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## A mild method for the replacement of a hydroxyl group by halogen: 2. Unified procedure and stereochemical studies.

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### ABSTRACT

*N,N*-Dimethyl- and *N,N*-diisopropyl-1-halo-2-methyl-1-propenylamines are readily available reagents for the mild deoxyhalogenation of alcohols and hydroxyacids. In this study we showed that the reactivity of the reagents can be tuned by varying the size of the alkyl groups on the reagents: the replacement of methyl by isopropyl groups led to a significant increase of reactivity. We then described a unified procedure for all deoxyhalogenations using the readily available  $\alpha$ -chloroamines as reagents with (bromination, iodination) or without (chlorination) an alkaline bromide or iodide. Finally, we showed that deoxyhalogenation reactions of secondary alcohols were highly stereospecific and generally occurred with inversion of configuration.

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### 1. Introduction

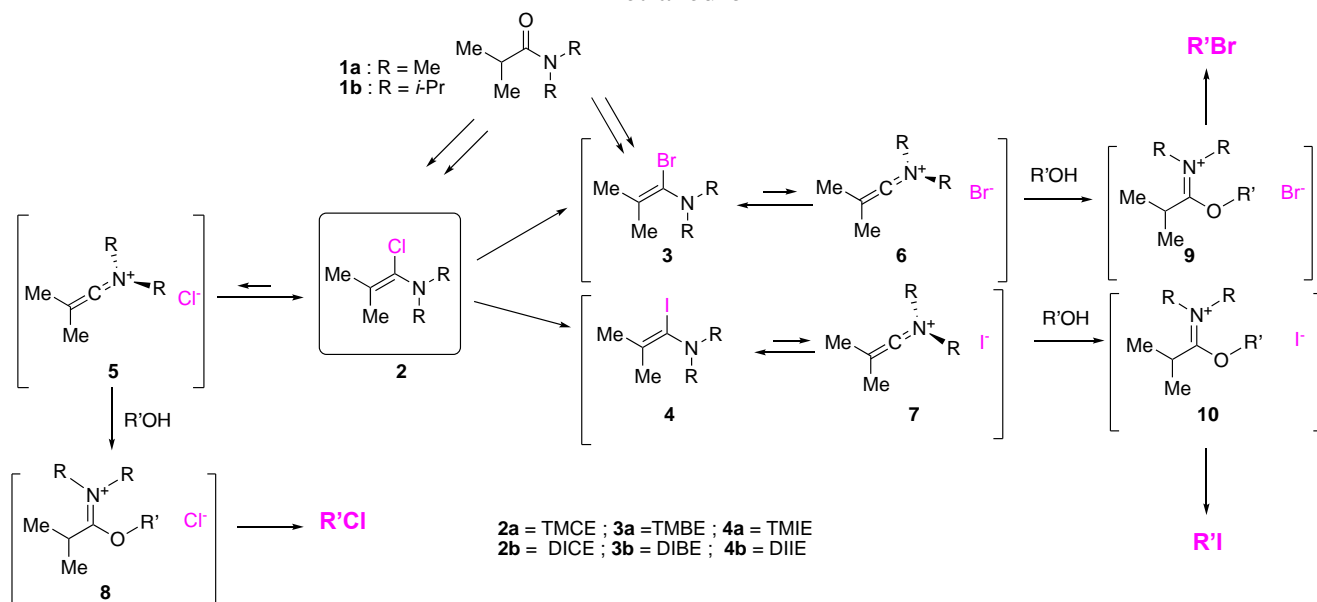
Hydroxyl-containing molecules are plentiful and often cheap starting materials in organic synthesis. Thus, they have been extensively used as a convenient source of organic halides. Several inexpensive and commercially available reagents (eg HCl, HBr, SOCl<sub>2</sub>, OPCl<sub>3</sub>...) have been used for this transformation which has also been successful on an industrial scale [1]. However, the strong acidity of these reagents prohibits their use with acid-sensitive molecules. Accordingly, there has been much effort to find milder procedures of deoxyhalogenation of alcohols and other hydroxyl-containing compounds. Thus, deoxychlorination reactions can be efficiently performed with oxalyl chloride and a base [1]. Also, the reaction of a phosphine or a phosphite with chlorine or bromine or the corresponding carbon tetrahalides (Appel reaction) generates

an intermediate which converts alcohols into chlorides or bromides under mild and non-acidic conditions [1,2]. However, these methods use toxic reagents or produce much waste.

Several years ago we discovered that tertiary amides such as **1a** and **1b** could be easily converted into *N,N*-dimethyl- and *N,N*-diisopropyl-1-chloro- and -bromo-2-methyl-1-propenylamines **2a,b** and **3a,b** in the presence of phosgene (or phosgene dimer or trimer) or more conveniently with phosphorous oxychloride or bromide (Scheme 1) [3]. The corresponding iodoamines **4a, b** could be prepared by halide exchange between **2a,b** and an alkaline iodide [4]. We had indeed demonstrated that  $\alpha$ -haloamines were in equilibrium with the corresponding keteniminium halides **5, 6** and **7** and behaved thus as powerful electrophilic reagents [5]. This equilibrium was responsible for the ability of  $\alpha$ -haloamines to perform the replacement of a hydroxyl group by chlorine, bromine and iodine [5-7]. Addition of hydroxyl-containing compounds such as alcohols, carboxylic and other hydroxy-acids to the very electrophilic keteniminium salts led to alkoxy- or acyloxy iminium salts **8, 9** and **10**. These behaved as activated derivatives of the hydroxyl-containing substrates:

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**Scheme 1.** Deoxyhalogenation of alcohols (R' = Alkyl) and carboxylic acids (R' = R''CO)

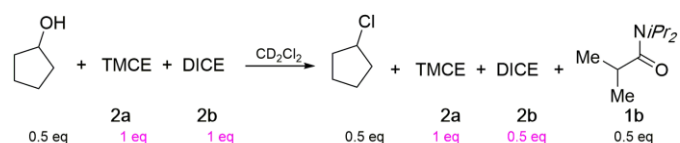
the carbon atom carrying the oxygen group became quite sensitive to nucleophilic reagents and allowed nucleophilic attack by a halide ion to yield the corresponding alkyl or acyl halides [6,7]. These reactions generally took place at room temperature or below without the formation of hydrogen halides. As a result of these mild conditions this new method of deoxyhalogenation showed a wide substrate scope. Thus,  $\alpha$ -haloenamines were shown to convert a wide variety of oxyacids into highly pure acyl halides in very good yields [6-8]. Furthermore, the method allowed the use of these sensitive acyl halides without purification since the reaction mixture only contained the fairly inert tertiary amide **1a** or **1b** as co-product. Thus, TMCE and TMBE were successfully used to prepare amino acid chlorides or bromides carrying sensitive protecting groups for peptide coupling reactions [9, 10]. Remarkably this sequence of reaction occurred without racemization. Immobilized  $\alpha$ -haloenamines reagents have also been prepared and used in syntheses of protected amino acid halide monomers and oligomers for the preparation of polyamides [11]. A wide variety of alcohols were converted into the corresponding chlorides, bromides or iodides under these very mild conditions which allowed the presence of many sensitive functional groups. Interestingly the selectivity of these reagents could be finely *tuned* by varying the size of the alkyl groups on nitrogen. Thus, the simple replacement of two methyl by two isopropyl groups on nitrogen allowed to selectively convert primary alcohols in the presence of secondary alcohols *without the use of protecting groups*. We should also emphasize the *high atom economy* of the method: the *co-product* generated in the halogenation reaction is an isobutyramide (**1a** or **1b**) which is the *starting material* for the synthesis of the  $\alpha$ -haloenamine.

A few years ago, we published the first detailed account of our studies of this novel deoxyhalogenation procedure. It dealt with the scope and the chemoselectivity of the reaction [7]. We now report our studies of (1) an improved procedure for the deoxybromination and iodination reactions, (2) the stereochemistry of these halo-deoxygenation reactions.

## 2. Results and discussion

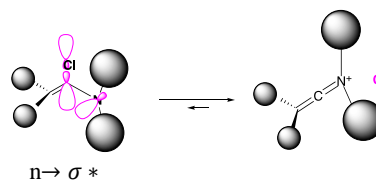
### 2.1. A unified deoxyhalogenation procedure

Expectedly, the commercially available TMCE **2a** has been preferred by most users of the deoxychlorination reaction. We had however demonstrated that DICE **2b** should be the preferred reagent when a problem of *chemoselectivity* arose [7]. DICE **2b** is not commercially available but can be conveniently prepared in kg amounts from the corresponding amide **1b**, phosphorous oxychloride and triethylamine [3b]. We recently found that there could be another reason to prefer DICE **2b** to TMCE **2a**: the presence of bulkier groups on nitrogen was indeed found to considerably increase the *reactivity* of the reagent as shown by the competition experiment described in Scheme 2. Even with only a two-fold excess of reagents **2a** and **2b**, cyclopentanol exclusively reacted with the bulkier reagent **2b**. Thus, it can be concluded that DICE was not only *more selective* but also *more reactive* than TMCE.



**Scheme 2.** Relative reactivities of TMCE and DICE

This increased reactivity probably resulted from the repulsion between the alkyl groups on nitrogen and carbon which forces the molecule to adopt a conformation with the nitrogen lone pair antiperiplanar to the C-Cl bond, favouring thus the formation of a keteniminium chloride (Scheme 3). As shown earlier [7], the increased selectivity of DICE resulted from a higher steric

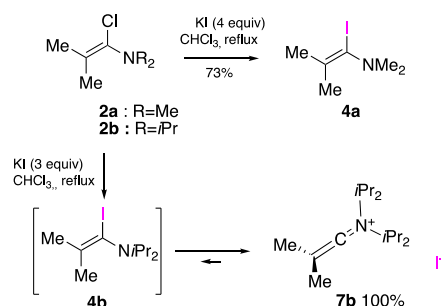


**Scheme 3.** Conformation favouring ionization of DICE

discrimination in the addition of the alcohol to the keteniminium carrying bulkier groups (Scheme 1).

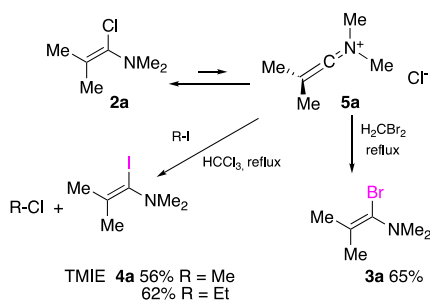
Both TMCE and DICE are bench stable reagents, but they are very sensitive to moisture. However small amounts of hydrolysis products **1a** or **1b** in the reagents were shown to be harmless for the deoxychlorination reaction.

The corresponding deoxybromination reagents TMBE **3a** and DIBE **3b** (Scheme 1) could also be prepared in multigram quantities from *N,N*-2-trimethyl-propanamide or *N,N*-diisopropylisobutyramide and phosphorous oxybromide in the presence of triethylamine [3b]. Tetramethyliodoamine TMIE **4a** was readily prepared by the reaction of TMCE **2a** with a three- to six-fold excess of a suspension of 4 equivalents dry KI (or NaI, LiI) in refluxing chloroform (or DCM) to yield around 75% of TMIE after purification by distillation (Scheme 4) [4]. A halogen exchange was also observed when DICE **2b** was reacted with a suspension of KI in chloroform (Scheme 4). However, the covalent  $\alpha$ -iodoamine **4b** was not observed: it spontaneously ionized to keteniminium iodide **7b**. Clearly the steric interactions resulting from large substituents on nitrogen (see Scheme 3) and the presence of a weaker carbon-halogen bond are responsible for the complete ionization of **4b**. Disappointingly a chlorine vs bromine exchange was not observed when TMCE was reacted with a suspension of KBr in refluxing chloroform for 12 hours. Explaining this difference between KI and KBr would be difficult since both reactions were performed in heterogeneous conditions. However, both **2a** and **2b** underwent a fast halide exchange with a 2.5 excess of LiBr or LiI in acetonitrile at room temperature ( $^1\text{H}$ - and  $^{13}\text{C}$ -NMR).



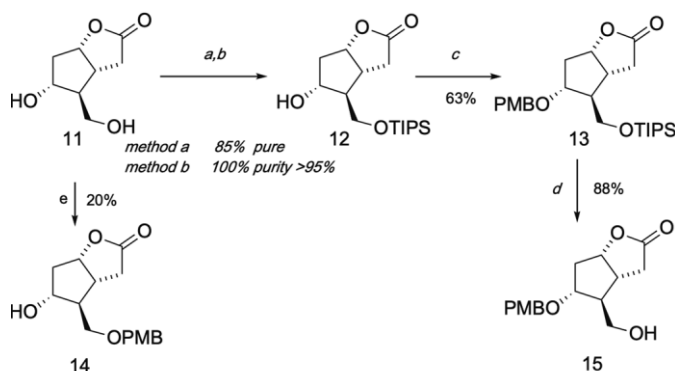
Scheme 4. Synthesis of  $\alpha$ -iodoamines **4a,b** and keteniminium iodide **7b**.

Interestingly, we also observed a halogen exchange when TMCE **2a** was reacted with a four-fold excess of methyl iodide in refluxing chloroform (Scheme 5). This could again be readily explained by the equilibrium between TMCE **2a** and the corresponding keteniminium chloride TMK **5a**. Ionization would be followed by a nucleophilic attack of the chloride ion on the alkyl iodide to form the corresponding alkyl chloride and TMIE **4a**. We also observed that TMBE could be conveniently prepared in 65% yield after distillation by refluxing a solution of TMCE **2a** in dibromomethane for 20 hours.



Scheme 5. Reaction of TMCE with alkyl iodides and dibromomethane.

We felt that users of these reactions would welcome the possibility of performing deoxybromination and -iodinations in a “one-pot” procedure involving the readily available  $\alpha$ -chloroamine reagents TMCE **2a** or DICE **2b** and a source of bromide or iodide ion. We decided to test this “one-pot” procedure on derivatives of diol **11** derived from Corey’s lactone. It was expected that the deoxychlorination of this diol could be somewhat challenging. The reactivity of both hydroxyl group should indeed be decreased by either the presence of two alkyl groups  $\beta$  to the primary hydroxyl group or by steric factors resulting from the presence of a lactone ring *cis* to the secondary hydroxyl group. We thus decided to prepare derivatives of **11** carrying a protecting group on one alcohol group (Scheme 6).



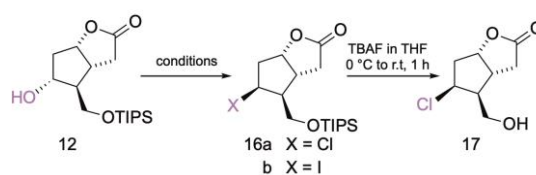
a) TIPSOTf (1.1 equiv),  $\text{Et}_3\text{N}$  (1.5 equiv), DMF, 0 °C to r.t., 8 h.; b) TfOH (1.1 equiv), TIPSH (1.15 equiv) in DCM then  $\text{Et}_3\text{N}$  (1.5 equiv), DMF, 0 °C to r.t., 8 h.; c) NaH (1.3 equiv), *t*BuOH (cat.), THF, 0 °C, 30 min then PMB-Cl (3 equiv),  $n\text{Bu}_4\text{N}^+\text{I}^-$  (0.5 equiv), 0 °C to r.t., 36 h; d) TBAF (1.1 equiv) THF, 0 °C, 15 min then r.t. 1 h.; e) NaH, PMB-Cl, DMF, 0 °C to r.t., 12 h.

Scheme 6. Synthesis of protected derivatives of diol **11**.

The mono-protected derivatives **12**, **14** and **15** were prepared as shown. In a preliminary experiment using a *tert*-butyldimethyl silyl protecting group for the primary alcohol of **11**, we had shown that the deoxychlorination gave a complex mixture of products. This could have resulted from the presence of the *cis*-lactone ring or (and) the cleavage of the *tert*-butyldimethyl silyl group.

We thus moved to the more stable TIPS protecting group [12] and studied the deoxychlorination of **12** (Scheme 7). A molar solution of TMCE **2a** in DCM gave the expected chloride **16a** but yields were moderate (Scheme 7, conditions a) and we still observed some desilylation (20% TIPSOH). The results were much better with DICE (conditions b) which gave 75% yield of the desilylated alcohol **17**.

We then proceeded with the “one-pot” deoxyiodination of **12**. In a first experiment (Scheme 7, conditions c), a suspension of LiI in a solution of TMCE (1.1 eq.) **2a** in dry dichloromethane was stirred for 10 min. at 0 °C. Adding the alcohol at 0 °C and

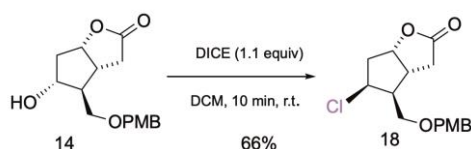


Conditions Yields % purified **16a** **16b** **17**

- a TMCE, 1 M in DCM 41 - -  
 b DICE, 0.5 M in DCM - - 75  
 c TMCE + LiI (1.5 eq), DCM  
 rt 10 min then 12, 0 °C to r.t. 43 (3:1 mixture of 16a/16b)  
 d TMCE + LiI (1.5 eq), DCM  
 rt 60 min then 12, 0 °C to r.t. - 46 -

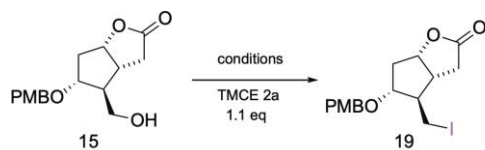
**Scheme 7.** The first one-pot deoxyiodinations of an alcohol with TMCE and LiI

stirring the mixture for 3 hours at room temperature yielded a 3:1 mixture of iodo- and chloro-lactone **16a/16b**. As anticipated, leaving the TMCE-LiI suspension in DCM for 1 hour at 0 °C before adding the alcohol (conditions d) was sufficient to suppress the formation of the chlorinated compound **16a**. This rewarding result demonstrated the feasibility of a deoxyiodination of an alcohol from the *in-situ* combination of a chlorinating reagent TMCE and a source of iodide ion. However, yields were moderate as a result of the presence of a trialkylsilyl protecting group on the primary alcohol. TIPSOH was detected in all reactions. The use of a more stable PMB protecting group on the primary alcohol as in **14** and a more reactive reagent (DICE) led to a slight improvement of the yields (66%) of purified **18** (Scheme 8).



**Scheme 8.** Deoxychlorination in the presence of a more stable protecting group.

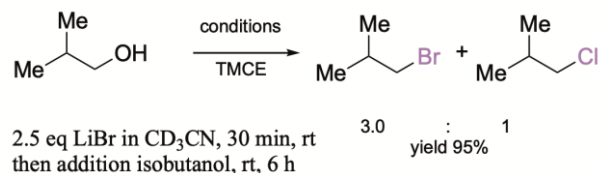
We also applied this one-pot procedure to the deoxyiodination of the primary alcohol of **15** (Scheme 9). In spite of presence of two alkyl groups  $\beta$  to the hydroxyl, the deoxyiodination procedure worked beautifully under very mild conditions: yields were high with both LiI (entry a) and KI (entries c and d) in the presence of TMCE **2a**. We did not see any spectacular solvent or cation effects on the yields of deoxyiodination. Under these mild conditions, we did not observe any cleavage of the PMB group [13]. This was however observed when the solution was warmed at 50 °C (entry b).



Conditions	Yields % (1H-NMR)
a LiI (1.5 eq) and <b>2a</b> (1.1 eq) in DCM, r.t. 1.5 h then <b>15</b> at 0 °C, and 4 h. at r.t.	82
b LiI (2 eq) and <b>2a</b> (1.1 eq) in DCM, r.t. 1 h then <b>15</b> at 0 °C, 3 h at r.t. and 1 h, 50 °C	mixture (cleavage PMB)
c KI (3 eq) and <b>2a</b> (1.1 eq) in DCM, r.t. 1.5 h then <b>15</b> at 0 °C and 4 h at r.t.	87
d KI (3 eq) and <b>2a</b> (1.1 eq) in MeCN, r.t. 1.5 h then <b>15</b> at 0 °C and 4 h at r.t.	92

**Scheme 9.** One-pot deoxyiodination of primary alcohol **15**.

We then tried to achieve a Cl vs Br exchange by reacting LiBr with a solution of TMCE in acetonitrile for 30 min. After addition of isobutanol to the resulting mixture, we rewardingly obtained a 3:1 mixture of isobutyl bromide and isobutyl chloride (Scheme 10). We envisioned that it would be possible to favour the deoxybromination reaction by increasing the concentration of LiBr which is more soluble in this polar solvent. This was indeed



**Scheme 10.** One-pot procedure for the deoxybromination of isobutanol.

**Table 1** One-pot deoxybromination and deoxyiodination of alcohols

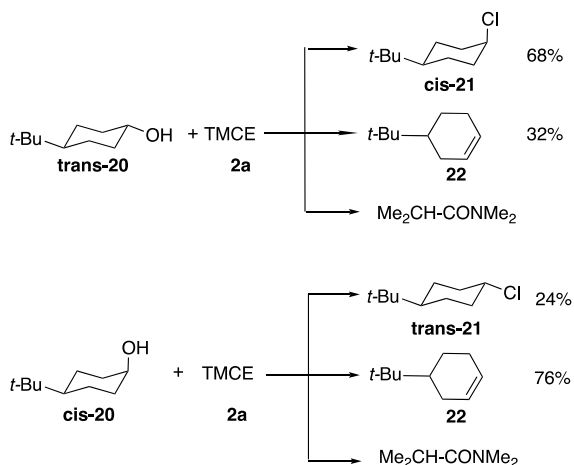
	Alcohol	Salt	Conditions	Halide % (NMR)
a		LiBr (2.5)	CD <sub>3</sub> CN, rt,	100
b		LiBr (2.5)	CDCl <sub>3</sub> , rt,	100
c		KI (2.5)	CD <sub>3</sub> CN, rt,	100
d		LiI (2.5)	CD <sub>3</sub> CN, rt,	100
e		KI (2.5)	CD <sub>3</sub> CN, rt,	100
f		LiI (2.5)	CDCl <sub>3</sub> , rt,	100

the case as illustrated in Table 1 (entry a) for the deoxybromination of 1-naphthalenemethanol, a primary alcohol. A 2.5-fold excess of LiBr was sufficient to quantitatively produce 1-bromomethyl-naphthalene and amide **1a** as shown by <sup>1</sup>H and <sup>13</sup>C NMR. Interestingly, in all reactions of Table 1, TMCE was added to the solvent already containing *both the salt and the alcohol*. Surprisingly, the reaction also worked in chloroform in spite of the poor solubility of LiBr in this solvent: using the same conditions, cyclopentanol quantitatively yielded cyclopentyl bromide (entry b). A quantitative yield of cyclopentyl iodide was also obtained when TMCE was added to a 2.5-fold excess of LiI suspended in a solution of cyclopentanol in deuteriochloroform. The procedure could also be applied to the deoxyiodination of alcohols with TMCE and either LiI and KI (Table 1, entry c to f). The reactions were quite fast (< 30 min).

We have thus demonstrated that a unified procedure for deoxyhalogenation reactions was now possible: deoxychlorination can be conveniently performed with the readily available TMCE or DICE reagents and *the same reagents* can also be used to perform the deoxybromination and deoxyiodination of alcohols by adding an alkali bromide or iodide to the mixture. These reactions worked well in solvents like acetonitrile, dichloromethane or chloroform in spite of the fact that the mixture was often heterogeneous. This had often an impact on reaction times. The salts and the glassware had to be carefully dried. To remain on the safe side, it is recommended to wait for 15 min before adding the alcohol to the mixture although, in some cases the reaction was shown to work by mixing all reactants from the beginning. The presence of small amounts of *N,N*-dimethyl- and *N,N*-diisopropyl isobutyramide **1a** and **1b** in TMCE or DICE is not harmful since they are coproduced in the reaction. Of course, in that case the amount of TMCE or DICE would have to be adjusted.

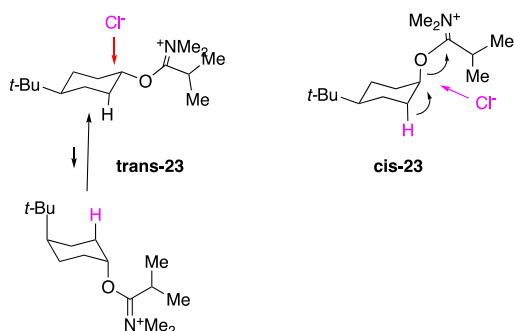
## 2.2. Stereochemistry of the deoxyhalogenation reactions

The stereochemical course of these deoxyhalogenation reactions had not been addressed in our earlier reports [6, 7]. A first hint about the stereochemical course of these deoxyhalogenation reactions was already provided in Schemes 7 and 8: the substitution of the secondary hydroxyl group of **12** and **14** only gave the diastereoisomer resulting from an inversion of configuration. We also found that the reaction of *trans*-4-*tert*-butyl cyclohexanol **trans-20** with TMCE yielded a 2:1 mixture of the *cis*-4-chloro-*tert*-butyl cyclohexane **cis-21** and 4-*tert*-butyl cyclohexene **22** (Scheme 11). The reaction with *cis*-4-*tert*-butyl cyclohexanol **cis-20** gave a low yield of *trans*-4-chloro-*tert*-butyl cyclohexane **trans-21**. The major product was 4-*tert*-butyl cyclohexene **22**.



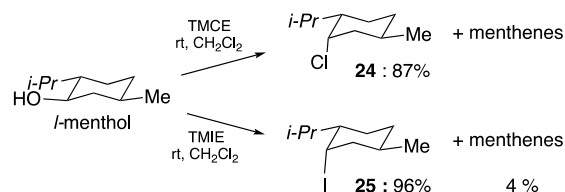
**Scheme 11.** Stereospecific deoxychlorination of *cis* and *trans* 4-*t*-butyl cyclohexanols

The substitution reactions were thus *stereospecific*: both *cis* and *trans* alcohols reacted with *inversion* of configuration in agreement with a classical  $S_N2$  mechanism. The formation of *tert*-butyl cyclohexene resulted from a *trans*-elimination ( $E_2$ ) from the reactive *cis* and *trans* intermediates (Scheme 12). As expected, more elimination product was obtained from the *cis*-alcohol since in the most stable conformation of its reactive iminium intermediate, the leaving group is axial. Elimination from the *trans* isomer could only occur from a much less stable conformation carrying two axial bulky groups (Scheme 12). These observations excluded the formation of the cyclohexene derivative from the 1-chloro-4-*t*-butylcyclohexane product since, in that case, more olefin would have been expected from the *trans* alcohol which yields a product with an axial chloride.



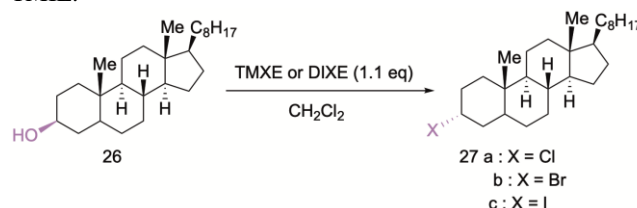
**Scheme 12.** Reactive intermediates for  $S_N2$  and  $E_2$  reactions

The reactions of *l*-menthol with both TMCE **2a** and TMIE **3a** were also stereospecific and only few elimination products were observed (Scheme 13).



**Scheme 13.** Chloro- and iodo-dehydroxylation of *l*-menthol

This probably resulted from the equatorial position of the reactive iminium intermediate generated by the addition of *l*-menthol to the keteniminium halides derived from TMCE or TMIE.



Reagents	Conditions	X	Yields (%)
a TMCE	12 h., r.t.	Cl	90
b TMBE	12 h., r.t.	Br	87
c TMCE + 2.5 equiv LiBr	5 h. 0 °C to r.t.	Br	20
d DICE + 2.5 equiv LiBr	5 h. 0 °C to r.t.	Br	96
e TMIE	12 h., r.t.	I	86
f DICE + 2.5 equiv NaI	5 h. 0 °C to r.t.	I	72
g DICE + 2.5 equiv CsI	5 h. 0 °C to r.t.	I	70

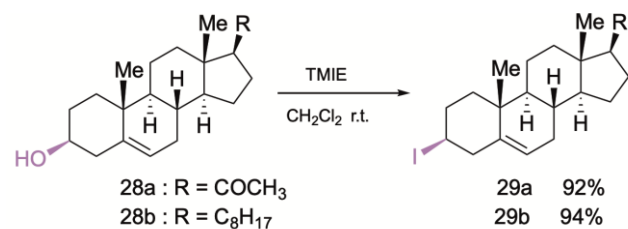
**Scheme 14** Deoxyhalogenation of 3- $\beta$ -cholestanol

$\alpha$ -Haloenamines **2a**, **b** **3a** and **4a** also smoothly effected the deoxyhalogenation of 3- $\beta$ -cholestanol **26** at room temperature to yield 3- $\alpha$ -halo-cholestanes **27a**, **b**, **c** in high yields (Scheme 14). All reactions proceeded with inversion of configuration as with most halogenating agents except for thionyl chloride [14, 15]. No or very little elimination occurred. This resulted from the weak basicity of the reagents and the mild conditions of this procedure. The deoxyiodination could be performed with the isolated  $\alpha$ -iodoamine TMIE or with the *in situ* generated TMIE: in the latter case TMCE and NaI (entry f) or CsI (entry g) were left for 0.5-1 hour at 0 °C before adding cholestanol. Here again reaction mixtures were heterogeneous which make meaningless any discussion about reaction times.

Homoallylic alcohols such as cholesterol and pregnenolone are known to behave differently with halogenating agents as a result of the intermediate formation of a homoallylic carbocation. The reaction often gave mixture of substitution, rearrangement and elimination products and usually the substitution took place with retention of configuration giving a 3- $\beta$ -halide [16]. A notable exception was observed with carbodiiminium iodides [15b] which reacted with cholesterol to give a 30% yield of 3- $\alpha$ -iodo-5-cholestene.

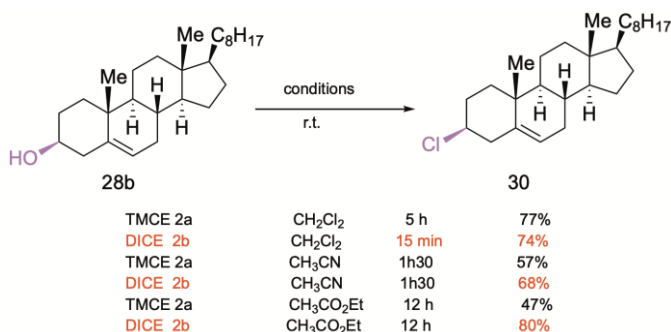
We found that both pregnenolone **28a** and cholesterol **28b** reacted with pure TMIE to give a high yield of the purified  $\beta$ -

iodides **29a, b** (Scheme 15). This reaction also proceeded with complete retention of configuration.



Scheme 15. Deoxygenation of pregnenolone **28a** and cholesterol **28b**.

Finally, we studied the influence of the nature of the reagent (TMCE vs DICE) and of the solvent on the deoxychlorination of cholesterol **28b** (Scheme 15). In all cases, we obtained the 3- $\beta$ -chloride **30** as the major product.



Scheme 16. Deoxychlorination of cholesterol with TMCE and DICE.

We were also able to isolate  $\leq 10\%$  of the 3- $\alpha$  isomer and  $\leq 5\%$  of diene. Scheme 16 also indicates that the reaction was successful in a solvent like ethyl acetate and confirmed that DICE was more reactive than TMCE. The reported yields are those of purified material.

### 3. Conclusion

In summary we have shown that it was possible to perform deoxybromination and -iodination reactions by *in situ* conversion of the readily available TMCE and DICE into the corresponding bromo- or iodoenamines using a bromide or an iodide salt. Our studies also revealed that increasing the size of the nitrogen substituents in the haloamine reagent dramatically increased the reactivity of the reagent. We had shown before [7] that it also increased the selectivity of the  $\alpha$ -haloamine. Thus, DICE, DIBE and DIIE are all more reactive AND more selective than the corresponding TMCE, TMBE and TMIE. Not surprisingly the present study showed that the reaction with secondary alcohols took place with clean inversion of configuration. Homoallylic alcohols such as cholesterol or pregnenolone reacted with retention of configuration as expected. Although it had been thoroughly studied for more than hundred years, the deoxyhalogenation reaction still draws the attention of synthetic chemists in particular in process chemistry [17]. We believe that this mild, sustainable, chemo- and diastereoselective deoxyhalogenation method will be welcome by synthetic chemists interested in the selective transformation of sensitive substrates. We will soon describe other applications as well as an extension of this method to the replacement of hydroxyl groups by fluorine.

## 4. Experimental part

### 4.1. Materials and Methods

The experimental work was performed at UCLouvain (Belgium) and more recently at IECB (Univ. Bordeaux, France). Unless otherwise noted, solvents and reagents were reagent grade and used without further purification. Chloroform were distilled over P<sub>4</sub>O<sub>10</sub>. Acetonitrile, dichloromethane and THF were dried with Glass Contour solvent purification system. Reactions were performed under argon atmosphere in oven-dried round-bottom flasks with magnetic stirring. Sensitive reagents and solvents were transferred using plastic or oven-dried glass syringes and steel needles using standard techniques. At UCLouvain, <sup>1</sup>H NMR spectra were recorded at 60 MHz (Varian T 60), 200 MHz (Varian Gemini-200 and XL-200), 300 MHz (Brücker Avance 300) and 500 MHz (Brücker AM 500). <sup>13</sup>C NMR spectra were recorded at 50 MHz (Varian Gemini-200, VXR-200). At IECB, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR were recorded with Bruker Avance II 300 (at 300 MHz and 75 MHz, respectively) in CDCl<sub>3</sub>, CD<sub>2</sub>Cl<sub>2</sub> and DMSO-*d*<sub>6</sub>. Chemical shifts are reported in parts per million (ppm) on the  $\delta$  scale relative to Me<sub>4</sub>Si ( $\delta = 0$  for <sup>1</sup>H NMR) and CDCl<sub>3</sub> ( $\delta = 77.2$  for <sup>13</sup>C NMR) as an internal reference and the coupling constants are reported in units of Hertz [Hz]. Multiplicities were abbreviated as follows: s (singlet), br. s (broad singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), dq (doublet of quadruplet) or m (multiplet). Infra-red spectra were recorded on a Perkin-Elmer 681 spectrometer, a Bruker IRFT IFS 55 spectrometer on zinc selenide plates and a Jasco FT/IR-4600 Spectrometer on a single-reflection diamond ATR accessory. At UCL, mass spectra were recorded on Varian Mat 44 and Finnigan Mat-TSQ 70 using electronic impact at 70 eV, chemical ionization (100 eV, acetone or mixture of nitrogen oxide and methane) or FAB. At IECB low resolution mass spectra (MS)/High resolution mass spectra (HRMS) were recorded with a ThermoElectron LCQ Advantage and a ThermoElectron Exactive spectrometer, respectively. Column chromatography was conducted with silica gel 60 Å (Sigma-Aldrich, 230-400 mesh particle size, 40-63  $\mu$ m). Flash chromatography was performed using silica gel 60 or 40-70 (230-400 mesh). Thin layer chromatography (TLC) on Merck silica gel 60 F254 precoated plates. Visualization was made with ultraviolet light ( $\lambda = 254/365$  nm) or using an aqueous potassium permanganate staining solution. GLC chromatography was performed using Varian Aerograph 1400 (detector FID, nitrogen) or Carlo Erba Fractovap (detector FID, nitrogen) on either a SE30 column or a capillary column type 3700 (length 30 polydimethylsiloxane). RP-HPLC analyses were carried out on a C<sub>18</sub> gravity column (4.6  $\times$  100 mm, 3  $\mu$ m HPLC grade acetonitrile and Milli-Q water were used for reverse phase (RP) HPLC analyses. Melting points were recorded using a Büchi B-540 apparatus and are uncorrected.

### 4.2. Synthesis of $\alpha$ -haloenamines

TMCE **2a**, DICE **2b** and TMBE **3a** were prepared from amides **1a** and **1b** following the previously described procedures [3b]. TMBE **3a** could also be prepared from TMCE by halogen exchange (5.2.1.). Both TMBE **3a** and TMIE **4a** were also obtained in the following reactions:

#### *1-Bromo-N,N,2-trimethyl-1-propen-1-amine 3a (TMBE).*

##### *Method a*

A solution of 8.03 g TMCE **2a** in 30 ml dry dibromomethane CH<sub>2</sub>Br<sub>2</sub> was refluxed for 20 hours in a flask protected from light (aluminum foil). Distillation gave 6.95 g (65%) of **3a**, Eb.: 58-62

$^{\circ}\text{C}/30\text{ Torr}$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.25 (s, 6H), 1.78 (s, 6H);  $^{13}\text{C NMR}$  (20 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.04, 125.71, 43.46, 21.36.

#### Method b

This is the method used for the “one-pot” deoxybromination of alcohols. 1-Chloro-*N,N*,2-trimethyl-1-propen-1-amine (132.3  $\mu\text{l}$ , 1 mmol) **2a** was added to a solution of dry LiBr (217.12 mg, 2.5 mmol) in  $\text{CD}_3\text{CN}$  (1 ml). The mixture was stirred for 30 min to exclusively yield the title compound **3a** and *N,N*,2-trimethylpropionamide **1a**.  $^1\text{HNMR}$  (300 MHz,  $\text{CD}_3\text{CN}$ ) confirmed the disappearance of **2a**, showing only the two characteristic singlets for **3a** at 2.28 ppm and 1.73 ppm for ( $\text{N}(\text{CH}_3)_2$ ) and ( $\text{C}(\text{CH}_3)_2$ ) respectively and the signals for **1a**.  $^{13}\text{C NMR}$  (75.48 MHz,  $\text{CD}_3\text{CN}$ ) showed signals at 137.85 (CBr), 125.45 ( $\text{C}(\text{CH}_3)_2$ ), 42.65 ( $\text{N}(\text{CH}_3)_2$ ), 20.46 ( $\text{CH}_3$ )<sub>2</sub>.

#### 1-Iodo-*N,N*,2-trimethyl-1-propen-1-amine **4a** (TMIE).

##### Method a

Anhydrous KI (60 g, 0.36 mole) was suspended into a solution of TMCE **2a** in 40 ml anhydrous chloroform. The reaction flask was protected from moisture by an oil trap and from light by an aluminum foil. The suspension was refluxed for 5 h then filtered under a stream of argon. The precipitate was washed with 2 x 20 ml of dichloromethane. Evaporation of the solvents from the combined organic phases at atmospheric pressure followed by vacuum distillation yielded 23.1 g (75%) **4a**. Eb.: 61-63  $^{\circ}\text{C}/9\text{ Torr}$ .  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.05 (s, 6H), 1.88, 6H);  $^{13}\text{C NMR}$  (20 MHz,  $\text{CDCl}_3$ ):  $\delta$  132.84, 129.06, 45.52, 23.30.

##### Method b

A solution of 4 g (0.03 mole) TMCE **2a** and 7g (0.05 mole) methyl iodide in 15 ml dry chloroform was refluxed for 5 days in a flask protected from light (aluminum foil). Distillation gave 3.8 g (56%) **4a**. Replacing methyl by ethyl iodide gave 62% yield of **4a** after 70 hours reflux.

### 4.3. Syntheses of hydroxy-lactones **12**, **14**, **15**.

#### 4.3.1. Synthesis of hydroxy-lactone **12**

##### Method a

$\text{Et}_3\text{N}$  (18.2 mL, 1.5 equiv.) was added to diol **11** (15g, 87.1 mmol) in DMF (150 mL). TIPSOTf (25.7 mL, 1.1 equiv) was slowly syringed in the solution at 0  $^{\circ}\text{C}$ . The mixture was stirred at room temperature for 36 hours. Then water (7-10 volumes) was added and the crude mixture was extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . Evaporation of the solvent left an oily residue which was purified by flash chromatography over silica gel (petroleum ether and ethyl acetate 4:1 to 3:2). Yield: 24.3 g (85%) of pure hydroxy-lactone **12**. White solid; TLC (petroleum ether : ethyl acetate, 3:2)  $R_f$  = 0.43;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.07-1.13 (m, 21H), 2.00-2.07 (m, 3H), 2.46-2.57 (m, 2H), 2.61-2.70 (m, 1H), 2.82 (dd,  $J$  = 9.8, 17.8 Hz, 1H), 3.73 (dd,  $J$  = 6.8, 9.9 Hz, 1H), 3.86 (dd,  $J$  = 5.1, 9.9 Hz, 1H), 4.11-4.23 (m, 2H), 4.95 (td,  $J$  = 3.0, 7.0 Hz, 1H) ppm;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.8, 18.0, 35.3, 39.5, 40.9, 55.5, 64.6, 75.7, 83.8, 177.2 ppm.; ESI-MS calculated for  $\text{C}_{17}\text{H}_{33}\text{O}_4\text{Si}$  ( $[\text{M}+\text{H}]^+$ ) : 329.2, found 329.2.

##### Method b

A solution of TIPSOTf was prepared by dropwise addition of TIPSH (1.15 equiv, 333.9 mmol, 68.4 mL) to a solution of TFOH (28.3 mL, 1.1 equiv, 319.4 mmol) in 100 mL of dry DCM at 0  $^{\circ}\text{C}$  under argon atmosphere. The ice bath was maintained until

complete formation of  $\text{H}_2$  gas. The reaction mixture was stirred for an additional hour at room temperature. Then it was cannulated at 0  $^{\circ}\text{C}$  under inert atmosphere into a flask containing 50 g of diol **11** (290.4 mmol), 60.8 mL of  $\text{Et}_3\text{N}$  (1.5 equiv, 435.6 mmol) and 300 mL of anhydrous DMF. The reaction mixture was stirred overnight at room temperature. After addition of water (7-10 volumes), the crude mixture was extracted with ethyl acetate. The extract was washed with brine and dried over  $\text{MgSO}_4$ . Evaporation of the solvent quantitatively yielded **12** as an oil which was more than did not need further purification (purity > 95%). It was directly used in the next step.

#### 4.3.2. Synthesis of hydroxy-lactone **14**

3.16 g (1.3 equiv., 79.1 mmol) of sodium hydride and 60 mL of DMF were introduced in a flame dried 500 mL flask. A solution of compound **11** in 20 mL of DMF was added dropwise to the mixture at 0  $^{\circ}\text{C}$  (ice-bath). After 1 hour, p-methoxybenzyl chloride (24.7 mL, 3 equiv., 237.4 mmol) was added to the reaction mixture and the allowed to run for 12 hours at the same temperature. The reaction was quenched by slow addition of water and the resulting mixture was extracted with ethyl acetate (3x). The organic phase was washed with brine and dried over  $\text{MgSO}_4$ . After evaporation of the volatile material, the crude residue was purified by chromatography over silica gel (petroleum ether: ethyl acetate 95:5 to 80:20) to yield 20% of pure compound **14** as yellow oil; TLC (petroleum ether : ethyl acetate, 4:1)  $R_f$  = 0.4;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.08-2.17 (m, 1H), 2.40 (d,  $J$  = 15.3 Hz, 1H), 2.58 (dd,  $J$  = 18.4, 3.3 Hz, 1H), 2.90 (dd,  $J$  = 18.4, 11.0 Hz, 1H), 3.05-3.06 (m, 1H), 3.27-3.36 (m, 1H), 3.83 (s, 3H), 4.31-4.33 (m, 1H), 4.31 (d,  $J$  = 11.4 Hz, 1H), 4.54 (d,  $J$  = 11.4 Hz, 1H), 5.11 (t,  $J$  = 6.6 Hz, 1H), 6.9 (d,  $J$  = 8.7 Hz, 2H), 7.25 (d,  $J$  = 8.6 Hz, 2H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 35.5, 37.3, 40.3, 55.3, 56.9, 70.9, 82.1, 84.3, 113.9, 129.3, 129.5, 159.4, 176.5, 177.4 ppm.

#### 4.3.3. Synthesis of hydroxy-lactone **15**

##### 4.3.3.1. PMB protection of alcohol **12**.

3.16 g (1.3 equiv., 79.1 mmol) of sodium hydride, 60 mL of THF and 0.2 mL of tBuOH were introduced in a flame dried 500 mL flask. A solution of compound **2** in 20 mL of THF was added dropwise to the mixture at 0  $^{\circ}\text{C}$  (ice-bath). After 1 hour, the reaction mixture was treated first with p-methoxybenzyl chloride (24.7 mL, 3 equiv., 237.4 mmol) then by tetrabutylammonium iodide (11.2 g, 0.5 equiv., 39.5 mmol, addition in one portion). After 15 min at 0  $^{\circ}\text{C}$  the mixture was stirred for 14 hours at room temperature. The reaction was quenched by slow addition of water and the resulting mixture was extracted with ethyl acetate (3x). The organic phase was washed with brine and dried over  $\text{MgSO}_4$ . After evaporation of the volatile material, the crude residue was purified by chromatography over silica gel. (petroleum ether: ethyl acetate 95:5 to 80:20) to yield 17.2 g (63%) of pure compound **13**. as pale yellow oil; TLC (petroleum ether : ethyl acetate, 4:1 )  $R_f$  = 0.38;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.06-1.10 (m, 21H), 2.17-2.30 (m, 3H), 2.51-2.61 (m, 1H), 2.76-2.83 (m, 2H), 3.68 (ddd,  $J$  = 5.3, 10.1, 15.3 Hz, 2H), 3.82 (s, 3H), 3.97 (dd,  $J$  = 4.7, 9.7 Hz, 1H), 4.36 (d,  $J$  = 11.4 Hz, 1H), 4.52 (d,  $J$  = 11.4 Hz, 1H), 4.96-5.01 (m, 1H), 6.87-6.93 (m, 2H), 7.23-7.34 (m, 2H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.9, 18.0, 35.7, 37.4, 39.4, 54.7, 55.3, 63.2, 70.8, 81.0, 84.4, 113.8, 129.3, 130.2, 159.2, 177.3 ppm.

##### 4.3.3.2. Cleavage of TIPS group

Tetrabutylammonium fluoride (42.1 mL, 42.1 mmol, 1M in THF) was added dropwise to a solution of a 17.2 g (38.3 mmol) of **12** in 70 mL THF at 0  $^{\circ}\text{C}$ . After 15 min at 0  $^{\circ}\text{C}$ , the ice bath was removed, and the reaction was allowed to warm up to room

temperature. After full consumption of starting material (TLC analysis) the reaction was immediately (caution: longer reaction time will decrease the yield) quenched by addition of a saturated solution of ammonium chloride (50 mL). The organic phase was extracted with ethyl acetate (3 times), washed with water then brine and finally dried over magnesium sulfate to give a crude residue after evaporation of volatiles under vacuum. The crude material was purified by chromatography over silica gel (ethyl acetate and petroleum ether 4:1 to 5:0) to yield 9.9 grams of **15** (88% yield); light yellow oil; TLC (ethyl acetate 100%)  $R_f$  = 0.34;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.03-2.08 (m, 3H), 2.40 (d,  $J$  = 15.6 Hz, 1H), 2.60-2.73 (m, 2H), 3.37 (d,  $J$  = 6.3 Hz, 2H), 3.67 (s, 3H), 3.80 (dd,  $J$  = 3.9, 8.8 Hz, 1H), 4.23 (d,  $J$  = 11.3 Hz, 1H), 4.36 (d,  $J$  = 11.3 Hz, 1H), 4.82-4.87 (m, 1H), 6.76 (d,  $J$  = 8.6 Hz, 2H), 7.13 (d,  $J$  = 8.6 Hz, 2H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 35.8, 37.0, 39.6, 54.5, 55.1, 62.6, 70.5, 81.5, 84.7, 113.7, 129.1, 130.2, 159.1, 177.8 ppm.; ESI-MS calculated for  $\text{C}_{16}\text{H}_{24}\text{O}_5\text{N}$  ( $[\text{M}+\text{NH}_4]^+$ ): 310.1654, found 310.1650.

#### 4.4. Deoxyhalogenations of hydroxy-lactones **12**, **14** and **15**.

##### 4.4.1. Deoxychlorination of **12**: synthesis of chlorhydrine **17**

DICE **2b** (4.83 mL, 1.1 equiv, 23.4 mmol) was added dropwise at 0 °C under argon atmosphere to a solution of hydroxy-lactone **12** (7 g, 21.3 mmol) in 25 mL of dry DCM. The resulting mixture was left for 30 minutes at room temperature. After full consumption (checked by TLC) of starting material, the solvent was evaporated and the crude residue was dissolved in 20 mL of anhydrous THF and cooled to 0 °C. Tetrabutylammonium fluoride (21.3 mL, 21.3 mmol, 1M in THF) was then added dropwise at 0 °C, then the ice bath was removed and the reaction was allowed to warm up to room temperature. After full consumption of starting material (TLC analysis) the reaction was immediately (caution: longer reaction time will decrease the yield) quenched by addition of a saturated solution of ammonium chloride (50 mL). The organic phase was extracted with ethyl acetate (3 times), washed with water then brine and finally dried over magnesium sulfate to give a crude residue after concentration in vacuo. The crude material was purified by chromatography on silica gel (ethyl acetate and petroleum ether 1:1 to 1:0) to yield 3 grams of chlorhydrine **17**. Light yellow oil (3g, 75 % yield over 2 steps); TLC (petroleum ether: ethyl acetate, 1:1)  $R_f$  = 0.19.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.21-2.30 (m, 1H), 2.42 (dt,  $J$  = 4.7, 15.6 Hz, 1H), 2.54 (d,  $J$  = 16.2 Hz, 1H), 2.74-2.95 (m, 3H), 3.86 (dd,  $J$  = 5.7, 10.9 Hz, 1H), 3.94 (dd,  $J$  = 8.9, 10.9 Hz, 1H), 4.68 (td,  $J$  = 1.5, 5.6 Hz, 1H), 5.18 (td,  $J$  = 4.4, 7.1 Hz, 1H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 33.6, 39.4, 43.9, 52.9, 62.2, 62.9, 83.7, 176.6 ppm.; ESI-MS calculated for  $\text{C}_8\text{H}_{10}\text{O}_3$  ( $[\text{M}-\text{H}]^-$ ): 189.0318, found 189.0321.

##### 4.4.2. Deoxyiodination of **12**: Synthesis of iodo-lactone **16b**

TMCE **2a** (1.1 equiv) was added dropwise under argon atmosphere to a suspension of LiI (1.5 equiv.) in dry DCM. The resulting mixture was left for 1 hours at room temperature. Lactone **12** was then added at 0 °C and the reaction was allowed to reach room temperature. After reaction completion (TLC check), the solvent was evaporated and the desired compound **16b** was purified by chromatography over silica gel (petroleum ether: ethyl acetate 95:5 to 80:20);  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.08 (s, 21H), 2.19-2.23 (m, 1H), 2.34 (dt,  $J$  = 15.4, 4.9 Hz, 1H), 2.55 (d,  $J$  = 16.1 Hz, 1H), 2.69-2.90 (m, 3H), 3.84 (dd,  $J$  = 10.0, 6.5 Hz, 1H), 3.97 (dd,  $J$  = 10.0, 6.9 Hz, 1H), 4.60 (m, 1H), 5.15 (td,  $J$  = 7.1, 4.5 Hz, 1H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.9, 18.0, 33.8, 39.7, 43.9, 53.5, 62.7, 63.4, 83.7, 176.8 ppm.

##### 4.4.3. Deoxychlorination of **14**: Synthesis of chloro-lactone **18**

DICE **2b** (1.1 equiv.) was added dropwise under argon atmosphere to a solution of lactone **14** in 5 mL of dry DCM. The resulting mixture was left for 10-15 minutes at room temperature. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the desired product was purified by column chromatography using petroleum ether and ethyl acetate (4:1) as eluant to isolate pure product **18**.  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.23-2.36 (m, 2H), 2.50 (d,  $J$  = 16.2 Hz, 1H), 2.68-2.84 (m, 3H), 3.56 (dd,  $J$  = 9.3, 6.2 Hz, 1H), 3.68 (dd,  $J$  = 9.2, 6.2 Hz, 1H), 3.81 (s, 3H), 4.46-4.47 (m, 2H), 4.58-4.61 (m, 1H), 5.08-5.14 (m, 1H), 6.9 (d,  $J$  = 8.7 Hz, 2H), 7.25 (d,  $J$  = 8.6 Hz, 2H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 33.5, 40.0, 43.8, 51.0, 55.3, 63.0, 69.5, 73.1, 83.5, 113.8, 129.2, 130.0, 159.3, 176.5 ppm.

##### 4.4.4. Deoxyiodination of **15**: synthesis of iodo-lactone **19**

TMCE **2a** (1.1 equiv) was added dropwise under argon atmosphere to a suspension of LiI or KI (see scheme 9 for stoichiometry details) in dry DCM. The resulting mixture was left for 1-1.5 hours at room temperature. Lactone **15** was then added at 0 °C and the reaction was allowed to reach room temperature. After 4 hours, the NMR yields were determined by integration of the characteristic protons of iodo-lactone **19**. After evaporation of the volatile material, the crude residue of one sample was purified by chromatography over silica gel (petroleum ether: ethyl acetate 95:5 to 80:20) to isolate pure compound **19**;  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.16-2.25 (m, 3H), 2.55 (dd,  $J$  = 17.4, 2.1 Hz, 1H), 2.66-2.74 (m, 1H), 2.82 (dd,  $J$  = 17.4, 10.2 Hz, 1H), 3.58 (d,  $J$  = 6.2 Hz, 2H), 3.81 (s, 3H), 3.90 (dd,  $J$  = 10.2, 5.1 Hz, 1H), 4.35 (d,  $J$  = 11.4 Hz, 1H), 4.54 (d,  $J$  = 11.4 Hz, 1H), 4.97 (td,  $J$  = 6.5, 2.8 Hz, 1H), 6.9 (d,  $J$  = 8.7 Hz, 2H), 7.25 (d,  $J$  = 8.6 Hz, 2H) ppm.;  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 35.5, 37.1, 39.3, 54.0, 55.3, 63.1, 70.8, 81.2, 83.9, 113.9, 129.3, 130.0, 159.3, 177.2 ppm.

#### 4.5. Deoxyhalogenations of cyclopentanol and 1 naphthalenemethanol (Table 1)

TMCE (1 mmol) was syringed in a solution of 1 mmol of 1-naphthalenemethanol or cyclopentanol and dry LiBr, LiI or KI (2.5 mmol) in deuterated acetonitrile or chloroform under argon atmosphere. The suspension was stirred at room temperature for 15-30 min.  $^{13}\text{C NMR}$  of the crude mixtures revealed the formation of the titled compounds through detection of the characteristic signals at  $\delta$  32.04 ppm,  $\delta$  4.17 ppm corresponding to naphthyl  $\text{CH}_2\text{-Br}$ ,  $\text{CH}_2\text{-I}$  respectively and at  $\delta$  53.59 ppm,  $\delta$  29.81 ppm for cyclopentyl  $\text{CH-Br}$ ,  $\text{CH-I}$  respectively.

#### 4.6. Deoxyhalogenations of *cis*- and *trans*-*t*-butyl-cyclohexanol and *l*-menthol

##### 4.6.1. Deoxychlorination of *cis*-*t*-butyl-cyclohexanol

TMCE **2a** (0.094.5 g, 0.7 mmol) was syringed into a solution of 0.1 g (0.64 mmol) *cis*-*t*-butyl-cyclohexanol in  $\text{CDCl}_3$  under a stream of argon. The solution was left at room temperature for 3 hrs. The crude mixture was analyzed by GC and  $^1\text{H NMR}$  (comparison with authentic samples). It showed the expected amide **1a** and a 3:1 mixture of 4-*t*-butylcyclohexene and *trans*-*t*-butyl chloride.

##### 4.6.2. Deoxychlorination of *trans*-*t*-butyl-cyclohexanol

TMCE **2a** (0.236 g, 1.77 mmol) was syringed into a solution of 0.251 g (1.64 mmol) *trans*-*t*-butyl-cyclohexanol in  $\text{CDCl}_3$

under a stream of argon. The solution was left at room temperature for 12 h. The crude mixture was analyzed by GC and  $^1\text{H}$  NMR (comparison with authentic samples). It showed the expected amide **1a** and a 1:2.15 mixture of 4-*t*-butylcyclohexene and *cis-t*-butyl chloride.

#### 4.6.3. Deoxychlorination of *l*-Menthol

TMCE **2a** (1.00 g, 7.5 mmol) was syringed into a solution of *l*-menthol (1.063 g, 6.8 mmol.) in  $\text{CDCl}_3$  at 0 °C under a stream of argon. The solution was left at room temperature for 5 h. The crude mixture was analyzed by GC and  $^1\text{H}$  NMR (comparison with authentic samples). It showed the expected amide **1a** and neomenthyl chloride **24** ( $^1\text{H}$  NMR: 87%).

#### 4.6.4. Deoxyiodination of *l*-Menthol

TMIE **4a** (1.00 g, 4.4 mmol) was syringed into a solution of *l*-menthol (0.63 g, 4.0 mmol.) in  $\text{CDCl}_3$  at 0 °C under a stream of argon. The solution was left at room temperature for 5 h. The crude mixture was analyzed by GC and  $^1\text{H}$  NMR (comparison with authentic samples). It showed the expected amide **1a** and neomenthyl iodide **25**.

### 4.7. Deoxyhalogenations of sterols

#### 4.7.1. Deoxychlorination of 3- $\beta$ -cholestanol **26**: synthesis of product **27a**

TMCE **2a** (1.1 equiv.) was added dropwise under argon atmosphere to a solution of cholestanol **26** in 5 mL of dry DCM. The resulting mixture was left for 12 hours at room temperature. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the desired product was purified by column chromatography using petroleum ether as eluant. 90% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.69 (s, 3H), 0.82 (s, 3H), 0.89 (d,  $J$  = 1.3 Hz, 3H), 0.91 (d,  $J$  = 1.3 Hz, 3H), 0.94 (d,  $J$  = 6.5 Hz, 3H), 1.03-2.03 (m, 31H), 4.53-4.55 (m, 1H) ppm.;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  = 11.9, 12.1, 18.1, 20.8, 22.6, 22.9, 23.9, 24.2, 28.0, 28.1, 28.3, 30.2, 35.5, 35.8, 36.1, 36.2, 36.6, 39.2, 39.5, 40.0, 42.6, 53.9, 56.3, 56.5, 60.7 ppm.

#### 4.7.2. Deoxybromination of 3- $\beta$ -cholestanol **26**: synthesis of product **27b** [18].

DICE **2b** (1.1 equiv) was added dropwise under argon atmosphere to a suspension of LiBr (2.5 equiv.) in 5 mL of dry DCM. The resulting mixture was left for 1 hour at room temperature. 3- $\beta$ -cholestanol **26** was then added at 0 °C and the reaction run for further 4 hours. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the desired product was purified by column chromatography using petroleum ether as eluant. 96% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.68 (s, 3H), 0.82 (s, 3H), 0.87 (d,  $J$  = 1.3 Hz, 3H), 0.90 (d,  $J$  = 1.3 Hz, 3H), 0.92 (d,  $J$  = 6.5 Hz, 3H), 1.02-2.03 (m, 31H), 4.74-4.77 (m, 1H) ppm.;  $^{13}\text{C}$  RMN (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.9, 12.2, 18.5, 20.6, 22.4, 22.7, 23.7, 24.0, 27.8, 28.0, 28.1, 30.9, 31.7, 32.8, 35.3, 35.7, 36.1, 37.2, 39.4, 39.8, 40.0, 42.5, 53.7, 55.9, 56.1, 56.3 ppm.

#### 4.7.3. Deoxyiodination of 3- $\beta$ -cholestanol **26**: synthesis of product **27c**

DICE **2b** (1.1 equiv) was added dropwise under argon atmosphere to a suspension of NaI or CsI (2.5 equiv.) in 5 mL of dry DCM. The resulting mixture was left for 1 hours at room temperature. 3- $\beta$ -cholestanol **26** was then added at 0 °C and the reaction run for further 4 hours. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the desired product was purified by column chromatography using petroleum ether as eluant. 72% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.68 (s, 3H), 0.82 (s, 3H), 0.89 (d,  $J$  = 1.3 Hz, 3H), 0.91 (d,  $J$  = 1.3 Hz, 3H), 0.94 (d,  $J$  = 6.5 Hz, 3H),

1.08-2.03 (m, 31H), 4.97-4.99 (m, 1H) ppm.;  $^{13}\text{C}$  RMN (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 12.1, 13.4, 18.6, 20.8, 22.5, 22.7, 23.7, 24.1, 27.7, 27.9, 28.1, 31.7, 32.6, 34.3, 35.2, 35.7, 36.1, 36.4, 38.1, 38.6, 39.4, 39.9, 41.9, 42.5, 53.7, 56.2, 56.4 ppm.

#### 4.7.4. Deoxyiodination of pregnenolone **28a**: synthesis of product **29a**

TMIE (0.5 g, 2.2 mmol.) **2a** was syringed into a solution of 0.64 g (2 mmol) in dichloromethane at room temperature. After 12 h, the solvent was removed in vacuo and then solid residue was treated with anhydrous acetone and filtered. Recrystallisation in acetone gave **29a** as a colorless solid, m.p. 128-129 °C. The structure was assigned by comparison with literature data, eg:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.62 (s, 3H), 1.04 (s, 3H), 2.12 (s, 3H), 4.04 (txt,  $^3J_{\text{H3ax-Hax}}=11.95$ ,  $^3J_{\text{H3ax-Heq}}=4.76$ , 1H), 5.34 (m, 1H).

#### 4.7.5. Deoxyiodination of cholesterol **28b**: synthesis of product **29b**

TMIE (0.6 g, 2.67 mmol.) **2a** was syringed into a solution of 0.94 g (2.4 mmol) in dichloromethane at room temperature. After 12 h, the solvent was removed in vacuo and the solid residue was recrystallized in acetone to give **29b** as a colourless solid, m.p. 106 °C, identical to an authentic sample [19, 20].

#### 4.7.6. Deoxychlorination of cholesterol **28b**: synthesis of product **30** [21].

DICE **2b** (1.1 equiv.) was added dropwise under argon atmosphere to a solution of cholesterol **28b** in 5 mL of dry DCM. The resulting mixture was left for 15 minutes at room temperature. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the desired product was purified by column chromatography using petroleum ether as eluant. 74% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.68 (s, 3H), 0.87 (d,  $J$  = 1.26 Hz, 3H), 0.90 (d,  $J$  = 1.32 Hz, 3H), 0.92 (d,  $J$  = 6.5 Hz, 3H), 1.05 (s, 3H), 1.04-2.70 (m, 28H), 3.73-3.75 (m, 1H), 5.38-5.39 (m, 1H) ppm.;  $^{13}\text{C}$  RMN (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 11.6, 18.5, 19.1, 20.7, 22.3, 22.7, 23.5, 24.1, 27.9, 28.1, 31.5, 33.2, 35.7, 36.0, 36.3, 38.9, 39.3, 39.6, 42.1, 43.2, 49.8, 55.9, 56.4, 60.1, 122.3, 140.6 ppm.

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## Graphical Abstract

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### A mild method for the replacement of a hydroxyl group by halogen: 2. Unified procedure and stereochemical studies.

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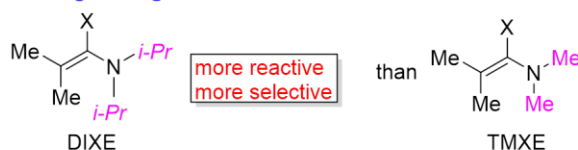
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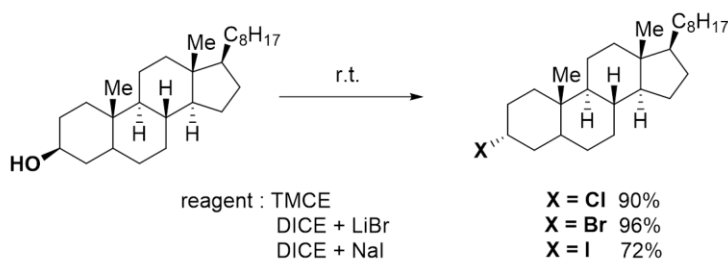
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#### 1. tuning of reagent



#### 2. Unified procedure for the stereospecific deoxyhalogenation of alcohols



All deoxyhalogenation can be performed with the readily available chloroamines with (chlorination) or without an alkali bromide (bromination) or iodide (iodination).