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High Selectivities in Electrophilic Additions to Cyclobutene Compounds

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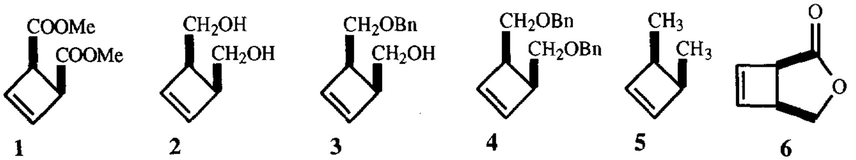
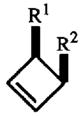
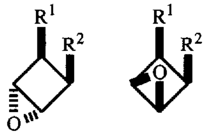
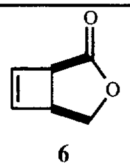
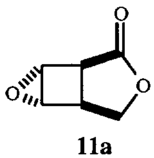
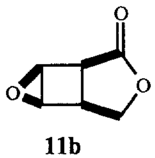
Abstract : Epoxidation of **2**, **3**, **4** with *m*-CPBA mainly led to the *cis*-attack products whereas **1** and **6** led to the other selectivity. The result was reversed, from **4**, with Payne's reagent. Bromohydroxylation of **4** involved an intermediate bromonium ion *syn* to the substituents. Haloselenylations occurred with the *syn*-selectivity from **1**, **2**, **3** and **4**, to the *anti*-selectivity from **6**, and without selectivity from **5**. NOE enhancement measurements and several chemical correlations led to the stereochemical assignments. Formation of the intramolecular reaction products **24** and **25** was also pointed out. Copyright © 1996 Elsevier Science Ltd

In the course of our research program on synthesis of nucleoside analogues, we had to prepare disubstituted[1] and tetrasubstituted[2,3] cyclobutane intermediates bearing the suitable substituents in the appropriate relationship. We thus prepared cyclobutane nucleoside analogues by nucleophilic ring opening of epoxides[2] and by nucleophilic substitution of mesylates.[4] We also synthesized a cyclopropane nucleoside analogue from a cyclobutane intermediate by a synthetic pathway involving a C_4-C_3 ring contraction as the key step.[3] Preparation of the cyclobutane intermediates involved, in most cases, stereoselective electrophilic additions to cyclobutenes. Therefore we have been thoroughly examining, for the last few years, the stereochemical result of such reactions with cyclobutene compounds (*e.g.* **1-6**). These reactions often led to high selectivities. Among the cyclobutane products thus obtained, several proved to be useful in nucleoside synthesis. This paper mainly deals with epoxidation and haloselenylation reactions. Preparation of the starting materials **2** and **4** were described in one of our preceding papers.[2] Compound **3** was obtained by monobenzylation of **2** and lactone **6** by reduction of the corresponding anhydride[5] (another possibility is through the oxidation of diol **2**[6]). The same anhydride easily led to **1** by treatment with methanol with sulfuric acid as catalyst and compound **5** was prepared according to literature[7] with minor modifications. It was obtained together with small amounts of impurities.



1 **2** **3** **4** **5** **6**

Table 1. Results of epoxidation reactions

Starting material 	Reagent (Experimental conditions)	Products 
$R^1 = R^2 = CO_2Me$ **1**	*m*-CPBA (3 days, r.t.)	**7a** **7b** 86:14[a] **1** : **7a** + **7b** = 1.3:1[ab]
$R^1 = R^2 = CH_2OH$ **2**	*m*-CPBA (8 h., r.t.)	**8a** **8b** 17:83[a,c,d] **8a** + **8b** : 90% yield
$R^1 = CH_2OBn$, $R^2 = CH_2OH$ **3**	*m*-CPBA (15 h., r.t.)	**9a** **9b** 22:78[a,e] **9a** + **9b** : 76% yield
$R^1 = R^2 = CH_2OBn$ **4**	*m*-CPBA (8 h., r.t.)	**10a** **10b** 28:72[a,f,g] **10a** + **10b** : 91% yield
4	Payne's reagent PhCN, 30% H_2O_2 (8 days, r.t.)	**10a** **10b** 72:28[a,h] **10a** + **10b** : 69% yield, 7% of **4** recovered
 **6**	*m*-CPBA (5 days, r.t.)	  **11a** **11b** 81:19[i] **11a** + **11b** : 89% yield

[a] ^1H NMR ratio.

[b] Products could not be separated, however a **1** + **7a** mixture was obtained by chromatography on silica gel.

[c] Both products could not be separated.

[d] In ref 2 an approximate **8a/8b** ratio was measured by ^{13}C NMR and no proofs were given for the stereochemical assignments (proofs are pointed out in this paper, see text).

[e] Both products could be partly separated by chromatography on silica gel (there were overlapping fractions).

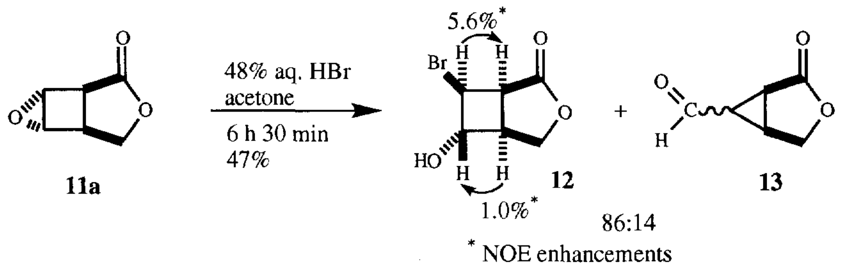
[f] Result from ref 2 with a slight improvement of yield.

[g] Both products could be separated by chromatography on silica gel ; however overlapping fractions contained mixtures of both products (4.4%).

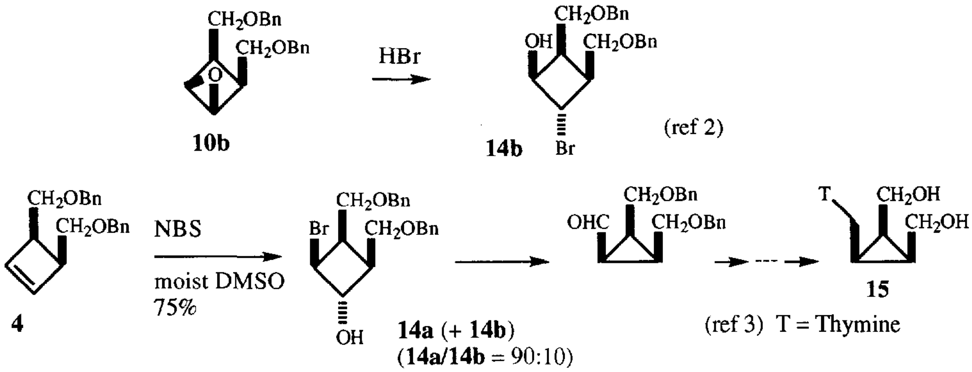
[h] Improvement with respect to ref 2 (higher reaction time).

[i] Both products were isolated by chromatography on silica gel.

Our results on epoxidations are gathered in Table 1. Results from compounds **2** and **4** have been previously communicated,[2] however slight improvements in yield (from **4**), on products ratio measurement (from **2**), and proof for stereochemical assignments for products **8a** and **8b** are included in this paper. We observed that reactions with *meta*-chloroperbenzoic acid were very slow when starting from compounds with electron withdrawing groups **1** and **6**. In the case of compound **1** the reaction could not go to completion as a 43.5% conversion was attained in three days that was only slightly increased to 50% when the reaction time was increased to nineteen days. Moreover, separation of **1**, **7a** and **7b** could not be achieved, therefore this result is not useful on a synthetic point of view. Reactions with Payne's reagent (PhCN, 30% H_2O_2),[8] magnesium monoperoxyphtalate[9] or dimethyl dioxirane[10] also led to poor results. Reaction of *meta*-chloroperbenzoic acid with lactone **6**, a cyclobutene compound bearing only one electron withdrawing group, needed five days and a mixture of both products **11a** and **11b** was thus obtained in good yield. In these two experiments from **1** and **6**, the major product **7a** or **11a**, respectively, corresponded to the attack from the less sterically hindered side. As it was anticipated, reactions with compounds **2**, **3** and **4** were much faster and took a few hours at room temperature. They mainly led to the *cis*-products **8b**, **9b** and **10b**. On the other hand, in the case of **4**, the stereochemical control was reversed with Payne's reagent. Stereochemistries of **10a** and **10b** were assessed earlier[2]. Several NOE experiments with the crude mixture of **1**+ **7a** +**7b**, with mixtures of **7a** + **1** (**7a**/**1** = 72 : 28) and of **8a** + **8b**, and with pure **9b** showed slight enhancements for the *trans*-relationships (0.5 to 3.3%) and medium ones for the *cis*-ones (4.8 to 7.9%) (*e.g.* : H-1 H-4 : 3.3% for **7a** and 7.9% for **7b** ; H-4 H-1 : 0,5% for **8a** and 4.8% for **8b** ; H-4 H-1 : 5.5% for **9b**). Although several enhancements are not negligible even for *trans*-epoxides, as we observed it in a related case[2], they are higher for *cis*-ones and our results are consistent with structures pictured in Table 1. Moreover these assignments for **8a** and **8b** were checked by chemical correlation : benzylation of a **8a** + **8b** mixture in the 18:82 ratio, respectively, led to a **10a** + **10b** mixture in the 19:81 ratio, respectively, in 86% yield. On the contrary, NOE experiments could not lead to any conclusion for compounds **11a** and **11b**. Therefore we treated the predominant isomer **11a** with hydrobromic acid. This reaction led not only to one of the both expected bromohydrins **12** but also to the C4-C3 ring contraction product **13** (Scheme 1 ; for related reactions see ref 3 and ref cited therein). Regiochemistry as well as stereochemistry of **12** could be undoubtedly assigned by successive spin decoupling experiments starting from OH that appears as a doublet, then by NOE experiments. Aldehyde **13** is not stable at room temperature and we could not determine its stereochemistry. Our results clearly show that the predominant epoxide **11a** is the *trans*-product.

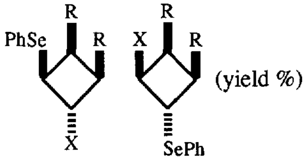


Scheme 1

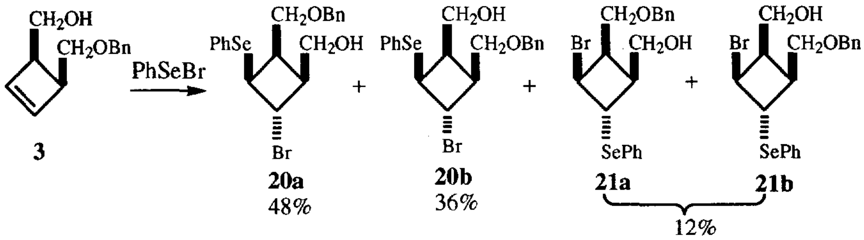


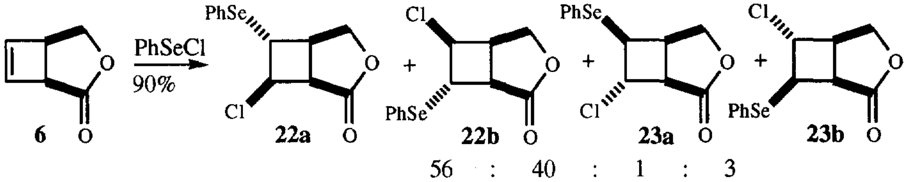
Scheme 2

Table 2. Haloselenylation reactions

Starting material 	Reagent (Reaction time)	Products  (yield %)
R = CO_2Me **1**	PhSeCl (4 h) X = Br	**16a** 92:8 **16b** (94); **16'a** >95:5 **16'b** (93)
R = CH_2OH **2**	PhSeBr (1 h)	**17a** 86:14 **17b** (70)
R = CH_2OBn **4**	PhSeBr (4 h) X = Cl	**18a** 94:6 **18b** (82); **18'a** 95:5 **18'b** (82)
R = CH_3 **5**	PhSeCl (4 h)	**19a** **19b** 44:56 (yield not determined)[a]

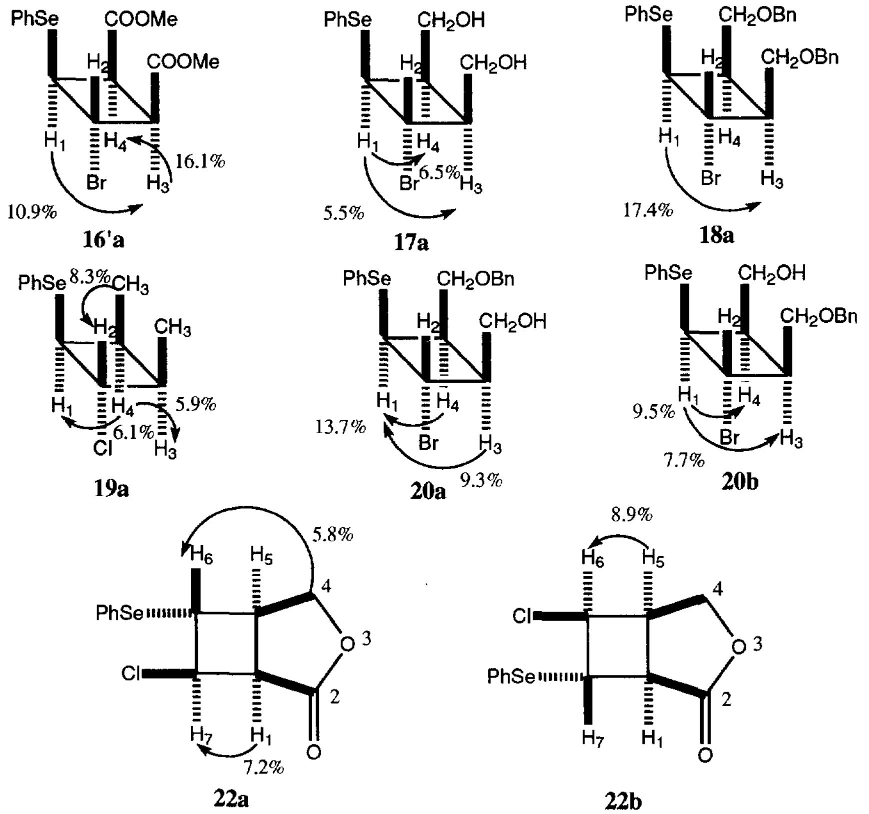
[a] The starting material **5** could not be obtained in quite pure form





A consequence of our results on epoxidations of **4** is that **10b** is more easily available than **10a**, as Payne's reagent led to higher reaction time and lower yield. Epoxides **10a** and **10b** could lead[2] to the corresponding bromohydrins **14a** and **14b** but we found that the most convenient way to **14a** was through bromohydroxylation of **4** (N-bromosuccinimide + moist dimethylsulfoxide[11]). The predominant attack by "Br^+" occurred *syn* to the benzyloxymethyl groups[12] as in reaction with *m*-CPBA (**14a/14b** = 90 : 10). Bromohydrin **14a** was an intermediary in synthesis of a novel cyclopropane nucleoside **15** (experimental details for preparation of **14a** and **14b** by bromohydroxylation are given in this paper and those for preparation of **15** in ref 3) (Scheme 2).

Addition of phenylselenyl halides to compounds **1-4** proceeded *via* the intermediary selenonium ions syn to the substituents[13] whereas reaction with **5** was not stereoselective. On the contrary the steric control was predominant from **6**. On the other hand reactions from **3** and **6** were not regioselective (Table 2). All the reaction times were from 1 to 4 h and we did not observe any dramatic slowing down in haloselenylation of **1** and **6**, contrarily to the case of epoxidation reactions.

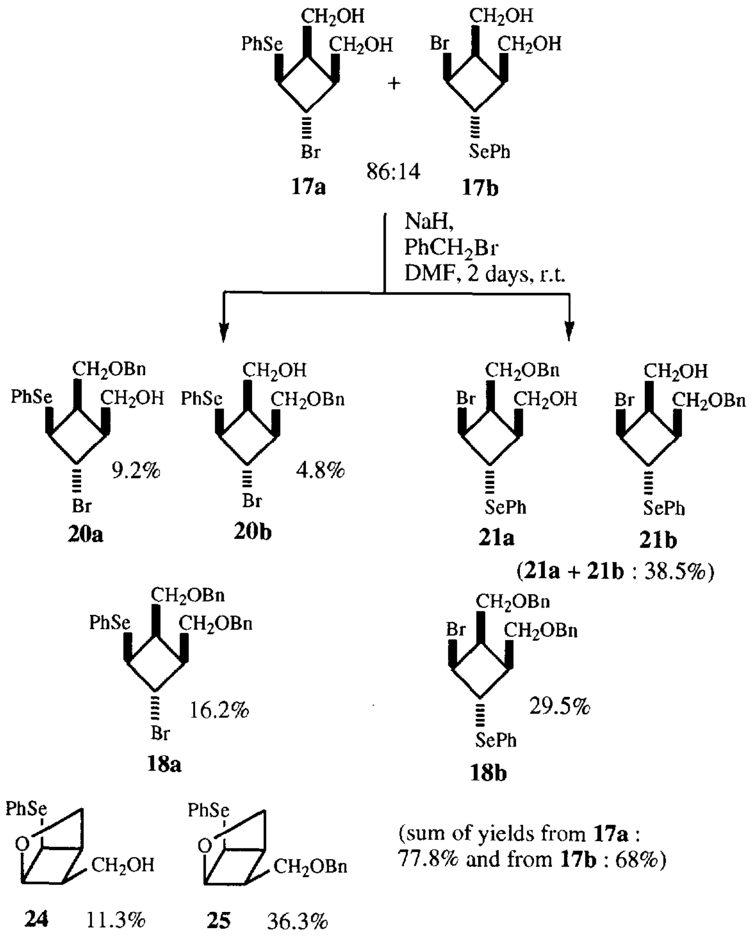


Scheme 3 Selected NOE enhancements

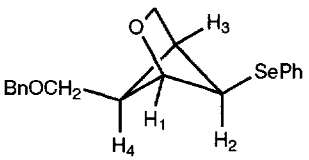
In most cases one of isomers at least was isolated, except for **21a** and **21b** which could not be separated, and the further structure determinations were straightforward by several successive NMR experiments. Carbons linked to the PhSe group were assigned on the basis of coupling with ^{77}Se (*e.g.* ^{1}J ^{13}C-^{77}Se : **16a** : 96.8 Hz ; **17a** : 125.1 Hz ; **18'a** : 94.4 Hz ; **22a** : 90.4 Hz ; **22b** : 92.8 Hz). The subsequent ^{13}C /^{1}H correlations led to assignments of the corresponding cyclobutane protons then to the other ones by successive spin decoupling experiments. At last, NOE experiments gave informations on stereochemistries (Scheme 3).

Finally we treated a mixture of **17a** and **17b** with sodium hydride and benzyl bromide with the aim of correlating compounds **17** with **18** (Scheme 4). As a matter of fact reactions were complicated by the extra obtention of the monobenzylated products **20a**, **20b**, **21a** and **21b** although we used a long reaction time. This result is likely due to the steric hindrance. We also isolated products **24** and **25** resulting from the intramolecular nucleophilic substitution of **17a** and **20b**, respectively. We started from 306 mg of the **17a** + **17b** mixture (263.2 + 42.8 mg). As we obtained 98 mg of **25**, the predominant starting material was necessarily the compound with bromine *trans* to the hydroxymethyl group. Therefore we could calculate yields indicated in scheme 4 taking into account origin **17a** or **17b** of each product. Sums of these thus calculated yields are 77.8 and 68% from **17a** and **17b**, respectively, which is satisfying and coherent with the assignments of structure for **17a** and **17b**. Some NMR results for **25** are given in scheme 5. The most characteristic features are the strong NOE effect between H_2 and H_4 and the strong coupling constant H_1-H_3(4.4 Hz).

Our results show that *m*-CPBA epoxidation of compounds **2**, **3** and **4** follow basically the same pattern as haloselenylation, however mechanisms of these both reactions are not the same. In the case of haloselenylation, the high *syn*-selectivity preference of the electrophilic attack is likely due to stabilization of the intermediary selenonium ion by the lone pair of one oxygen.[13c,d] Selectivity of the peracid epoxidations of **2** and **3** also is coherent with previous reports of literature as it has been postulated that a hydrogen bond between a hydroxy group at the homoallylic position and an oxygen of the peracid should lead to arrival of the incoming oxygen *syn* to this hydroxy group.[14] However, in examples of literature, replacement of the hydroxy group, by an alkoxy or acyloxy group usually leads to the attack from the less sterically hindered side. A possible interpretation of the unexpected result for reaction of **4** with *m*-CPBA might involve a hypothetic hydrogen bonding between the slightly acidic peracid and a benzyloxymethyl group ; however we could not obtain any experimental evidence for this bonding. Such interactions between *m*-CPBA and a benzyloxymethyl group have been previously postulated together with a cooperative interaction involving a hydroxy group.[15] In the case of peroxybenzimidic acid that is still less acidic than *m*-CPBA this hydrogen bonding interaction should be less probable and the steric control should be predominant. Our result on haloselenylation of **1** is coherent with those of **2**-**4** and bromohydroxylation of **4** also led to the *syn*-attack of the electrophilic species. On the other hand, epoxidations of **1** and **6** were very slow and led to the *anti* selectivity and haloselenylation of **6** quickly yielded both *anti*-attack products, predominantly.



Scheme 4 : Chemical correlations in reaction from the **17a** + **17b** mixture



25

$J_{H1\text{-}H3} = 4.4$ Hz

NOE experiments

saturated H	enhancements
H_4	H_2 : 22
H_3	H_2 : 3.1
H_1	H_2 : 3.0

Scheme 5 NMR results for **25**

In conclusion we observed high selectivities in the electrophilic additions to cyclobutene compounds and it was possible, in most cases, to obtain one or several of the isomers issued from compounds **1-6**, in pure form. These products are thus available for synthetical applications.

Experimental Section

NMR spectra were recorded on a Bruker AC 400 instrument (400 and 100 MHz for ^{1}H and ^{13}C, respectively). Samples were dissolved in $CDCl_3$ unless stated, with tetramethylsilane as the internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded with a Genesis Matteson infrared spectrophotometer. Melting points were measured on a Reichert apparatus and are uncorrected. Elemental analyses were performed by the service de microanalyse, CNRS, ICSN, Gif sur Yvette. High resolution mass measurements were performed at the CRMPO (Rennes) with a Varian mat 311 spectrometer.

cis-3,4-Bis(methoxycarbonyl)-1-cyclobutene **1**

cis-3-cyclobutene-1,2-dicarboxylic anhydride[7b,16] (2 g, 16.1 mmol), 40 mL of MeOH and 0.1 mL of 18 M H_2SO_4 were heated at 50° C for 7 h with stirring. Cooling, evaporation, addition of CH_2Cl_2 (40 mL), washing (brine, 3 x 10 mL), drying ($MgSO_4$) and another evaporation gave **1** as an oil (2.69 g, 98%). This compound was already prepared.[17] ^{1}H NMR δ 6.27 (s, 2H, H-1 and H-2), 3.94 (s, 2H, H-3 and H-4), 3,70 (s, 6H, Me) ; ^{13}C NMR δ 171.1 (2 C=O), 136.6 (C-1 and C-2), 52.0 (2 CH_3), 48.8 (C-3 and C-4) ; IR (cm^{-1}) 1733, 1342, 1278, 1207, 1168.

cis-4-Benzyloxymethyl-*cis*-3-hydroxymethyl-1-cyclobutene **3**

A solution of **2** (1.61 g, 14.1 mmol) in dry DMF (40 mL) was cooled to 0°C under argon then NaH (640 mg of 60% dispersion in mineral oil, 16.0 mmol) was added portionwise with stirring. Benzyl bromide (1.94 mL, 16.0 mmol) was added dropwise to this mixture and the reaction was allowed to proceed for 3 h at room temperature. An excess of MeOH was then added and the mixture was stirred for 1 h at room temperature. Evaporation, adding of AcOEt (100 mL), washing (H_2O, 2 x 50 mL), drying ($MgSO_4$) and another evaporation left the crude product. Purification by chromatography on silica gel (80 g, cyclohexane/AcOEt 5 : 1 --> 3 : 1) led to 2.24 g (75%) of **3** as a colorless oil. ^{1}H NMR δ 7.38-7.28 (m, 5H, Ph), 6.04 (d, 1H, H-1 or H-2 (AB system), J = 2.9 Hz), 6.00 (d, 1H, H-2 or H-1 (AB system), J = 2.9 Hz), 4.56 (m, 2H, benzylic (AB system), J = 11.9 Hz), 3.73-3.58 (m, 4H, 3H of two CH_2 and OH), 3.52 (dd, 1H of one CH_2, J = 10.0, 3.0 Hz), 3.31 (m, 1H, H-3 or H-4), 3.24 (m, 1H, H-4 or H-3) ; ^{13}C NMR δ 137.9 (C-1 or C-2), 137.2 (s, Ph) 136.6 (C-2 or C-1), 128.5 (d, Ph), 128.0 (d, Ph), 73.5 (t), 69.7 (t), 61.8 (t) 48.7 (d), 45.3 (d) ; IR (cm^{-1}) 3444, 1495, 1463, 1358, 1076, 1031, 740, 700 ; HR-MS : calcd for $C_{13}H_{16}O_2$: 204.1150. Found : 204.1152.

cis-3,4-Dimethyl-1-cyclobutene **5**[7]

Triethylamine (2.22 mL, 15.8 mmol) was added to a solution of **2** (0.600 g, 5,26 mmol) in CH_2Cl_2 (15 mL). This solution was cooled to 0°C and CH_3SO_2Cl (0.986 mL, 12.6 mmol) was added dropwise with stirring. After 45 min, CH_2Cl_2 (20 mL) was added. Washing (successively with 10% HCl (8 mL) 5% $NaHCO_3$ (5 mL) brine (2 x 20 mL)), drying ($MgSO_4$), evaporation and chromatography on silica gel (85 g, CH_2Cl_2 then CH_2Cl_2/AcOEt 98 : 2 --> 95 : 5) led to 1.4 g (99%) of *cis*-3,4-bis (mesyloxymethyl)-1-cyclobutene (m.p. 47-48°C (Et_2O) (white crystals)). ^{1}H NMR δ 6.17 (s, 2H, H-1 and H-2), 4.42 (dd, 2H, H-5 and H-6, J = 10.3, 5.9 Hz), 4.36 (dd, 2H, H-5' and H-6', J = 10.3, 7.9 Hz), 3.42 (m, 2H, H-3 and H-4), 3.05 (s, 6H, Me) ; ^{13}C NMR δ 137.4 (C-1, C-2), 68.5 (2 CH_2), 44.4 (C-3, C-4), 37.4 (2 CH_3) ; IR (cm^{-1}) 1349, 1174, 946 ; Anal. Calcd for $C_8H_{14}O_6S_2$: C, 35.55 ; H, 5.22 ; S, 23.72. Found : C, 35.62 ; H, 5.31 ; S, 23.91. *cis*-3,4-Bis(mesyloxymethyl)-1-cyclobutene (1.15 g, 4.25 mmol) was added portionwise under argon at 0°C and with stirring to a suspension of $LiAlH_4$ (0.680 g, 17.0 mmol) in bis(2-methoxyethyl) ether (31.6 mL). The reaction mixture was stirred at room temperature and monitored by TLC (CH_2Cl_2/AcOEt 2 : 1). After 23 h, the reaction mixture was submitted to an argon stream and warmed to 30°C so as **5** was trapped successively at the liquid nitrogen temperature then in a second trap containing CH_2Cl_2 and maintained at -78°C. We obtained in the first trap 0.168 g of **5** together with a by-product and in the second-one **5** together with several by-products and in CH_2Cl_2 solution. ^1H NMR δ 6.06 (s, 2H, H-1 and H-2), 2.92 (m, 2H, H-3 and H-4), 1.00 (d, 6H, CH_3, J = 7.4 Hz).

<u>2-Oxo-3-oxabicyclo[3.2.0]-6-heptene</u> **6**

NaBH4 (3.21 g, 84.6 mmol) was added under argon to a stirred solution of *cis*-3-cyclobutene-1,2-dicarboxylic anhydride[7b,15] (7g, 56.4 mmol) in THF (111 mL). The mixture was cooled to -78°C then MeOH (14 mL) was added dropwise for 1h. The reaction mixture was stirred at the same temperature for 1 h more, then 1M HCl (49 mL) and 6M HCl (14 mL) were added. The mixture was stirred for 0.5 h at room temperature, then solvents were evaporated. Extraction with CH_2Cl_2 (6 x 60 mL), drying ($MgSO_4$) and evaporation left the crude product. Purification by chromatography on silica gel (290 g, CH_2Cl_2 then CH_2Cl_2/Et_2O 98:2) gave **6** as a colorless oil (4.90 g, 79%). This compound was already prepared.[6] ^1H NMR δ 6.37 (d, 1H, H-6 or H-7 (AB system), J = 2.6 Hz), 6.33 (d, 1H, H-6 or H-7 (AB system), J = 2.6 Hz), 4.30 (m, 2H, CH_2), 3.66 (d, 1H, H-1, J = 3.5 Hz), 3.62 (m, 1H, H-5, $J_{H-5/H-1}$ = 3.5 Hz) ; ^{13}C NMR δ 175.3 (<u>C</u>=O), 141.5 (vinyl. <u>C</u>H), 139.0 (vinyl. <u>C</u>H), 68.0 (<u>C</u>H2), 46.5 (d), 41.8 (d). IR (cm^{-1}) 1760, 1371, 1171.

<u>*cis*-3,*cis*-4-Bis(methoxycarbonyl)-1,2-epoxycyclobutane **7b** and *trans*-3,*trans*-4-bis(methoxycarbonyl)-1,2-epoxycyclobutane **7a**</u>

m-CPBA (294 mg of the 75% reagent, 1.28 mmol) was added portionwise and with stirring to a solution of **1** (198 mg, 1.16 mmol) in CH_2Cl_2 (2 mL) with $NaHCO_3$ (27 mg, 0.32 mmol) in suspension, at 0°C. The reaction mixture was stirred for 72 h at room temperature, then a part of *m*-chlorobenzoic acid was removed by filtration on a sintered-glass funnel and filtrate was washed (saturated $NaHCO_3$ (2 mL) then brine (2 x 5 mL) and dried ($MgSO_4$)). Evaporation led to a **1** + **7a** + **7b** mixture as shown by ^1H NMR (**1**/**7a** + **7b** = 1.3:1 ; **7a**/**7b** = 6 : 1). Purification by chromatography on silica gel was not possible however a **1** + **7a** fraction could be obtained, then used in NOE experiment. Higher reaction times only led to slight improvements in conversion. Reactions with Payne's reagent, magnesium monoperoxyphtalate or dimethyl dioxirane also gave poor results. NMR data from mixture : **7a** : ^1H NMR δ 4.21 (s, 2H, H-1 and H-2), 3.73 (s, 6H, CH_3), 3.22 (s, 2H, H-3 and H-4) ; ^{13}C NMR δ 169.8 (2 <u>C</u>=O), 55.2 (C-1, C-2), 52.1 (2 <u>C</u>H3), 48.7 (C-3, C-4). **7b** : ^1H NMR δ 4.15 (s, 2H, H-1 and H-2), 3.72 (s, 6H, CH_3), 3.54 (s, 2H, H-3 and H-4).

<u>Compounds **8a**, **8b**, **10a**, **10b**</u>

These compounds were prepared as described in ref. 2 with slight improvements (see table 1). Epoxides **8a** and **8b** could not be separated ; **8a** : ^1H NMR (incomplete description) δ 3.91 (m, 4H, CH_2), 3.71 (s, 2H, H-1 and H-2), 2.48 (m, 2H, H-3 and H-4) ; **8b** : ^1H NMR δ 3.85 (s, 2H, H-1 and H-2), 3.78 (m, 4H, CH_2), 3.40 (br s, 2H, OH), 2.79 (m, 2H, H-3 and H-4) ; IR (**8a** + **8b**) : 3357, 2944, 1334, 1029, 838.

<u>*trans*-4-Benzyloxymethyl-*trans*-3-hydroxymethyl-1,2-epoxycyclobutane **9a** and *cis*-4-benzyloxymethyl-*cis*-3-hydroxymethyl-1,2-epoxycyclobutane **9b**</u>

m-CPBA (4.91 g of the 50-60% reagent, 14.2 mmol), $NaHCO_3$ (500 mg, 5.92 mmol) were added with stirring to a solution of **3** (1.94 g , 9.49 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for

15 h at room temperature. Filtration and evaporation led to a mixture of **9a** and **9b** in the 22:78 ratio, respectively. Chromatography on 150 g of silica gel (cyclohexane/AcOEt 2:3 ->1:4) yielded three fractions : successively **9a** (colorless oil, 143 mg, 6.8%) contaminated with a small amount of *m*-chlorobenzoic acid ; **9a** + **9b** (450 mg, 21.5%) ; **9b** (colorless oil, 990 mg, 47.7%) contaminated with a small amount of *m*-chlorobenzoic acid. **9a** : ^{1}H NMR δ 7.39-7.26 (m, 5H, Ph), 4.56 (m, 2H, benzylic (AB system), J = 11.8 Hz), 3.85 (dd, 1H, J = 11.8, 9.8 Hz), 3.78-3.65 (m, 4H), 3.61 (dd, 1H, J = 10.1, 5.7 Hz), 3.20 (br s, 1H, OH), 2.54 (m, 1H, H-3 or H-4), 2.46 (m, 1H, H-4 or H-3) ; ^{13}C NMR δ 128.6 (d, Ph), 128.1 (d, Ph), 73.6 (t), 66.2 (t), 58.7 (t), 55.3 (d), 55.1 (d), 46.2 (d), 43.1 (d) ; IR (cm^{-1}) 3424, 1455, 1365, 1257, 1074, 1027, 817, 750, 700 ; **9b** : ^{1}H NMR δ 7.37-7.26 (m, 5H, Ph), 4.51 (m, 2H, benzylic (AB system), J = 11.8 Hz), 3.85 (m, 1H, H-1 or H-2, $J_{H-1/H-2}$ = 2.4 Hz), 3.83 (m, 1H, H-2 or H-1, $J_{H-2/H-1}$ = 2.4 Hz), 3.74 (dd, 1H of one CH_2, J = 11.7, 9.5 Hz), 3.66 (m, 3H of two CH_2), 2.95 (br s, 1H, OH), 2.86 (m, 1H, H-3 or H-4, $J_{H-3/H-2}$ = 1.1 Hz), 2.78 (m, 1H, H-4 or H-3, $J_{H-4/H-1}$ = 1.0 Hz) ; ^{13}C NMR δ 137.1 (s, Ph), 128.5 (d, Ph), 128.00 (d, Ph), 127.97 (d, Ph), 73.5 (t), 67.0 (t), 59.1 (t), 52.7 (d), 51.8 (d), 44.8 (d), 41.7 (d) ; IR (cm^{-1}) 3401, 1455, 1365, 1259, 1074, 1027, 836, 750, 700.

6,7-*exo*-Epoxy-2-oxo-3-oxabicyclo[3.2.0]heptane **11a** and 6,7-*endo*-epoxy-2-oxo-3-oxabicyclo[3.2.0] heptane **11b**

m-CPBA (17.6 g of the 75% reagent, 71.6 mmol) was added portionwise and with stirring to a solution of **6** (4.92 g, 44.7 mmol) in CH_2Cl_2 (50 mL) at 0°C. The reaction mixture was stirred for 3 days at room temperature, then 4.65 g of 75% *m*-CPBA (26.9 mmol) were added. After 1 day more stirring, 1.16 g of 75% *m*-CPBA (6.72 mmol) were added again and stirring was pursued for another day. Filtration on a sintered-glass funnel and evaporation left the crude product. ^{1}H NMR showed a 81:19 **11a/11b** ratio. Chromatography on silica gel (CH_2Cl_2 then CH_2Cl_2/Et_2O 98:2) firstly led to **11a** (4.51 g, 79.9%) then to **11b** (529 mg, 9.4%) as colorless oils. **11a** : ^{1}H NMR δ 4.51 (dd, 1H, H-4, J = 10.4, 2.2 Hz), 4.46 (dd, 1H, H-4', J = 10.4, 7.4 Hz), 4.20 (dd, 1H, H-6, J = 2.5, 2.0 Hz), 4.05 (dd, 1H, H-7, J = 3.3, 2.0 Hz), 3.24 (dd, 1H, H-1, J = 3.9, 3.3 Hz), 3.09 (m, 1H, H-5) ; ^{13}C NMR δ 173.4 (C=O), 67.7 (CH_2), 55.6 (d), 55.0 (d), 49.3 (d), 44.4 (d) ; IR (cm^{-1}) 1760, 1322, 1176, 1060, 991, 815 ; MS m/z (rel. int.) 126 (M^+, 0.1), 97 [$(M-CHO)^+$,2], 95 [$(M-CH_2OH)^+$,7], 81(58), 68(82), 54(36), 53(66), 39(100), 28(80) ; HR-MS : calcd for ($C_6H_6O_3$-CHO) : 97.0289. Found : 97.0294 ; calcd for ($C_6H_6O_3$-CH_2OH) : 95.0133. Found : 95.0134. **11b** : ^{1}H NMR δ 4.36 (dd, 1H, H-4, J = 9.7, 3.1 Hz), 4.24 (d, 1H, H-6 or H-7, J = 2.1 Hz), 4.18 (dd, 1H, H-4', J = 9.7, 6.9 Hz), 4.08 (d, 1H, H-7 or H-6, J = 2.1 Hz), 3.34 (dd, 1H, H-1, J = 8.9, 1.2 Hz), 3.22 (m, 1H, H-5) ; ^{13}C NMR δ 173.9 (C=0), 67.5 (CH_2), 54.6 (d), 54.2 (d), 42.7 (d), 37.7 (d) ; IR (cm^{-1}) 1772, 1378, 1267, 1170, 1132, 985, 944, 831.

Obtention of **10a** + **10b** from the **8a** + **8b** mixture

NaH (170 mg of 60% dispersion in mineral oil, 4.26 mmol) then *n*-Bu_4NI (107 mg, 0.28 mmol) were added portionwise and with stirring to a solution of **8a** + **8b** in the 18:82 ratio, respectively (185 mg, 1.42 mmol) in 6.5 mL of THF, at 0°C and under argon. Benzyl bromide (414 μL, 3.41 mmol) was then added dropwise and the reaction mixture was stirred for 5 h at room temperature. Methanol in excess was then added at 0°C. After 1 h more stirring, warming up to r.t., evaporation, adding of AcOEt (15 mL), washing of the organic phase (2 x 3 mL of water then 10 mL of brine), drying ($MgSO_4$) and evaporation led to **10a** + **10b** in the 19:81 ratio, respectively, as shown by ^{1}H NMR. Purification by chromatography on silica gel (27 g, cyclohexane/AcOEt 7:1 then 5:1) led to 380 mg (86%) of **10a** + **10b** identified by the spectral data.

7-*endo*-Bromo-6-*exo*-hydroxy-2-oxo-3-oxabicyclo[3.2.0]heptane **12** and 6-carboxaldehyde-2-oxo-3-oxa bicyclo[3.1.0]hexane **13**

HBr (48% aqueous solution, 12.1 mL, 107 mmol) was added with stirring to a solution of **11a** (4.50 g, 35.7 mmol) in acetone (290 mL). The reaction mixture was stirred for 6 h 30 min at room temperature then it was neutralized by addition of 95 mL of saturated aqueous $NaHCO_3$. Evaporation, extraction with AcOEt (5 x 50 mL, drying ($MgSO_4$) and another evaporation led to the crude product. A 86:14 ratio for **12/13** was measured by ^{1}H NMR. Chromatography on silica gel (CH_2Cl_2/Et_2O 9:1 -> 4:1) successively yielded **13** (315 mg, 7.0%) as a colorless oil, then **12** (2.93 g, 39.6%) (m.p. 107-108°C (Et_2O) (white crystals)). **13** : ^{1}H NMR δ 9.49 (d, 1H, CHO, J = 4.9 Hz), 4.61 (dd, 1H, H-4, J = 10.3, 4.9 Hz), 4.51 (d, 1H, H-4', J = 10.3 Hz), 2.86 (m, 1H, H-5), 2.71 (dd, 1H, H-1, J = 8.4, 5.9 Hz), 2.39 (m, 1H, H-6, J = 8.4, 4.9 Hz), ^{13}C NMR δ 196.3 (CHO), 172.1 (other C=O), 66.7 (CH_2), 30.6 (d), 27.2 (d), 25.6 (d). **12** : ^{1}H NMR (acetone d6) δ 5.43 (d, 1H, OH, J = 6.9 Hz), 4.58 (dd, 1H, H-7, J = 9.5, 7.0 Hz), 4.36 (m, 2H, H-4 and H-4', $J_{H4-H4'}$ = 9.3 Hz), 4.25 (m, 1H, H-6), 3.41 (m, 1H, H-1, $J_{H-1/H-7}$ = 9.5 Hz, $J_{H-1/H-5}$ = 7.6 Hz, $J_{H-1/H-6}$ = 1.5 Hz), 3.09 (m, 1H, H-5). ^{13}C NMR (acetone d6) δ 174.0 (C=O), 80.6 (d), 71.0 (CH_2), 47.2 (d), 44.9 (d), 38.4 (d) ; IR (cm^{-1}) 3453, 1749, 1444, 1369, 1238, 1170, 968, 655 ; Anal. calcd for $C_6H_7O_3Br$: C, 34.81 ; H, 3.41 ; Br, 38.59. Found : C, 37.71 ; H, 3.31 ; Br 38.19.

cis-3, *cis*-4-Bis(benzyloxymethyl)-*trans*-2-bromo-1-hydroxycyclobutane **14b** and *trans*-3, *trans*-4-bis (benzyloxymethyl)-*trans*-2-bromo-1-hydroxycyclobutane **14a**

NBS (1.25 g, 6.80 mmol) was added to a solution of **4** (1 g, 3.40 mmol) in DMSO (10 mL) and water (122 µL, 6.80 mmol), with stirring, at 10°C. The reaction mixture was stirred for 15 min at 10°C then for 23 h at room temperature. Dilution (20 mL of AcOEt), washing (successively with 50 mL of water, 20 mL of 5% aqueous $NaHCO_3$, 20 mL of water, 30 mL of water, 40 mL of brine), drying ($MgSO_4$) and evaporation yielded **14a** + **14b** (**14a/14b** = 90:10 by ^{1}H NMR). Purification by chromatography on silica gel (125 g, cyclohexane/AcOEt 10:1 ->5:1) successively led to **14b** (107 mg, 8%) then to **14a** (888 mg, 66.8%) identified by the spectral data.[2]

General procedure for haloselenylations of **1-6**

A solution of PhSeBr (970 mg, 4.11 mmol) or PhSeCl (787 mg, 4.11 mmol) in CH_2Cl_2 (10 mL) was added dropwise, with stirring, to a solution of the cyclobutene compound **1-6** (4.11 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temperature for 1 h (**2**) or 4 h (**1**, **3**, **4**, **5**, **6**), then solvent was evaporated. Ratio of isomers was measured by ^{1}H NMR in most cases. The crude product was purified by chromatography. For reactions from **1**, **2** and **4** spectral data are given for the predominant product. Reaction with **1** (PhSeCl), chromatography eluent : cyclohexane then cyclohexane/AcOEt 3:1, yield 94%, **16a/16b** = 92:8 ; **16a** : oil ; ^{1}H NMR δ 7.55 (m, 2H, Ph), 7.34-7.22 (m, 3H, Ph), 4.91 (dd, 1H, H-2), 3.96 (dd, 1H, H-1), 3.87 (dd, 1H, H-4), 3.77 (s, 3H, H-7), 3.73 (s, 3H, H-8), 3.39 (dd, 1H, H-3) ; ^{13}C NMR δ 170.9 (C=O) 169.2 (C=O), 134.1 (d, Ph), 129.3 (d, Ph), 128.0 (d, Ph), 57.8 (C-2), 52.3 (C-8), 52.2 (C-7), 49.0 (C-3), 46.4 (C-4), 45.5 (C-1) ; IR (cm^{-1}) 1752, 1438, 1359, 1207 ; Reaction with **1** (PhSeBr), chromatography eluent : cyclohexane/AcOEt 7:1, yield 93%, **16a'/16b'**>95:5 ; **16a'** : oil ; ^{1}H NMR δ 7.59 (m, 2H, Ph), 7.30 (m, 3H, Ph), 4.96 (dd, 1H, H-2), 4.05 (dd, 1H, H-1), 3.92 (dd, 1H, H-4), 3.77 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.51 (dd, 1H, H-3) ; ^{13}C NMR δ 170.9 (C=O), 169.3 (C=O), 134.2 (d, Ph), 129.3 (s, Ph), 129.2 (d, Ph), 128.0 (d, Ph), 52.3 (q), 52.2 (q), 48.9 (d), 48.5 (d), 46.2 (d), 45.7 (d) ; IR (cm^{-1}) 1739, 1436, 1359, 1203 ; MS m/z (rel. int.) 408 (M^+, 30), 406 (M^+, 38), 242 (100), 240 (52), 183 (47), 157 (33), 113 (72), 111 (48), 77 (34), 59 (34) ; HR-MS : calcd for $C_{14}H_{15}O_4SeBr$: 405.9319. Found : 405.9310. Reaction with **2**, chromatography eluent : CH_2Cl_2 then CH_2Cl_2/AcOEt 9:1, yield 70%, **17a/17b** = 86:14 ; **17a** : m.p. 76-77°C (Et_2O, petroleum) ; ^{1}H NMR δ 7.58 (m, 2H, Ph), 7.28 (m, 3H, Ph), 4.45 (dd, 1H, H-2, J = 9.2, 9.0 Hz), 4.17 (dd, 1H, H-1, J = 9.4, 9.2 Hz), 3.95 (m, 2H, H-5 and H-5', $J_{H-5/H-5'}$ = 11.8 Hz), 3.82 (m, 2H, H-6 and H-6'), 3.10 (m, 1H, H-4), 2.97 (m, 2H, H-3 and OH), 2.84 (br s, 1H, OH) ; ^{13}C NMR δ 133.5 (d, Ph), 130.1 (s, Ph), 129.2 (d, Ph), 127.5 (d, Ph), 60.8 (t), 59.5 (t), 49.7 (d), 47.6 (d), 47.5 (d), 43.3 (d) ; IR (cm^{-1}) 3234, 1436, 1012 ; Anal. Calcd for $C_{12}H_{15}O_2SeBr$: C, 41,17 ; H, 4.32 ; Br, 22.82 ; Se, 22.55. Found : C, 40.79 ; H, 4.22 ; Br, 22.92 ; Se 22.77. Reaction with **4** (PhSeBr), chromatography eluent : cyclohexane/Et_2O 50:1, yield 82%, **18a/18b** = 94:6 ; **18a** : m.p. 55-56°C (petroleum) (white crystals) ; ^1H NMR δ 7.61 (m, 2H, SePh), 7.37-7.23 (m, 13H, Ph), 4.52 (d, 1H, benzylic, J = 11.5 Hz), 4.48 (d, 1H, benzylic, J = 11.9 Hz), 4.42 (dd, 1H, H-2, J = 8.9, 8.2 Hz), 4.38 (d, 1H, benzylic, J = 11.9 Hz), 4.32 (d, 1H, benzylic, J = 11.5 Hz), 4.13 (dd, 1H, H-1, J = 9.4, 9.0 Hz), 3.73 (dd, 1H, CH_2 (AB system) J = 9.7, 2.3 Hz), 3.69 (dd, 1H, CH_2 (AB system) J = 9.7, 3.6 Hz), 3.67 (d, 1H, CH_2, J = 8.3 Hz), 3.59 (dd, 1H, CH_2, J = 8.3, 4.6 Hz), 3.05 (m, 2H, H-3 and H-4); ^{13}C NMR δ 138.1 (s, Ph), 137.9 (s, Ph), 133.4 (d, Ph), 131.7 (s, Ph), 129.0 (d, Ph), 128.41 (d, Ph), 128.37 (d, Ph), 128.0 (d, Ph), 127.9 (d, Ph), 127.74 (d, Ph), 127.70 (d, Ph), 127.1 (d, Ph), 73.3 (benzylic C), 73.2 (benzylic C), 68.2 ($\underline{C}H_2$), 67.9 ($\underline{C}H_2$), 50.4 (d), 49.6 (d), 48.1 (d), 41.7 (d) ; MS m/z (rel. int.) 530 (M^+, 1), 107 (5), 97(3), 92(7), 91(100), 79(5), 78(5), 77(8), 67(5), 65(9), 51(5) ; IR (cm^{-1}) 1101, 1052, 742, 688 ; Anal. Calcd for $C_{26}H_{27}O_2SeBr$: C, 58.88 ; H 5.13 ; Br, 15.07 ; Se 14.89. Found : C, 58.83 ; H, 5.13 ; Br, 14.98 ; Se, 14.33. Reaction with **4** (PhSeCl), chromatography eluent : cyclohexane then cyclohexane/Et_2O 50:1, yield 82%, **18'a/18'b** = 95:5 ; **18a'** : m.p. 50-51°C (petroleum) (white crystals) ; ^1H NMR δ 7.59 (m, 2H, SePh), 7.37-7.23 (m, 13H, Ph), 4.52 (d, 1H, benzylic, J = 11.4 Hz), 4.48 (d, 1H, benzylic, J = 11.9 Hz), 4.39 (d, 1H, benzylic, J = 11.9 Hz), 4.36 (dd, 1H, H-2, J = 8.9, 7.3 Hz), 4.33 (d, 1H, benzylic, J = 11.4 Hz), 3.99 (dd, 1H, H-1, J = 9.3, 8.9 Hz), 3.73 (dd, 1H, H-5 (AB system), J = 9.8, 3.2 Hz), 3.69 (dd, 1H, H-5' (AB system), J = 9.8, 3.6 Hz), 3.67 (d, 1H, H-6, J = 8.3 Hz), 3.61 (dd, 1H, H-6', J = 8.3, 5.3 Hz), 3.03-2.97 (m, 1H, H-4), 2.95-2.87 (m, 1H, H-3) ; ^{13}C NMR δ 138.1 (s, Ph), 137.9 (s, Ph), 133.2 (d, Ph), 131.8 (s, Ph), 129.0 (d, Ph), 128.4 (d, Ph), 128.3 (d, Ph), 127.93 (d, Ph), 127.88 (d, Ph), 127.72 (d, Ph), 127.68 (d, Ph), 127.0 (d, Ph), 73.3 (benzylic C), 73.1 (benzylic C), 68.2 ($\underline{C}H_2$), 67.8 ($\underline{C}H_2$), 60.6 (C-2), 49.2 (C-1), 47.5 (C-3), 39.5 (C-4) ; IR (cm^{-1}) 1103, 1054, 738, 690 ; Anal. Calcd for $C_{26}H_{27}O_2SeCl$: C, 64.27 ; H, 5.60 ; Cl, 7.30. Found : C, 64.42 ; H, 5.53 ; Cl, 7.36. Reaction with **5**, chromatography eluent : cyclohexane then cyclohexane/AcOEt 6:1, **19a/19b** = 44:56 ; **19b** : oil ; ^1H NMR, δ 7.53 (m, 2H, Ph), 7.35-7.20 (m, 3H, Ph), 4.02-3.95 (m, 2H, H-1 and H-2), 2.88-2.78 (m, 1H, H-3 or H-4), 2.66-2.56 (m, 1H, H-4 or H-3), 1.09 (d, 3H, CH_3, J = 7.5 Hz), 1.08 (d, 3H, CH_3, J = 6.9 Hz) ; ^{13}C NMR δ 133.2 (d, Ph), 129.9 (s, Ph), 129.0 (d, Ph), 127.0 (d, Ph), 64.3 (d), 49.7 (d), 43.2 (d), 34.6 (d), 12.7 (q), 12.4 (q) ; MS m/z (rel int.) 274 (M^+, 31), 198 (100), 196 (43), 89 (35), 81 (52), 78 (35), 77 (46), 67 (30), 41 (41), 28 (63) ; IR (cm^{-1}) 2960, 1477 ; HR-MS : Calcd for $C_{12}H_{15}SeCl$: 274.0027. Found : 274.0036 ; **19a** : ^1H NMR δ 5.12 (dd, 1H, H-2, J = 8.9, 8.3 Hz), 4.99 (dd, 1H, H-1, J = 8.4, 8.3 Hz), 3.33 (m, 1H, H-4), 2.69-2.65 (m, 1H, H-3), 1.36 (d, 3H, H-5, J = 7.4 Hz), 1.23 (d, 3H, H-6, J = 6.9 Hz). Reaction with **3**, chromatography eluent : cyclohexane/Et_2O 20:1, 15:1 then 10:1, yield 96%, **20a/20b/21a+21b** = 48/36/12 ; **20a** : oil ; ^1H NMR δ 7.55 (m, 2H, SePh), 7.40-7.26 (m, 8H, Ph), 4.60 (d, 1H, benzylic (AB system), J = 11.4 Hz), 4.56 (d, 1H, benzylic (AB system), J = 11.4 Hz), 4.27 (dd, 1H, H-2, J = 9.2, 9.1 Hz), 4.13 (dd, 1H, H-1, J = 9.3, 9.2 Hz), 3.76 (m, 2H, H-5 and H-5'), 3.72-3.63 (m, 2H, H-6 and H-6', $J_{H-6/H-6'}$ = 12.3 Hz), 3.17 (m, 1H, H-4), 2.98 (m, 1H, H-3), 2.88 (dd, 1H, OH, J = 7.3, 5.8 Hz) ; ^{13}C NMR δ 136.8 (s, Ph), 133.5 (d, Ph), 130.0 (s, Ph), 129.2 (d, Ph), 128.6 (d, Ph), 128.2 (d, Ph), 128.1 (d, Ph), 127.5 (d, Ph), 73.9 (t), 68.5 (t), 60.15 (t), 50.0 (d), 47.8 (d), 47.3 (d), 40.9 (d) ; IR (cm^{-1}) 3423, 1477, 1070, 1022, 738, 692 ; **20b** : oil ; ^1H NMR δ 7.61 (m, 2H, SePh), 7.39-7.25 (m, 8H, Ph), 4.60 (d, 1H, benzylic, J = 11.8 Hz), 4.55 (dd, 1H, H-2, J = 9.2, 8.4 Hz), 4.54 (d, 1H, benzylic, J = 11.8 Hz), 4,13 (dd, 1H, H-1, J = 9.3, 8.4 Hz), 3.86 (m, 2H, H-5 and H-5', $J_{H-5/H-5'}$ = 12.4 Hz, $J_{H-5'/OH}$ = 7.8 Hz, $J_{H-5/OH}$ = 5.8 Hz), 3.69 (dd, 1H, H-6, J = 10.5, 5.5 Hz), 3.63 (dd, 1H, H-6', J = 10.5, 3.2 Hz), 3.42 (dd, 1H, OH, J = 7.8, 5.8 Hz), 3.07-3.00 (m, 1H, H-4), 2.99-2.92 (m, 1H, H-3, $J_{H-3/H-4}$ = 9.8 Hz, $J_{H-3/H-2}$ = 9.2 Hz) ; ^{13}C NMR δ 136.8 (s, Ph), 133.5 (d, Ph), 140.9 (s, Ph), 129.1 (d, Ph) 128.7 (d, Ph), 128.2 (d, Ph), 128.0 (d, Ph), 127.3 (d, Ph), 73.8 (t), 66.7 (t), 60.4 (t) 48.7 (d), 48.6 (d), 48.1 (d), 44.3 (d). IR (cm^{-1}) 3434, 1367, 1259, 1076, 1025, 742, 696 ; **21b** : ^1H NMR δ 7.60 (m, 2H, SePh), 7.38-7.25 (m, 8H, Ph), 4.53 (d, 1H, benzylic (AB system), J = 11.8 Hz), 4.49 (d, 1H, benzylic (AB system), J = 11.8 Hz), 4.30 (dd, 1H, H-2, J = 8.8, 8.5 Hz), 3.97-3.82 (m ; 3H ; H-1, H-5 and H-5') ; 3.71 (dd, 1H, H-6, J = 10.1, 8.3 Hz), 3.61 (dd, 1H, H-6', J = 10.1, 4.1 Hz), 2.95 (dd, 1H, OH, J = 8.2, 5.4 Hz), 2.83 (m, 1H, H-3), 2.52 (m, 1H, H-4). Reaction with **6**, chromatography eluent : cyclohexane/AcOEt 4 : 1, yield 90%, **22a/22b/23a/23b** = 56:40:1:3 ; **22a** : m.p. 94-96°C (Et_2O) (white crystals) ; ^1H NMR δ 7.62 (m, 2H, Ph), 7.42-7.33 (m, 3H, Ph), 4.46 (dd, 1H, H-7, J = 8.9, 8.3 Hz), 4.32-4.25 (m, 2H, H-4 and H-4'), 3.78 (dd, 1H, J = 8.3, 7.0 Hz), 3.39 (dd, 1H, H-1, J = 8.9, 7.4 Hz), 2.99 (m, 1H, H-5, $J_{H-5/H-1}$ = 7.4 Hz, $J_{H-5/H-6}$ = 7.0 Hz) ; ^{13}C NMR δ 173.0 (C=O), 135.7 (d, Ph), 129.5 (d, Ph), 128.9 (d, Ph), 126.1 (s, Ph), 71.5 (C-4), 54.1 (d), 47.9 (C-6), 43.7 (d), 39.7 (d) ; Anal. Calcd for $C_{12}H_{11}O_2SeCl$: C, 47.78 ; H, 3.67 ; Cl, 11.75. Found : C, 47.91 ; H, 3.95 ; Cl, 12.17 ; **22b**, oil, ^1H NMR δ 7.63 (m, 2H, Ph), 7.40-7.34 (m, 3H, Ph), 4.83 (dd, 1H, H-4, J = 10.3, 3.9 Hz), 4.55 (dd, 1H, H-6, J = 7.7 Hz, 7.0 Hz), 4.44 (dd, 1H, H-4', J = 10.3, 8.9 Hz), 4.00 (dd, 1H, H-7, J = 7.0, 5.9 Hz), 3.34 (m, 1H, H-5), 3.05 (dd, 1H, H-1, J = 7.5, 5.9 Hz) ; ^{13}C NMR δ 175.6 (C=O), 135.4 (d, Ph), 129.5 (d, Ph), 128.9 (d, Ph), 126.6 (s, Ph), 67.7 (C-4), 57.9 (d), 46.1 (C-7), 42.4 (d), 38.3 (d) ; IR (cm^{-1}) 1772, 1373, 1172, 1008 ; MS m/z (rel. int.) 302 (M^+, 87) 227 (45), 211 (89), 183 (89), 181 (44), 89 (67), 78 (47), 77 (100), 65 (65), 51 (50) ; HR-MS : Calcd for $C_{12}H_{11}O_2SeCl$: 301.9613. Found : 301.9622. **23a** : ^1H NMR δ 7.66 (m, 2H, Ph), 7.33-7.28 (m, 3H, Ph), 4.37-4.32 (m, 2H, H-4 and H-4'), 4.30-4.23 (m, 2H, H-6 and H-7), 3.53 (dd, 1H, H-1, J = 8.9, 8.4 Hz), 3.34 (m, 1H, H-5) ; **23b** : oil ; ^1H NMR δ 7.55 (m, 2H, Ph), 7.37-7.24 (m, 3H, Ph), 4.76 (dd, 1H, H-4, J = 10.3, 3.0 Hz), 4.41 (dd, 1H, H-4', J = 10.3, 8.2 Hz), 4.19 (dd, 1H, H-6, J = 8.0, 7.3 Hz), 3.96 (dd, 1H, H-7, J = 7.3, 4.9 Hz), 3.32 (m, 1H, H-5, 3.22 (dd, 1H, H-1, J = 7.9, 4.9 Hz).

Benzylation of **17a + 17b**

NaH (105 mg of 60% dispersion in mineral oil, 2.62 mmol) was added portionwise with stirring, under argon and at 0°C to a solution of **17 a + 17b** (**17a/17b** = 86 : 14, **17a + 17b** = 306 mg, 0.87 mmol) in DMF (2.2 mL). Benzyl bromide (254 μL, 2.10 mmol) was then added and the reaction mixture was stirred for 2 days at room temperature. Methanol in excess was added at 0°C and after 1 h stirring at r.t. , evaporation, addition of 10 mL of AcOEt, washing (3 mL), drying ($MgSO_4$) and evaporation left the crude product. Chromatography on silica gel (28 g, cyclohexane/Et_2O 50 : 1, 20 : 1 --> 10 : 1 then AcOEt) successively yielded 84 mg of **18a + 18b** (**18a/18b** = 77 : 23), 98 mg of **25** (oil), 13 mg of **20b**, 25 mg of **21a + 21b** , 24 mg of **20a** and 23 mg of **24** (oil). **24** : ^1H NMR δ 7.49 (m, 2H, SePh), 7.34-7.24 (m, 3H, Ph), 4.50 (d, 1H, H-1, J = 5.6 Hz), 3.98 (d, 1H, H-5, J = 7.0 Hz), 3.69 (d, 1H, H-5', J = 7.0 Hz), 3.61 (dd, 1H, H-7, J = 11.1, 7.4 Hz), 3.51 (dd, 1H, H-7', J = 11.1, 6.4 Hz), 3.41 (d, 1H, H-2, J = 2.7 Hz), 3.03 (m, 1H, H-3), 2.12 (ddd, 1H, H-4, J = 7.0, 2.9 Hz), 1.82 (br s, 1H, OH) ; ^{13}C NMR δ 133.1 (d, Ph), 129.8 (s, Ph), 129.1 (d, Ph), 127.1 (d, Ph), 80.5 (d), 63.2 (t), 58.1 (t), 47.7 (d), 47.3 (d), 44.7 (d) ; **25** : ^1H NMR δ 7.48 (m, 2H, SePh), 7.36-7.23 (m, 8H, Ph), 4.51 (d, 1H, benzylic, J = 11.9 Hz), 4.46 (d, 1H, H-1, J = 4,4 Hz), 4.44 (d, 1H, benzylic, J = 11.9 Hz), 3.96 (d, 1H, H-5, J = 7.0 Hz), 3.62 (d, 1H, H-5', J = 7.0 Hz), 3.41 (d, 1H, H-2, J = 2.9 Hz), 3.43 (dd, 1H, H-7, J = 9.9 , 6.7 Hz), 3.36 (dd, 1H, H-7', J = 9.9, 6.7 Hz), 3.04 (m, 1H, H-3, $J_{H-3/H-4}$ = 2.9 Hz, $J_{H-3/H-2}$ = 2.9 Hz, $J_{H-3/H-5}$ (or H-5') = 0.2 Hz), 2.21 (td, 1H, H-4, $J_{H-4/H-7}$ = 6.7 Hz, $J_{H-4/H-3}$ = 2.9 Hz). ^{13}C NMR δ 138.1 (s, Ph), 133.0 (d, Ph), 129.9 (s, Ph), 129.1 (d, Ph), 128.4 (d, Ph), 127.71 (d, Ph), 127.69 (d, Ph), 127.0 (d, Ph), 80.8 (C-1), 73.2 (benzylic CH_2), 65.4 (C-7), 63.2 (C-5), 47.8 (C-2), 45.5 (C-4), 45.0 (C-3) ; MS m/z (rel. int.) 360 (M+, 3), 203 (16), 197 (17), 195 (8), 117 (8), 116 (19), 91 (100), 81 (7), 78 (7), 77 (7). IR (cm^{-1})1477, 1095, 1022, 734, 692 ; HR-MS : Calcd for $C_{19}H_{20}O_2Se$: 360.0629. Found : 360.0635.

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