylic bromination reaction which was shown not to proceed unless a radical initiator was present (scheme 4).

Indeed, 3-cholesterolacetate **13** does not react with NBS (1.5 equiv) in benzene at room temperature. Upon irradiation, however, and elution through silica gel alcohol **15** is formed. Without irradiation, but in the presence of 0.2 equiv of **8a** (2 h) a complex reaction mixture is obtained consisting of starting material, dibromoadduct **14** and about 5 % of alcohol **15**. Under the same conditions but performed now in the presence of the pure N-phenyltriazoline derivative **16**[15] instead of **8** no reaction was observed. This showed the triazoline part of the adduct **8** not to be responsible for initiating the reaction. Eventually, a quantitative peroxide determination[16] via the same modified iodometric method as originally used by Dauben[14] revealed the presence of ca 0.5 mol % peroxide in **8a**.



Scheme 4

Butyrate adduct 8b as alternative substrate and alternative halogenation conditions. In view of the more direct conversion of allylic bromide into diol **7**, the use of another protective group for the hydroxy group in **6** was also investigated. Treatment of the butyrate **8b** under the above brominating conditions (DDH or NBS, n-hexane-CH_2Cl_2 (7:1), rt) proceeded however more slowly (Table 2). Quantitative peroxide determination revealed the presence of much less hydroperoxide (ca 0.05 %) which is in line with the observed longer reaction times.

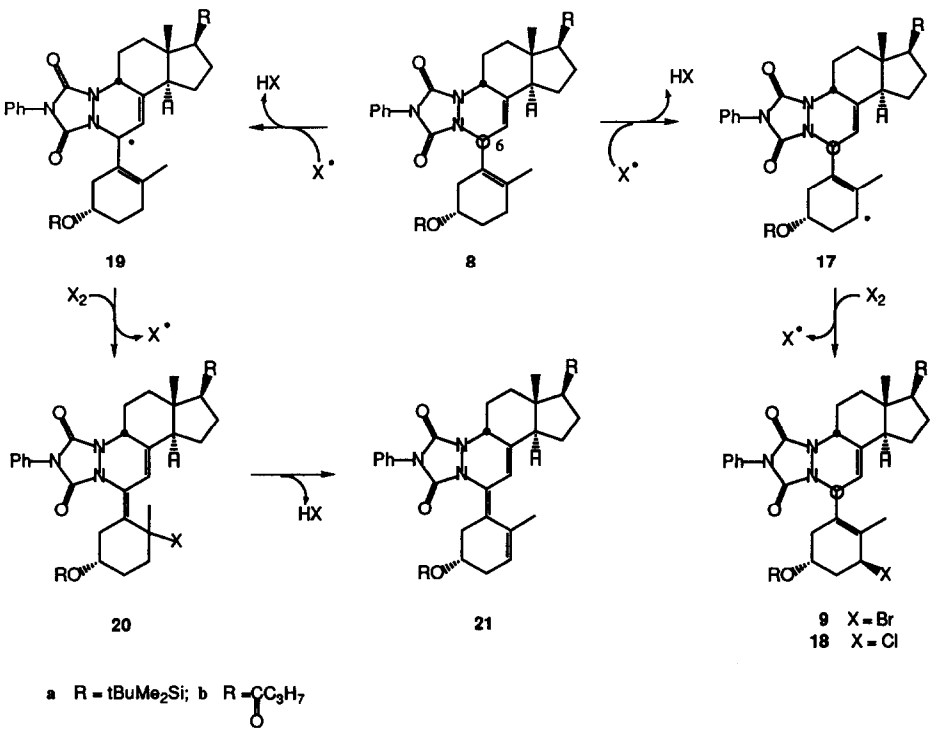
Table 2. Halogenation conditions for **8a**, **8b**

Substrate	reaction conditions/time for completion	product	(yield %)
8a	1.0 eq DDH, collidine, perkadox, n-hexane-CH_2Cl_2 (7:1), rt/19'	**9a**	(58 %)
8b	1.0 eq DDH, collidine, perkadox, n-hexane-CH_2Cl_2 (7:1), reflux/45'	**9b**	(41 %)
8a	1.5 eq NBS, pentane-CH_2Cl_2 (5.5:1), rt/1 h	**9a**	(95 %)[a]
8b	1.5 eq NBS, pentane-CH_2Cl_2 (5.5:1), rt/3 h	**9b**	(46 %)
8b	2.0 eq $Br_2(CCl_4)$, lutidine, isooctane-CH_2Cl_2 (4:1), rt/1 h	**9b**	(70 %)
8b	2.0 eq $Cl_2(CCl_4)$, lutidine, isooctane-CH_2Cl_2 (4:1), rt/30'	**18b**	(65 %)
8a	1.5 eq NCS, 2-propanol, benzene, reflux/30'	**18a**	(95 %)[a]
8b	1.5 eq NCS, 2-propanol, chloroform, reflux/1 h	**18b**	(95 %)[a]

[a] crude, without purification on silica gel.

It was recognized very early that according to the allylic bromination mechanism, the slow and even addition of bromine should lead to substitution, provided the HBr formed upon reaction was gradually

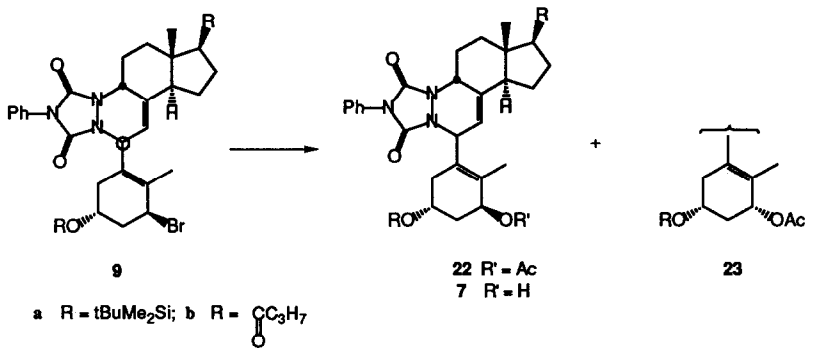
removed.[17] Treatment of **8a** or **8b** with a 1 M standard solution of Br_2 in CCl_4 over a 1 h period at room temperature in the presence of lutidine effectively led to the clean formation of the corresponding allylic bromides. Interestingly, the analogous addition of chlorine led to the expected allylic chlorides, respectively **18a** and **18b**, next to substantial amounts of the triene derivative **21** (~15-20 %). Careful examination of the bromination reaction, however, also revealed the presence of small amounts of the same triene **21** when the reaction was quenched after 5 min. The formation of triene **21** is rationalized in scheme 5. Abstraction of the tertiary hydrogen at C-6 leads to the resonance stabilized radical **19**, which upon subsequent halogenation is expected to lead to the tertiary halogenide **20**, and after dehydrohalogenation to triene **21**. There are several examples known in the literature whereby bromination of a tertiary position led to the elimination product.[18] The presence of larger amounts of triene **21** in the case of chlorination may be due to the less pronounced steric requirements of the smaller chlorine. No reaction was observed when **8** was treated with N-chlorosuccinimide (NCS) at room temperature or at reflux. Heating in the presence of isopropanol, however, also led to allylic chloride **18** and triene **21** (Table 2). This observation is in line with the known lesser reactivity of NCS compared to chlorine with regard to radical trapping. It is not yet clear what mechanism operates here.



Scheme 5

The conversion of allylic bromide 9 into diol 7 (scheme 6).

In view of the 1(S)-configuration in bromide **8** further substitution to the desired 1(S)-oxy group should proceed via retention. Early experiments with potassium acetate led either to no reaction (in CH_2Cl_2 or acetic acid) or to the predominant formation of the 1(R)-isomer **23** (KOAc, CH_2Cl_2, 18-crown-6, 24 h, rt).



9

22 R' = Ac
7 R' = H

23

a R = $tBuMe_2Si$; **b** R = $C(=O)C_3H_7$

Scheme 6

Acetates **22a** and **22b** with the desired 1(S)-configuration, were formed with a good stereoselectivity (~10:1) when the corresponding allylic bromides **9a** and **9b** were treated with Hg(II)acetate in CH_2Cl_2. Presumably substitution takes place after Hg(II)complexation with the least hindered side of the π-bond. Removal of the ester groups in **22b** under basic conditions (potassium carbonate, MeOH, reflux, 1 hr) leads to diol **7** in almost quantitative yield.

The overall sequence **8b** → **9b** → **22b** → **7** represents a short and efficient sequence in the context of 1α-hydroxy vitamin D_3 synthesis.

EXPERIMENTAL SECTION

All reactions were carried out under argon atmosphere with magnetic stirring (unless otherwise specified). Column chromatography was performed on SiO_2. HPLC separations were performed on a Knauer 64, a Waters 6000A or a Kontron 420 delivery system with RI detection. IR spectra were recorded on a Beckmann IR 4230 or a Perkin Elmer FTIR-1600 spectrometer, mass spectra on a Finnigan 4000 or a HP-5988 spectrometer. The ^1H NMR spectra were recorded in $CDCl_3$ at 360 or 500 MHz (WH-Brucker), the chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz.

The bromide 9a via DDH

To a vigorously stirred soln of adduct **8a** (4.4 g, 6.54 mmol) in CH_2Cl_2 (10 ml) and n-hexane (70 ml) are added collidine (1 ml), DDH (1.87 g, 6.54 mmol) and perkadox (cat.). The reaction was complete after 19 min (roomtemperature). The solids were filtrated and washed with CH_2Cl_2 (2 x 20 ml). The combined filtrates were washed with 2 N NaOH (20 ml) and saturated aqueous NaCl solution (2 x 10 ml). After removal of the solvents in vacuo (bath-temperature 30°C) the crude compound was recrystallised from n-hexane (250 ml) yielding bromide **9a** (2.84 g, 95 % NMR, 58 %; one crop. white needles).

Rf (pentane/acetone 9:1) : 0.52. IR (KBr) : 1770, 1714, 1634, 1598, 1502, 1488, 1470, 1416 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.34 (m, 1); 5.23 (m, 1); 5.18 (m, 1); 4.80 (dd, 1, J = 3 and 3 Hz); 4.46 (dm, 1, J = 13 Hz); 4.38 (dddd, 1, J = 4, 5, 10 and 11 Hz); 3.14 (ddd, 1, J = 3.9, 7.3 and 12.0 Hz); 2.6 (m, 1); 2.34 (m, 2); 2.18 (m, 1); 2.08 (ddd, 1, J = 4.1, 11.3 and 14.3 Hz); 2.01 (m, 2); 1.95 (s, 3); 1.88 (m, 2); 1.77 (ddd, 1, J = 7.8, 11.0 and 13.7 Hz); 1.53 (hp, 1, J = 6.6 Hz); 1.37 (m, 6); 1.15 (m, 3); 1.03 (m, 1);

0.93 (d, 3, J = 5.5 Hz); 0.9 (s, 9); 0.89 (d, 3, J = 2.5 Hz); 0.87 (d, 3, J = 4.5 Hz); 0.79 (s, 3); 0.09 (s, 6) ppm. MS : m/z 395 (2), 363 (6), 252 (6), 178 (26), 105 (22). Anal. found C, 64.79; H, 8.13; N, 5.67 : $C_{41}H_{62}O_3N_3BrSi$ requires C, 65.40; H, 8.90; N 5.58.

The bromide 9a via NBS

To a vigorously stirred soln of adduct **8a** (2 g; purity 92 %; 2.73 mmol) in CH_2Cl_2 (5.9 ml) and pentane (32.6 ml), N-bromosuccinimide (729 mg; 1.5 eq) was added, and stirring was continued for 1 h. The solids were filtrated and washed with CH_2Cl_2 (2 x 20 ml). The combined filtrates were washed with water (50 ml), sat. aq. $NaHCO_3$ soln (50 ml) and sat. aq. NaCl soln (50 ml) and dried over anh. $MgSO_4$. Removal of the solvent in vacuo (bath-temperature below 40°C) gave crude bromide **9a** (2.103 g; 94 %).

The bromide 9a via Br_2

To a vigorously stirred soln of adduct **8a** (1.460 g; purity 92 %; 2 mmol) and lutidine (466 µl; 2 eq.) in isooctane/CH_2Cl_2 9:1 (100 ml), a soln of bromine (206 µl; 2 eq.) in CCl_4 (2 ml) was added dropwise during 1 h. The solids were filtrated and washed with CH_2Cl_2 (2 x 20 ml). The combined filtrates were washed with water (50 ml), sat. aq. $NaHCO_3$ soln (50 ml) and sat. aq. NaCl soln (50 ml) and dried over anh. $MgSO_4$. Removal of the solvent in vacuo (bath-temperature below 40°C) gave crude bromide **9a** (1.5 g; quant.).

The bromide 9b via DDH

To a vigorously stirred soln of adduct **8b** (0.49 g, 0.80 mmol) in CH_2Cl_2 (1.5 ml) and n-hexane (10 ml) are added collidine (0.1 ml), DDH (0.23 g, 0.80 mmol) and perkadox (cat.). The mixture was refluxed for 45 min. The solids were filtrated and washed with CH_2Cl_2 (2 x 1 ml). The combined filtrates were washed with 0.5 N NaOH (1 ml) and water (2 x 2 ml) and dried over anh. Na_2SO_4. Removal of the solvent in vacuo (bath-temperature below 40°C) gave crude bromide **9b** (0.23 g, 41 %).
Rf (pentane/acetone 8:2) : 0.74. UV : λ_{max} = 230 µm (CH_2Cl_2). IR (KBr) : 1769, 1732, 1716, 1502, 1490, 1456, 1409 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.34 (m, 1); 5.32 (dddd, 1, J = 3.5, 5.7, 9.7 and 11.6 Hz); 5.26 (m, 1); 5.18 (m, 1); 4.77 (dd, 1, J = 2 and 3 Hz); 4.45 (dm, 1, J = 13 Hz); 3.11 (ddd, 1, J = 4.2, 7.5 and 12.3 Hz); 2.58 (m, 1); 2.54 (m, 1); 2.46 (dm, 1, J = 14 Hz); 2.27 (t, 2, J = 7.3 Hz); 2.20 (m, 2); 2.00 (m, 2); 1.97 (s, 3); 1.86 (m, 2); 1.75 (ddd, 1, J = 7.6, 11.6 and 13.6 Hz); 1.64 (hx, 2, J = 7.4 Hz); 1.53 (m, 1); 1.37 (m, 6); 1.14 (m, 3); 1.02 (m, 1); 0.94 (s, 3); 0.94 (t, 3, J = 7.4 Hz); 0.88 (d, 3, J = 2.4 Hz); 0.87 (d, 3, J = 2.4 Hz); 0.79 (s, 3) ppm. Anal. found C, 65.99; H, 7.74; N, 5.82 : $C_{39}H_{54}O_4N_3Br$ requires C, 66.09; H, 7.69; N, 5.93.

The bromide 9b via NBS

To a vigorously stirred soln of adduct **8b** (1.72 g; 2.73 mmol) in CH_2Cl_2 (5.9 ml) and pentane (32.6 ml), N-bromosuccinimide (729 mg; 1.5 eq) was added, and stirring was continued for 3 h. TLC-analysis still showed the presence of a minor amount of starting material. The solids were filtrated and washed with CH_2Cl_2 (2 x 20 ml). The combined filtrates were washed with water (50 ml), sat. aq. $NaHCO_3$ soln (50 ml) and sat. aq. NaCl soln (50 ml) and dried over anh. $MgSO_4$. After removal of the solvent in vacuo (bath-temperature

below 40°C) the crude compound was recrystallized in acetone (30 ml), yielding bromide **9b** as slight yellow needles (0.89 g; 46 %).

The bromide 9b via Br_2

To an efficiently stirred soln of the adduct **8b** (1.206 g; 2 mmol) and lutidine (466 µl; 2 eq) in isooctane/CH_2Cl_2 8:2 (100 ml), a soln of bromine (206 µl; 2 eq.) in CCl_4 (2 ml) was added dropwise during 1 h. The solids were filtrated and washed with CH_2Cl_2 (2 x 20 ml). The combined filtrates were washed with water (50 ml), sat. aq. $NaHCO_3$ soln (50 ml) and sat. aq. NaCl soln (50 ml) and dried over anh. $MgSO_4$. After removal of the solvent in vacuo (bath-temperature below 40°C) the crude compound was recrystallised in acetone (40 ml) giving bromide **9b** (991 mg, 70 %, one crop); slight yellow needles. Although the mother liquid still consisted mostly of the bromide, attempts for a second crop were unsuccessful. Rf (pentane/acetone 8:2) : 0.74.

The chloride 18a via NCS

A mixture of adduct **8a** (134 mg; 0.2 mmol), N-chlorosuccinimide (40 mg; 1.5 eq.) and 2-propanol (200 µl) in benzene (10 ml) was refluxed for 30 min. Hexane (10 ml) was added and the precipitates were removed by filtration. Removal of the solvent in vacuo gave crude chloride **18a** (140 mg; quant.).
IR (KBr) : 1765, 1715 (broad), 1490, 1460, 1410 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.33 (m, 1); 5.25 (m, 1); 5.18 (m, 1); 4.60 (m, 1, J < 3 Hz); 4.47 (dm, 1, J = 13.2 Hz); 4.17 (m, 1); 3.14 (ddd, 1, J = 3.7, 7.2 and 12.2 Hz); 2.60 (m, 1); 2.29 (m, 1); 2.25 (m, 2); 2.02 (m, 3); 1.93 (s, 3); 1.87 (m, 2); 1.76 (ddd, 1, J = 7.7, 11.1 and 13.5 Hz); 1.53 (hp, 1, J = 6.7 Hz); 1.46 (m, 6); 1.14 (m, 3); 1.01 (m, 1); 0.92 (d, 3, J = 5.0 Hz); 0.88 (m, 15); 0.78 (s, 3); 0.08 (s, 6) ppm.

The chloride 18b via NCS

A mixture of adduct **8b** (1 g; 1.587 mol), N-chlorosuccinimide (337.7 mg; 1.5 eq.) and 2-propanol (10 ml) in $CHCl_3$ (100 ml) was refluxed for 1 h. The reaction mixture was washed with aq. 2N NaOH soln (2 x 50 ml), with sat. aq. NaCl soln (50 ml) and dried over anh. $MgSO_4$. Removal of the solvent in vacuo gave crude chloride **18b** (1.005 g; 95 %).
Rf (pentane/acetone 8:2) : 0.50. IR (KBr) : 1714 (broad), 1600, 1504 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.34 (m, 1); 5.27 (m, 1); 5.24 (dddd, 1, J = 3.5, 5.6, 9.5 and 11.1 Hz); 5.18 (m, 1); 4.59 (dd, 1, J = 2 and 3 Hz); 4.46 (dm, 1, J = 11.4 Hz); 3.11 (ddd, 1, J = 4.3, 7.4 and 12.3 Hz); 2.59 (m, 1); 2.50 (dd obs., 1, J = 5.6 and 16.6 Hz); 2.37 (dm, 1, J = 13.7 Hz); 2.26 (t, 2, J = 7.3 Hz); 2.14 (m, 2); 2.00 (dd, 1, J = 7.37 and 13.5 Hz); 1.96 (s, 3); 1.86 (m, 2); 1.75 (ddd, 1, J = 7.6, 11.2 and 13.5 Hz); 1.64 (hx, 2, J = 7.4 Hz); 1.53 (m, 2); 1.37 (m, 6); 1.14 (m, 3); 1.02 (m, 1); 0.93 (t, 3, J = 7 Hz); 0.92 (d, 3, J = 5.6 Hz); 0.88 (d, 3, J = 2.3 Hz); 0.87 (d, 3, J = 2.3 Hz); 0.79 (s, 3) ppm.

The chloride 18b via Cl_2, isolation of the triene 21b

To a soln of adduct **8b** (1.206 g; 2 mmol) and lutidine (466 µl; 2 eq.) in isooctane/CH_2Cl_2 8:2 (100 ml) a 1 M CCl_4 soln of Cl_2 (4 ml; 2 eq.) was added dropwise over 30 min. The precipitate was filtrated and washed with CH_2Cl_2 (2 x 5 ml). The combined filtrates were washed with water (50 ml), sat. aq. $NaHCO_3$

soln, sat. aq. NaCl soln and dried over anh. $MgSO_4$. Purification by column chromatography (pentane/dichloromethane/acetone 8:1:1) yielded chloride **18b** (863 mg; 65 %) as a white solid. Further elution gave triene **21b** (231 mg; 18 %) as a slight yellow solid.

Spectral data of **21b** : Rf (pentane/acetone 8:2) : 0.40. UV : λ_{max} (CH_2Cl_2) = 225, 272 and 318 µm. IR (KBr) : 1733, 1694, 1600, 1503, 1456, 1427 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.36 (m, 1); 6.12 (ddd, 1, J = 2.7, 2.7 and 6.1 Hz); 5.35 (dd, 1, J = 1.7 and 6.7 Hz); 5.2 (dddd, 1, J = 3.6, 3.6 and 8.9 Hz); 4.65 (dm, 1, J = 13.4 Hz); 3.15 (ddd, 1, J = 4.2, 7.8 and 12.7 Hz); 2.60 (m, 1); 2.38 (dd, 1, J = 10.4 and 12.8 Hz); 2.31 (m, 1); 2.27 (t, 2, J = 6.9 Hz); 2.01 (m, 2); 1.84 (m, 3); 1.71 (s, 3); 1.68 (m, 1); 1.65 (hx, 2, J = 4.7 Hz); 1.53 (m, 2); 1.37 (m, 6); 1.15 (m, 3); 1.01 (m, 1); 0.95 (t, 3, J = 7.4 Hz); 0.91 (d, 3, J = 7.13 Hz); 0.88 (d, 3, J = 2.3 Hz); 0.87 (d, 3, J = 2.3 Hz); 0.75 (s, 3) ppm.

The 1(S)-acetate 22a

A mixture of bromide **9a** (323 mg; 0.429 mmol) and mercuric acetate (409 mg; 3 eq.) in CH_2Cl_2 (10 ml) was stirred for 1 h. The solids were filtrated and washed with CH_2Cl_2 (2 x 10 ml). Concentration of the combined filtrates in vacuo and purification by column chromatography (pentane/acetone 9:1) gave 1(S)-acetate **22a** and 1(R)-acetate **23** in a ratio better than 10:1 by ^1H NMR analysis (265 mg; 84 %). An analytical sample of the latter was obtained via HPLC-purification (hexane:CH_2Cl_2:acetone 9:1:0.3). For **22a** : Rf (pentane/acetone 8:2) : 0.60. IR (KBr) : 1765, 1730, 1705, 1590, 1490, 1460, 1410 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.33 (m, 1); 5.37 (dd, 1, J = 1.8 and 4.2 Hz); 5.27 (m, 1); 5.20 (m, 1); 4.48 (dm, 1, J = 13.0 Hz); 3.89 (dddd, 1, J = 3.4, 5.0, 9.5 and 11.7 Hz); 3.14 (ddd, 1, J = 3.8, 7.4 and 12.0 Hz); 2.61 (m, 1); 2.24 (dd obs., 1, J = 5.3 and 16.5 Hz); 2.08 (s, 3); 2.07-1.70 (m, 8); 1.78 (s, 3); 1.53 (hp, 1, J = 6.6 Hz); 1.36 (m, 6); 1.14 (m, 3); 1.02 (m, 1); 0.92 (d, 3, J = 5.4 Hz); 0.88-0.85 (m, 15); 0.78 (s, 3); 0.03 (s, 6) ppm. MS : m/z 675 (1), 674 (2), 540 (1), 435 (1), 447 (1), 363 (8), 252 (9), 178 (26), 117 (30).

For **23** : IR (KBr) : 1765, 1730, 1710, 1495, 1460, 1410 cm^{-1}. ^1H NMR (500 MHz) : 7.49 (m, 2); 7.43 (m, 2); 7.33 (m, 1); 5.44 (t, 1, J = 9 Hz); 5.27 (m, 1); 5.13 (m, 1); 4.57 (dm, 1, J = 11.5 Hz); 3.75 (m, 1); 3.15 (ddd, 1, J = 3.7, 7.1 and 11.8 Hz); 2.60 (m, 1); 2.27 (m, 1); 2.14 (m, 1); 2.05 (s, 3); 2.01 (m, 2); 1.86 (m, 2); 1.78 (m, 1); 1.71 (s, 3); 1.65 (m, 2), 1.53 (hp, 1, J = 6,6 Hz); 1.36 (m, 6); 1.14 (m, 3); 1.02 (m, 1); 0.94-0.85 (m, 18); 0.77 (s, 3); 0.03 (s, 6) ppm. MS : m/z 365 (1), 363 (12), 280 (2), 249 (3), 178 (50), 105 (28).

The 1(S)-acetate 22b

A mixture of bromide **9b** (284 mg; 0.4 mmol) and mercuric acetate (382 mg; 3 eq) in CH_2Cl_2 (10 ml) was stirred for 1 day. The solids were filtrated and washed with CH_2Cl_2 (5 ml). Removal of the solvent in vacuo and purification by HPLC (isooctane/acetone 9:1) gave 1(S)-acetate **22b** as a white foam (212 mg; 77 %). Rf (pentane/acetone 8:2) : 0.49. IR (KBr) : 1765, 1735, 1710, 1500, 1415 cm^{-1}. ^1H NMR (500 MHz) : 7.45 (m, 4); 7.34 (m, 1); 5.41 (br t, 1, J = 4 Hz); 5.30 (m, 1); 5.19 (m, 1); 5.02 (dddd, 1, J = 3.6, 5.2, 9.0 and 11.2 Hz); 4.47 (dm, 1, J = 13.2 Hz); 3.11 (ddd, 1, J = 4.3, 7.5 and 12.5 Hz); 2.60 (m, 1); 2.43 (br dd, 1, J = 5.4 and 16.4 Hz); 2.25 (t, 2, J = 7.3 Hz); 2.09 (s, 3); 2.04 (m, 3); 1.91 (ddd, 1, J = 4.7, 11.6 and 13.7 Hz); 1.87 (m, 2); 1.81 (s, 3); 1.76 (m, 1); 1.65 (m, 1); 1.62 (hx, 2, J = 7.4 Hz); 1.52 (hp, 1, J = 6.6 Hz); 1.35 (m, 6); 1.14 (m, 3); 1.02 (m, 1); 0.92 (t, 3, J = 7.4 Hz); 0.91 (d, 3, J = 3.6 Hz); 0.88 (d, 3, J =

2.4 Hz); 0.87 (d, 3, J = 2.5 Hz); 0.78 (s, 1) ppm. MS : m/z 363 (5), 243 (3), 195 (2), 178 (10), 155 (5), 115 (10), 105 (13).

The diol 7

A mixture of acetate **22b** (30 mg; 0.0436 mmol) and K_2CO_3 (12 mg; 2 eq.) in dry MeOH (1 ml) was refluxed for 1 h. The solid was removed by filtration, washed with MeOH (2 x 1 ml), and the solvent removed in vacuo. The residue was taken up in EtOAc (10 ml), washed with sat. aq. NaCl (2 x 5 ml), and dried over anh. $MgSO_4$. Removal of the solvent in vacuo gave crude diol **7** (26 mg, quant.). Rf (pentane/acetone 6:4) : 0.34. UV : λ_{max} = 222 nm (MeOH). IR (KBr) : 1765, 1710, 1600, 1500, 1420 cm^{-1}. ^1H NMR (360 MHz) : 7.48-7.32 (m, 5); 5.29 (m, 1); 5.19 (m, 1); 4.48 (m, 1); 4.27 (m, 1); 4.09 (m, 1); 1.93 (s, 3); 0.92 (d, 3, J = 5 Hz); 0.878 (d, 3, J = 6.5 Hz); 0.873 (d, 3, J = 6.5 Hz); 0.78 (s, 3) ppm. MS : m/z 575 ($M^{+\cdot}$, 10), 400 (25), 399 (72), 398 (100), 383 (28), 382 (35), 281 (80), 380 (30), 363 (40), 362 (28), 285 (34), 259 (20), 245 (20), 178 (95).

Allylic bromination of 3-cholesterolacetate (13) with NBS

A mixture of 3-cholesterolacetate **13** (171 mg; 0.4 mmol) and N-bromosuccinimide (78.3 mg; 1.1 eq) in n-hexane/CH_2Cl_2 9:1 (20 ml) was irradiated (500W spotlight) under reflux for 2 h. Removal of the solvent in vacuo and purification by column chromatography (hexane/CH_2Cl_2/acetone 9:1:0.2) gave dibromoadduct **14** (72 mg; 35 %). Rf (hexane/CH_2Cl_2/acetone 9:1:1) : 0.68. IR (KBr) : 1736, 1467, 1378, 1366, 1312, 1266 cm^{-1}. ^1H NMR (500 MHz) : 5.48 (m, 1); 4.83 (dd, 1, J = 1.9 and 4.2 Hz); 2.67 (ddd, 1, J = 4.3, 12.3 and 15.5 Hz); 2.59 (dd, 1, J = 10.4 and 14.0 Hz); 2.27 (ddd, 1, J = 1.6, 5.4 and 14.1 Hz); 2.04 (s, 3); 2.1-1.0 (m, 25); 1.47 (s, 3); 0.91 (d, 1, J = 6.5 Hz), 0.88 (d, 3, J = 2.1 Hz); 0.86 (d, 3, J = 2.1 Hz); 0.71 (s, 3) ppm.

Further elution (hexane/CH_2Cl_2/acetone 9:1:1) gave 7-hydroxy-cholesterolacetate (**15**) (56 mg; 32 %). Rf (hexane/CH_2Cl_2/acetone 9:1:1) : 0.36. IR (KBr) : 3600-3200, 1730, 1660, 1460, 1430, 1375 cm^{-1}. ^1H NMR (500 MHz) : 5.63 (dd, 1, J = 1.3 and 5.2 Hz); 4.64 (m, 1); 3.84 (m, 1); 2.37 (m, 2); 2.03 (s, 3); 2.0 (m, 2); 1.88 (m, 4); 1.73-1.0 (m, 16); 1.56 (s, 3); 1.01 (s, 3); 0.92 (d, 3, J = 6.5 Hz); 0.87 (d, 3, J = 2.1 Hz); 0.85 (d, 3, J = 2.1 Hz); 0.68 (s, 3) ppm.

Self-initiating capacity of 8a upon NBS-reaction with 3-cholesterolacetate (13)

To an efficiently stirred soln of 3-cholesterolacetate (**13**) (85.6 mg; 0.2 mmol) and adduct **8a** (28 mg; 0.2 eq.) in benzene (10 ml), N-bromosuccinimide (48.6 mg; 1.5 eq.) was added. After 4 h at rt, a complex reaction mixture was obtained (TLC), consisting mainly of starting material, next to dibromoadduct **14** and an unambiguously detectable amount of alcohol **15**; the latter showed a characteristic blue color when detected on TLC with MeOH/10 % H_2SO_4 (Δ). In a control experiment without adduct **8a** no reaction occurred.

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