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Synthesis of a Novel Trisubstituted Cyclobutane Nucleoside Analogue. Unexpected C4-C3 Ring Contractions in Related Reactions

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Abstract : Nucleoside analogue **7** was obtained by nucleophilic substitution between adenine and mesylate **5b**. On the other hand the same reaction starting from its isomer **5a** did not work and led to the surprising ring contraction products **8a** and **8b**. Another unexpected ring contraction leading to **15** was pointed out in the course of preparation of the deuteriated compounds **5a'** and **5a"**. Position of deuterium in products **8a'** and **8b'** or **8a"** and **8b"** issued from reactions with **5a'** or **5a"** gave useful mechanistic informations on this reaction.

The interesting and diversified aspects of syntheses of nucleosides and nucleoside analogues as well as the wide range of biological activities displayed by these compounds, especially as anti-tumor and anti-viral agents, gave rise to high interest of chemists during the past years. [1] A part of these efforts was in the area of cyclobutane nucleoside[2] analogues of oxetanocin.[3]

Results and Discussion

One of our previous papers deals with preparation of tetrasubstituted cyclobutane nucleoside analogues by nucleophilic attack of adenine to epoxides prepared from the dibenzylated compound **1**.[4] We anticipated that the same starting material could lead to alcohols **2a** and **2b** then to trisubstituted nucleoside analogues by nucleophilic substitution of the corresponding mesylates. Therefore we submitted **1** to hydroboration followed by oxidation. We thus obtained the expected less crowded product **2a** which was easily separated from the minor isomer **2b** by chromatography on silica gel. Stereochemistries of both alcohols were checked by NOE experiments. On the other hand preparation of the isomer **2b** was achieved by reduction of the predominant epoxide obtained by reaction of **1** with *meta*-chloroperbenzoic acid[4,5] (Scheme 1). We observed that reduction of epoxide **3** with $LiAlH_4$ gave an unexpected ring opening product **4** together with alcohol **2b**. Formation of this by-product was avoided when this reducing agent was replaced by AlH_3 ($LiAH_4/AlCl_3$ = 3:1)[6] which led to **2b** in a shorter reaction time and in nearly quantitative yield.

Reaction of mesylate **5b** with adenine[7] gave a mixture of three substitution products **6a**, **6b** and **6c** in a 80:15:5 ratio measured by ^1H NMR of the crude product.

Compound **6a** could be isolated in 43% yield by chromatography on silica gel and the following fractions contained pure **6b** then a mixture of **6b** + **6c** (**6b/6c** = 2 : 1). ^1H /^1H spin decoupling experiments, $^{13}C/^1H$ correlation and long range ^{13}C /^1H correlation (COLOC) led to assignments of most carbon and proton signals of **6a**. For instance, in COLOC experiment, C-4 was correlated with H-8 and H-2, C-5 with H-8 and C-6 with H-2, however correlation between C-4 or C-8 and H-1' could not be observed by this way. As

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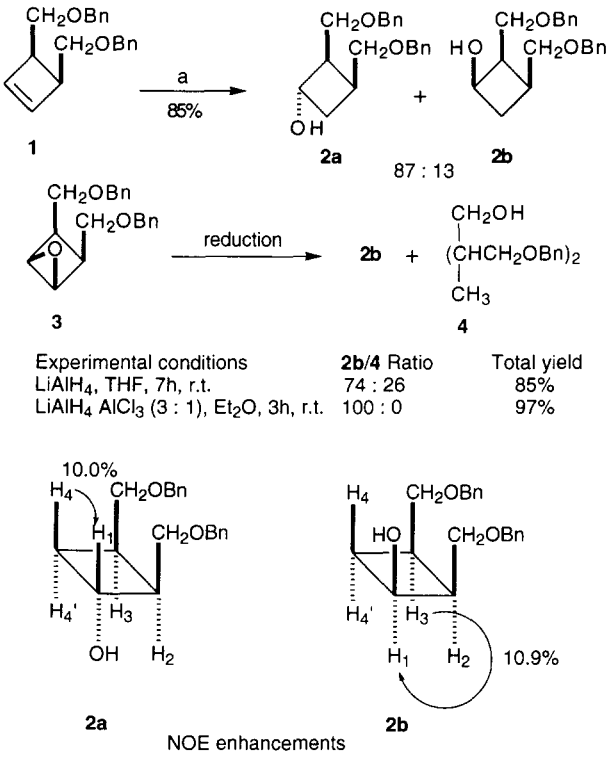
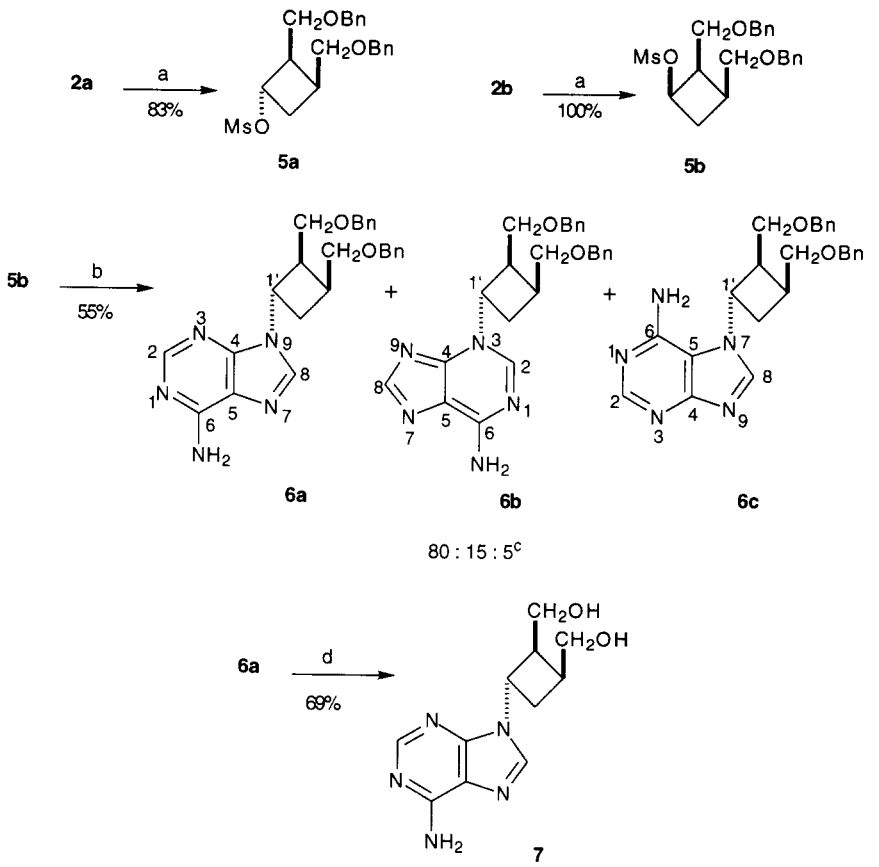


(a) 1) BH_3, THF, 15h, r.t.; 2) NaOH, 30% H_2O_2, 2h, 50°C.

SCHEME 1

it was necessary to point it out for the regiochemical assignment, we recorded proton coupled ^{13}C spectrum and ^{13}C spectrum with selective decoupling from H-1'. On the first one C-4 appeared as a complex multiplet and C-8 as a doublet of doublet (J = 209 and 3.8 Hz) whereas on the second one C-4 appeared as a doublet of doublet (J = 11.4 and 5.1 Hz) and C-8 as a doublet. These results clearly showed that **6a** was the N-9 attack product. Similarly **6b** was assigned as the N-3 attack product on the basis of its scalar couplings between H-1' and C-4 (2.8 Hz) and H-1' and C-2 (3.8 Hz). Finally experiments with the **6b** + **6c** mixture showed that H-1' of **6c** was coupled with C-8 (3.9 Hz). Such a coupling can only be observed for N-9 or N-7 products, therefore **6c** was assigned as the N-7 attack product. The predominant isomer was debenzylated using 20% palladium hydroxide on carbon with cyclohexene as the hydrogen donor[8] and the nucleoside analogue **7** was thus obtained (Scheme 2). This compound has been evaluated as inactive in *in vitro* anti HIV-1 screens (CEM 4 cells).



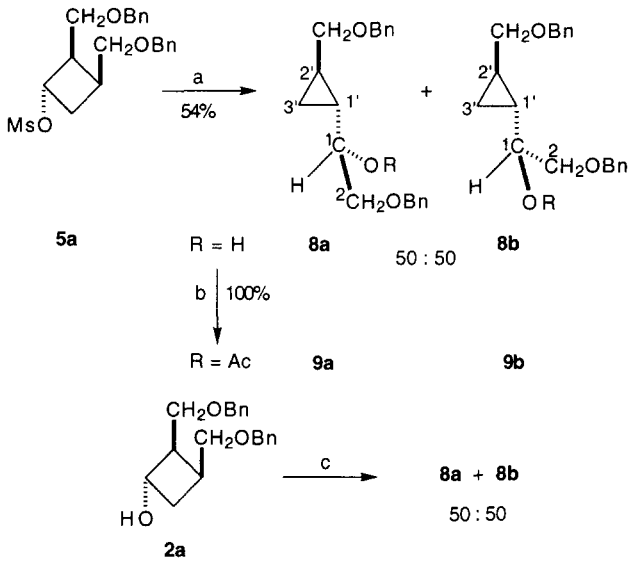
(a) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h 30min; (b) adenine, K_2CO_3, 18-crown-6, DMF, 110°C, 20h; (c) ^1H NMR ratio measured on the crude product; (d) 20% $Pd(OH)_2/C$, cyclohexene, EtOH, reflux, 41h.

SCHEME 2

We were surprised to observe that the other mesylate **5a** did not give any substitution product in the reaction with adenine. Instead we obtained two isomeric products **8a** and **8b**, in a 50 : 50 ratio, issued from an unexpected C_4-C_3 ring contraction reaction. One of both isomers (**8a** or **8b**) was isolated and NOE experiments showed a strong enhancement of H-1 (10.2%) upon saturation of H-2' in agreement with the *trans* relationship of both substituents. The other isomer (**8b** or **8a**) could not be separated and NOE experiment was not possible with the **8a** + **8b** mixture due to close chemical shifts of H-1, H-4' and H-4' bis of this isomer. Fortunately we could deduce ^1H NMR signals of its acetate from comparison between spectra of acetate of the other isomer and of the mixture of both acetates (**9a** + **9b**). This acetylation led to the deshielding of H-1 and made it possible NOE experiments with the **9a** + **9b** mixture that showed a 10.3% enhancement of H-1 upon saturation of H-2', for this acetate, which was thus also assigned as a *trans* product. Finally these experiments proved that **8a** and **8b** were both epimers of the *trans* products (Scheme 3). As

reaction with adenine did not give the expected product, we tried to synthesize triflate corresponding to **2a** which should presumably be more reactive than mesylate **5a** in the course of the nucleophilic substitution.

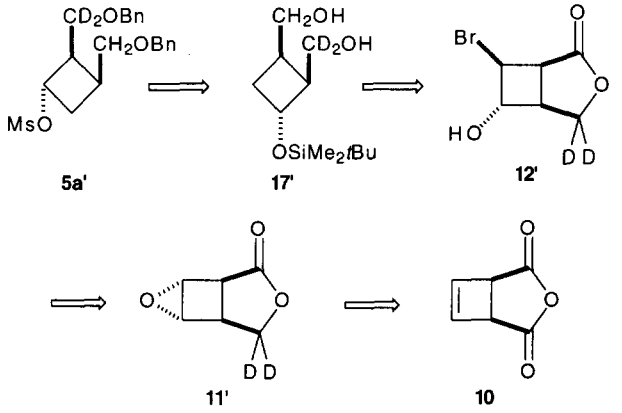
Actually, in the usual experimental conditions, we did not isolate this triflate and we directly obtained the ring contraction products **8a** and **8b**.



(a) adenine, K_2CO_3, 18-crown-6, DMF, 110°C, 15h; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 1h; (c) Tf_2O, pyridine, CH_2Cl_2, -25°C, 1h then 0°C, 15 min.

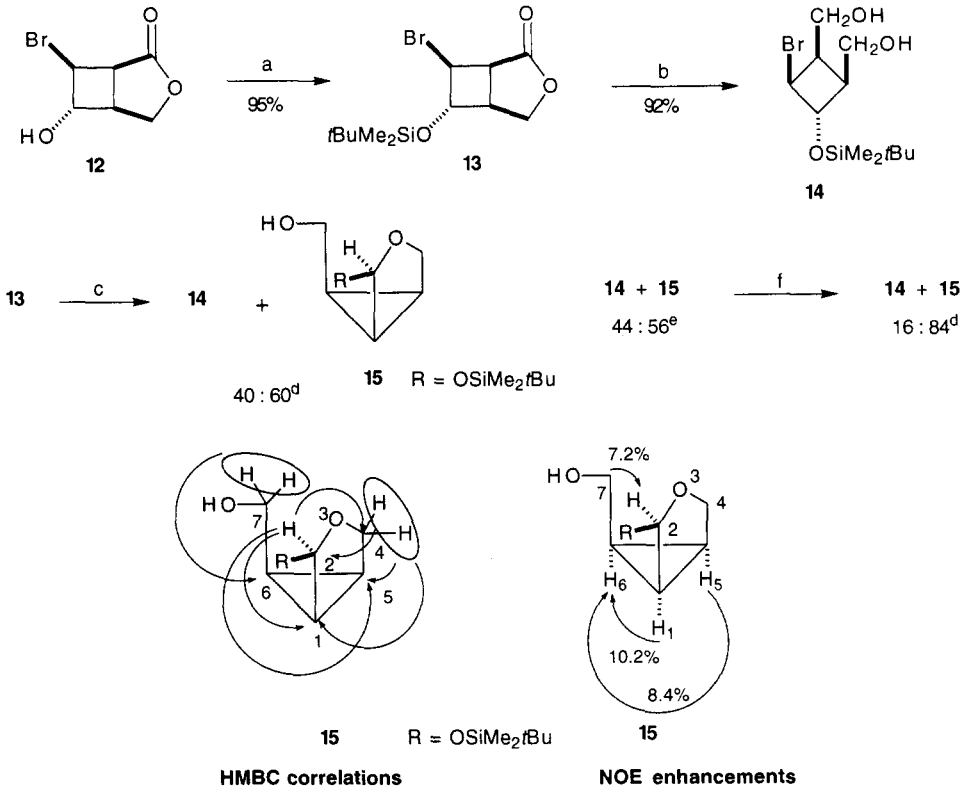
SCHEME 3

In attempt to point out what bonds were cleaved in this surprising ring contraction we planned to prepare two deuteriated compounds **5a'** and **5a''**. The retrosynthetic way to **5a'** is pictured in scheme 4.



SCHEME 4

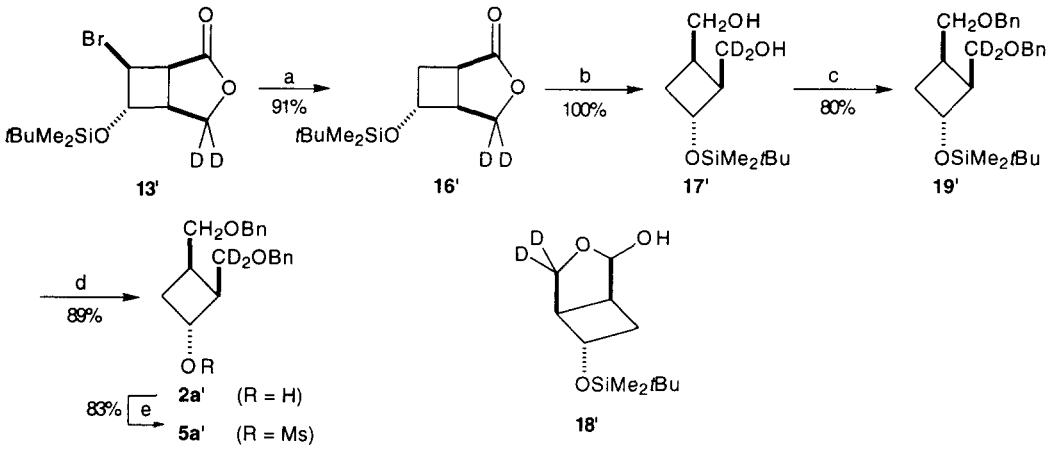
Compound **12'** was prepared in the same experimental conditions as its non deuteriated equivalent[5] with replacing $NaBH_4$ by $NaBD_4$. We supposed that the concomitant reduction of the lactone moiety and of the C-Br bond could occur and we tested it with the silylated product **13** obtained from the non deuteriated product **12**. In actual fact $LiAlH_4$ led to compound **14** without removal of Br even in more drastic conditions (24 h reflux instead of 5 h 20 min, r.t.). Reaction with $LiEt_3BH$ equally failed to give **17**. Instead it led to a mixture of **14** and of another unexpected C_4-C_3 ring contraction product **15**. The **14/15** ratio decreased when the mixture of **14** + **15** was submitted again to reaction with $LiEt_3BH$. This compound **15** was identified by NMR results particularly by the $^1H/^{13}C$ HMBC experiment. It was obtained as only one diastereomer and NOE experiment showed that it was the one with H-2 close to H-7 (Scheme 5).



(a) *t*-$BuMe_2SiCl$, imidazole, DMF, 62h; (b) $LiAlH_4$, THF, 5h 20min, r.t.; (c) $LiEt_3BH$, THF, 24h, r.t., then 21h, reflux; (d) ^1H NMR ratio of the crude product; (e) ^1H NMR ratio of the chromatographed product; (f) $LiEt_3BH$, THF, 72h, reflux.

SCHEME 5

As the one-step reduction of **13** to **17** failed, we reduced the deuteriated compound **13'** with *n*-Bu_3SnH. The reaction gave the expected product **16'** and the subsequent reduction with $LiAlH_4$ in excess gave **17'**. (Reaction with a lower amount of $LiAlH_4$ led to a mixture of **17'** and of lactol **18'**). Afterwards **17'** easily led to **5a'** (Scheme 6).

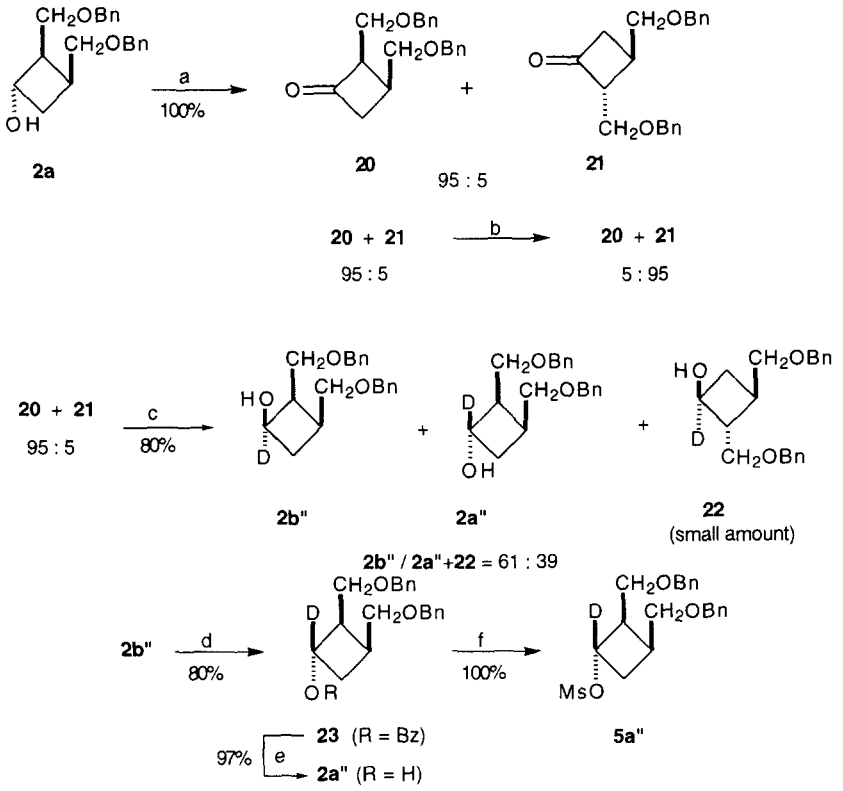


(a) *n*-Bu_3SnH, AIBN, Toluene, 7h, r.t.; (b) $LiAlH_4$ (5 eq), THF, 4h, r.t.; (c) NaH, $PhCH_2Br$, DMF, 5h, r.t.; (d) *n*-Bu_4NF, THF, 23h, r.t.; (e) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h 30min.

SCHEME 6

Preparation of the other deuteriated compound **5a"** started from the dibenzylated compound **2a.** Swern oxidation[9] gave ketone **20** together with a small amount of the epimer **21**. Attempts of separation of both compounds by chromatography on silica gel led to epimerization (we observed a similar result from another cyclobutanone, previously[10]). Therefore the **20** + **21** mixture was reduced with $NaBD_4$ and the predominant isomer **2b"** was isolated. The subsequent Mitsunobu reaction[11] was slow (6 days) but it gave a good result. Finally saponification then mesylation led to **5a"**(Scheme 7).

When the deuteriated compounds **5a'** and **5a"** were submitted to the same experimental conditions as **5a**, the deuteriated compounds pictured in scheme 8 were obtained. The exact mechanism[12] of this ring contraction is not fully clear. However results of the labeling show that it involves a nucleophilic attack of C-1 from the C-2-C-3 bond. Such an attack is coherent with the *trans* relationship of the substituents of products. The same breaking of a C-C bond *anti* to the leaving group was encountered in the course of the ring contraction from **14** to **15**. This reaction probably starts from a nucleophilic attack of an alcoholate group to carbon linked to the silylated group. This mechanism is in agreement with obtention of the product with H-2 close to CH_2OH (see Scheme 5). Another possibility, presumably less probable in this basic medium, should involve an intermediate carbonium ion.

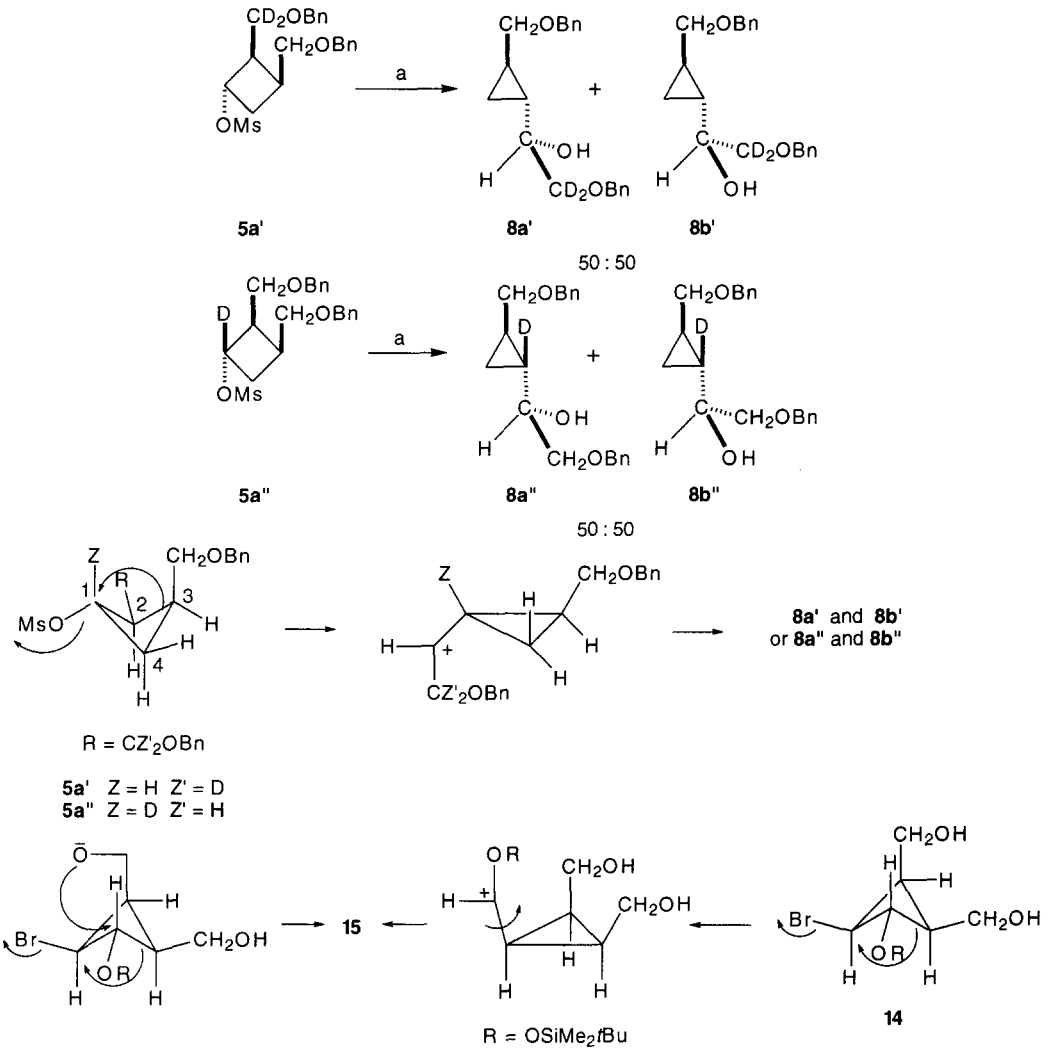


(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C -> r.t.; (b) chromatography on silica gel; (c) $NaBD_4$, EtOH, 25 min, r.t.; (d) PPh_3, DEAD, PhCOOH, THF, 0°C then 6 days, r.t.; (e) 15% NaOH, MeOH, 17h, r.t.; (f) MsCl, Et_3N, CH_2Cl_2, 0°C.

SCHEME 7

Conclusion

We show in this paper that the nucleoside analogue **7** is easily obtained by nucleophilic substitution. Curiously its more crowded epimer could not be obtained and a steric decompression occured by a new stereospecific C_4-C_3 ring contraction. A mechanistic approach to this surprising reaction was pointed out. We also propose a mechanism for another stereospecific ring contraction yielding **15**, which was encountered in the course of this work.



(a) adenine, K_2CO_3, 18-crown-6, DMF, 110°C, 15h.

SCHEME 8

Experimental

NMR spectra were recorded on a Bruker AC 400 instrument (400 and 100 MHz for ^1H and ^{13}C, respectively). Samples were dissolved in deuteriochloroform 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.

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

1M BH_3,.THF (48.4 mL, 48.4 mmol) was added dropwise for 30 min at 0°C and with stirring to a solution of *cis*-3,4-bis(benzyloxymethyl)cyclobut-1-ene **1**[4] (3.24 g, 11.0 mmol) in THF (17.4 mL). The reaction mixture was stirred at room temperature overnight and 3M NaOH (25 mL) then 30% H_2O_2 (16.7 mL) were added dropwise at 0°C. After 2h at 50°C, the mixture was cooled. Decantation, extraction of the aqueous phase with CH_2Cl_2 (4 x 15 mL), washing of the combined organic phases with brine (25 mL), drying ($MgSO_4$) and evaporation left the crude product. A 87 : 13 ratio for **2a/2b**, respectively, was measured by ^1H NMR. Chromatography on silica gel (260 g, cyclohexane/AcOEt 4 : 1 then 3 : 1) successively led to **2b** (621 mg, 18%, colorless oil) then to **2a** (2.43 g, 70.6%, colorless oil). **2a** : ^1H NMR δ 7.35-7.26 (m, 10H, Ph), 4.47 (m, 2H, benzylic, AB system, J = 12.0 Hz), 4.43 (s, 2H, benzylic), 4.20 (m, 1H, H-1), 3.61 (dd, 1H, H-6, $J_{H\text{-}6/H\text{-}6'}$ = 9.6 Hz, $J_{H\text{-}6/H\text{-}2}$ = 6.9 Hz), 3.57-3.51 (m, 2H, H-6' and H-5), 3.47 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.3 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.0 Hz), 2.63-2.56 (m, 1H, H-2), 2.54-2.46 (m, 1H, H-3), 2.15 (m, 1H, H-4), 1.97 (m, 1H, H-4'), 1.77 (br s, 1H, OH); ^{13}C NMR δ 138.39 (s, Ph), 138.38 (s, Ph), 128.35 (d, Ph), 128.33 (d, Ph), 127.72 (d, Ph), 127.59 (d, Ph), 127.57 (d, Ph), 127.52 (d, Ph), 73.09 (t), 73.04 (t), 70.80 (t), 69.35 (t), 69.18 (C-1), 47.36 (d), 32.54 (C-4), 28.59 (d); IR (film) cm^{-1} 3390, 1454, 1365, 1095, 1027, 736, 698 ; MS m/z (rel. intensity) 221 ([M-CH_2Ph]$^+$, 1), 108 (6), 107 (19), 105 (9), 97 (5), 92 (12), 91 (100), 79 (4), 77 (5), 28 (7); HR-MS calcd for ($C_{20}H_{24}O_3$-CH_2Ph) : 221.11776. Found : 221.1185. **2b** : ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 4.47 (d, 1H, benzylic, J = 11.8 Hz), 4.42 (s, 2H, benzylic), 4.39 (d, 1H, benzylic, J = 11.8 Hz), 4.31 (m, 1H, H-1), 3.86 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.7 Hz, $J_{H\text{-}5/H\text{-}3}$ = 5.4 Hz), 3.79 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.7 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 4.9 Hz), 3.56 (dd, 1H, H-6, $J_{H\text{-}6/H\text{-}6'}$ = 9.3 Hz, $J_{H\text{-}6/H\text{-}2}$ = 7.8 Hz), 3.48 (dd, 1H, H-6', $J_{H\text{-}6'/H\text{-}6}$ = 9.3 Hz, $J_{H\text{-}6'/H\text{-}2}$ = 4.9 Hz), 3.24 (d, 1H, OH, J = 8.9 Hz), 2.81 (m, 1H, H-3), 2.42 (m, 2H, H-4 and H-4'), 1.81 (m, 1H, H-2); ^{13}C NMR δ 138.17 (s, Ph), 137.77 (s, Ph), 128.45 (d, Ph), 128.39 (d, Ph), 127.90 (d, Ph), 127.82 (d, Ph), 127.79 (d, Ph), 127.69 (d, Ph), 73.42 (t), 73.08 (t), 70.55 (t), 67.75 (t), 66.43 (C-1), 42.56 (d), 35.47 (C-4), 29.48 (d); IR (film) cm^{-1} 3421, 1454, 1365, 1272, 1095, 1027, 738, 698; MS m/z (rel. intensity) 221 [(M-CH_2Ph)$^+$, 0.2], 130 (3), 115 (3), 108 (3), 107 (5), 97 (5), 92 (7), 91 (100), 65 (3), 28 (3); HR-MS calcd for ($C_{20}H_{24}O_3$-CH_2Ph) : 221.11776. Found : 221.1174.

In another experiment a solution of *cis*-3,*cis*-4-bis(benzyloxymethyl)-1,2-epoxycyclobutane **3**[4,5] (3.6 g, 11.6 mmol) in THF (40 mL) was added dropwise at 0°C under argon to a stirred suspension of $LiAlH_4$ (1.86 g, 46.4 mmol) in THF (80 mL). After 7h at room temperature, the reaction mixture was cooled to 0°C and 2M KOH (20 mL) was added dropwise. After 20-30 min stirring, Et_2O (50 mL) was added. Filtration, washing with Et_2O (3 x 30 mL), evaporation, adding of CH_2Cl_2 (100 mL), drying ($MgSO_4$) and another evaporation yielded the crude product consisting of compound **2b** together with 2,3-bis-(benzyloxymethyl)butane-1-ol **4** in the 74 : 26 ratio, respectively, as shown by ^1H NMR. Chromatography on silica gel (290 g, cyclohexane/AcOEt 5 : 1) successively led to **4** (186 mg, 5.1%, yellow oil), **4+2b** (1.57 g of a 30 : 70 ratio, respectively; 30.4% (**2b**); 12.9% (**4**)), **2b** (1.34 g, 37%). **4** : ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 4.50 (m, 4H, benzylic, AB system, J = 12.3 Hz), 3.77 (m, 1H, H-1, J = 11.5, 5.4, 4.8 Hz), 3.71 (m, 1H, H-1', J = 11.5, 7.3, 3.8 Hz), 3.62 (m, 2H, H-6 and H-6', AB system, J = 9.3 Hz), 3.41 (m, 2H, H-5 and H-5'), 2.99 (m, 1H, OH), 1.99 (m, 1H, H-3), 1.88 (m, 1H, H-2), 0.98 (d, 3H, CH_3, J = 6.9 Hz); ^{13}C NMR δ 138.12 (s, Ph), 138.09 (s, Ph), 128.54 (d, Ph), 128.40 (d, Ph), 128.38 (d, Ph), 127.64 (d, Ph), 127.59 (d, Ph), 126.95 (d, Ph), 73.39 (t), 73.36 (t), 73.20 (t), 71.72 (t), 63.56 (t), 43.64 (d), 32.43 (d), 15.36 (q); IR (film) cm^{-1} 3409, 2873, 1455, 1365, 1095, 736, 698; HR-MS calcd for ($C_{20}H_{26}O_3$-PhCHO) : 208.1463. Found : 208.1454.

The best results for preparation of **2b** were obtained from AlH_3. A mixture of $LiAlH_4$ (84 mg, 2.1 mmol) and of $AlCl_3$ (95 mg, 0.7 mmol) in Et_2O (3.5 mL) was stirred under argon for 15 min at 0°C, then a solution of **3** in Et_2O (3.5 mL) was added dropwise. The reaction mixture was stirred for 3h at room temperature, then the same work-up as above yielded **2b** (204 mg, 97%).

cis-2,*cis*-3-Bis(benzyloxymethyl)-1-mesyloxycyclobutane **5b**

Et_3N (892 µL, 6.33 mmol) was added to a solution of **2b** (1.32 g, 4.22 mmol) in CH_2Cl_2 (23.5 mL). This solution was cooled to 0°C, then CH_3SO_2Cl (396 µL, 5.07 mmol) was added dropwise with stirring. After 80 min at 0°C, CH_2Cl_2 was added. Washing (10% HCl (3.2 mL) then 5% $NaHCO_3$ (3.2 mL) then brine (3.2 mL)), drying ($MgSO_4$) and evaporation yielded **5b** as a colorless oil (1.65 g, 100%); ^1H NMR δ 7.35-7.26 (m, 10H, Ph), 5.07 (m, 1H, H-1), 4.47 (m, 2H, benzylic, AB system, J = 11.3 Hz), 4.46 (s, 2H, benzylic), 3.78 (m, 2H, H-6 and H-6', $J_{H\text{-}6/H\text{-}6'}$ = 9.2 Hz), 3.62 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.6 Hz, $J_{H\text{-}5/H\text{-}3}$ = 7.1 Hz), 3.48 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.6 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.6 Hz), 3.05 (m, 1H, H-2), 2.90 (s, 3H, CH_3), 2.57 (m, 1H, H-4), 2.41 (m, 1H, H-3), 2.26 (m, 1H, H-4'); ^{13}C NMR δ 138.14 (s, Ph), 138.08 (s, Ph), 128.36 (d, Ph), 127.74 (d, Ph), 127.69 (d, Ph), 127.64 (d, Ph), 127.63 (d, Ph), 73.36 (benzylic $\underline{C}H_2$), 73.11 (benzylic $\underline{C}H_2$), 72.46 (C-1), 70.17 ($\underline{C}H_2OBn$), 66.04 ($\underline{C}H_2OBn$), 42.97 (d), 38.06 ($\underline{C}H_3$), 33.13 (C-4), 29.41 (d); IR (film) cm^{-1} 1454, 1353, 1176, 1095, 970, 865, 746, 700; MS m/z (rel. intensity) 299 [$(M\text{-}CH_2Ph)^+$, 0.1], 107 (9), 97 (28), 92 (12), 91 (100), 79 (7), 69 (8), 67 (8), 65 (5), 41 (3); HR-MS calcd for ($C_{21}H_{26}O_5S$-CH_2Ph) : 299.0953. Found : 299.0962.

trans-2,*trans*-3-Bis(benzyloxymethyl)-1-mesyloxycyclobutane **5a**

The same work-up as above from **2a** (775 mg, 2.48 mmol), Et_3N (698 µL, 4.95 mmol), CH_3SO_2Cl (330 µL, 4.22 mmol) in CH_2Cl_2 (13.8 mL) for 90 min at 0°C led to the crude **5a** that was chromatographed on silica gel (cyclohexane/AcOEt 5 : 1). Pure **5a** was thus obtained as a colorless oil (800 mg, 83%). ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 5.00 (m, 1H, H-1, $J_{H\text{-}1/H\text{-}4,\ H\text{-}4'}$ = 7.6 Hz, $J_{H\text{-}1/H\text{-}2}$ = 7.4 Hz), 4.44 (m, 2H, benzylic, AB system, J = 11.8 Hz), 4.43 (s, 2H, benzylic), 3.62 (d, 2H, H-6 and H-6', J = 6.7 Hz), 3.51 (m, 2H, H-5 and H-5', $J_{H\text{-}5/H\text{-}5'}$ = 9.4 Hz), 2.97 (m, 1H, H-2), 2.92 (s, 3H, CH_3), 2.61 (m, 1H, H-3), 2.34 (m, 2H, H-4 and H-4', $J_{H\text{-}4,\ H\text{-}4'/H\text{-}1}$ = 7.6 Hz); ^{13}C NMR δ 138.06 (s, Ph), 138.00 (s, Ph), 128.41 (d, Ph), 128.37 (d, Ph), 128.20 (d, Ph), 127.90 (d, Ph), 127.72 (d, Ph), 127.69 (d, Ph), 75.96 (C-1), 73.25 (benzylic $\underline{C}H_2$), 73.18 (benzylic $\underline{C}H_2$), 69.54 ($\underline{C}H_2OBn$), 68.05 ($\underline{C}H_2OBn$), 44.93 (d), 38.09 ($\underline{C}H_3$), 30.83 (C-4), 29.63 (d); IR (film) cm^{-1} 1359, 1176, 1095, 968, 862, 740, 700.

9-[*trans*-2',*trans*-3'-bis(benzyloxymethyl)cyclobut-1'-yl]adenine **6a** , 3-[*trans*-2',*trans*-3'-bis(benzyloxymethyl)cyclobut-1'-yl]adenine **6b** and 7-[*trans*-2',*trans*-3'-bis(benzyloxymethyl)cyclobut-1'-yl]adenine **6c**

A solution of **5b** (2.47 g, 6.32 mmol) in DMF (22 mL) was added to a solution of adenine (1.72 g, 12.6 mmol) in DMF (6 mL). K_2CO_3 (1.80 g, 12.6 mmol) then 18-crown-6 (1.69 g, 6.32 mmol) were then successively added. The reaction mixture was stirred for 20h at 110°C. Cooling, evaporation of DMF, adding of CH_2Cl_2 then filtration on a sintered-glass funnel, and another evaporation, left the crude product. Chromatography on silica gel (290 g, CH_2Cl_2/MeOH 50 : 1) successively yielded **6a** (colorless oil, 1.16 g, 42.8%), **6b** (colorless oil, 141 mg, 5.2%) then a **6b/6c** mixture in the 2 : 1 ratio, respectively (200 mg, 7.4%). **6a** : ^1H NMR δ 8.34 (s, 1H, H-2), 7.96 (s, 1H, H-8), 7.38-7.23 (m, 10H, Ph), 7.19 (m, 2H, NH_2), 4.94 (m, 1H, H-1'), 4.51 (m, 2H, benzylic, AB system, J = 12.3 Hz), 4.43 (d, 1H, benzylic, J = 11.8 Hz), 4.38 (d, 1H, benzylic, J = 11.8 Hz), 3.74 (dd, 1H, H-6', $J_{H\text{-}6'/H\text{-}6''}$ = 9.6 Hz, $J_{H\text{-}6'/H\text{-}2'}$ = 6.6 Hz), 3.70-3.63 (m, 3H, H-6", H-5' and H-5"), 3.39 (m, 1H, H-2'), 2.81-2.77 (m, 1H, H-3'), 2.75-2.67 (m, 1H, H-4'), 2.50 (m, 1H, H-4"); ^{13}C NMR δ 155.51 (C-6), 152.60 (C-2), 150.12 (C-4), 139.46 (C-8), 138.09 (s, Ph), 138.02 (s, Ph), 128.39 (d, Ph), 128.30 (d, Ph), 127.75 (d, Ph), 127.67 (d, Ph), 127.58 (d, Ph), 127.57 (d, Ph), 120.02 (C-5), 73.28

(benzylic $\underline{C}H_2$), 73.14 (benzylic $\underline{C}H_2$), 69.86 ($\underline{C}H_2OBn$), 69.02 ($\underline{C}H_2OBn$), 51.16 (C-1'), 44.07 (C-2'), 31.13 (C-3'), 29.66 (C-4'); IR (film) cm^{-1} 3320, 1643, 1596, 1093, 738, 698; MS m/z (rel. intensity) 429 (M^+, 0.2), 216 (19), 190 (14), 175 (47), 162 (48), 161 (15), 138 (15), 135 (12), 134 (11), 91 (100); HR-MS calcd for $C_{25}H_{27}N_5O_2$: 429.2165. Found : 429.2173. **6b** : ^1H NMR δ 8.27 (s, 1H, H-2), 8.06 (s, 1H, H-8), 7.38-7.20 (m, 10H, Ph), 7.17 (m, 2H, NH_2), 5.09 (m, 1H, H-1'), 4.50 (m, 2H, benzylic), 4.42 (d, 1H, benzylic, J = 12.0 Hz), 4.38 (d, 1H, benzylic, J = 12.0 Hz), 3.75 (dd, 1H, H-6', $J_{H\text{-}6'/H\text{-}6''}$ = 9.3 Hz, $J_{H\text{-}6'/H\text{-}2'}$ = 5.9 Hz), 3.72-3.63 (m, 4H, H-2', H-6", H-5' and H-5"), 2.83 (m, 2H, H-3' and H-4'), 2.61 (m, 1H, H-4", $J_{H\text{-}4''/H\text{-}1'}$ = 7.1 Hz); ^{13}C NMR δ 154.52 (C-6), 153.75 (C-8), 150.12 (C-4), 141.05 (C-2), 137.95 (s, Ph), 137.84 (s, Ph), 128.35 (d, Ph), 128.30 (d, Ph), 127.74 (d, Ph), 127.65 (d, Ph), 127.61 (d, Ph), 127.51 (d, Ph), 121.19 (C-5), 73.27 (benzylic $\underline{C}H_2$), 73.13 (benzylic $\underline{C}H_2$), 69.75 ($\underline{C}H_2OBn$), 69.12 ($\underline{C}H_2OBn$), 57.79 (C-1'), 42.20 (C-2'), 30.95 (C-3'), 29.38 (C-4'). **6c** : ^1H NMR (partially described) δ 8.41 (s, 1H, H-2), 8.25 (s, 1H, H-8), 5.06-5.00 (m, 1H, H-1); ^{13}C NMR (partially described) δ 160.53 (C-4), 153.01 (C-2), 151.19 (C-6), 142.12 (C-8), 136.71 (s, Ph), 111.85 (C-5), 73.64 (benzylic $\underline{C}H_2$), 73.38 (benzylic $\underline{C}H_2$), 69.60 ($\underline{C}H_2OBn$), 67.79 ($\underline{C}H_2OBn$), 52.13 (C-1'), 45.87 (C-2'), 31.54 (C-3'), 29.14 (C-4').

9-[*trans*-2',*trans*-3'-bis(hydroxymethyl)cyclobut-1'-yl]adenine **7**

Cyclohexene (25.6 mL) and 20% $Pd(OH)_2$ on carbon (1.37 g of the ca 50% moisture commercial product prewashed with EtOH, (6 : 10 catalyst/substrate by weight)) were added under argon to a stirred solution of **6a** (1.14 g, 2.65 mmol) in EtOH (21.3 mL). Suspension was refluxed for 41h then, after cooling, catalyst was removed by filtration and solvent was evaporated. Recrystallization in EtOH provided **7** as white crystals (456 mg, 69%). M.p. 190-191°C; ^1H NMR (DMSO-d_6) δ 8.29 (s, 1H, H-8), 8.13 (s, 1H, H-2), 7.21 (br s, 2H, NH_2), 4.83 (m, 1H, H-1'), 4.75 (br s, 1H, OH), 4.60 (br s, 1H, OH), 3.71-3.55 (m, 4H, H-5', H-5", H-6' and H-6"), 3.20 (m, 1H, H-2'), 2.63 (m, 1H, H-4'), 2.51 (m, 1H, H-3'), 2.26 (m, 1H, H-4"); ^{13}C NMR (DMSO-d_6) δ 155.95 (s), 152.06 (d), 149.42 (s), 139.78 (d), 119.19 (s), 60.59 (t), 59.80 (t), 50.02 (d), 45.75 (d), 32.50 (d), 28.66 (t); IR (KBr) cm^{-1} 3426, 3326, 1654, 1602, 1571, 1482, 1320, 1025. Anal. Calcd for $C_{11}H_{15}O_2N_5$: C, 53.00; H, 6.06; N, 28.09. Found : C, 53.04; H, 6.12; N, 27.87.

Alcohols **8a** and **8b** and acetates **9a** and **9b**

Alcohols **8a** and **8b** were obtained in the same experimental conditions as above from **5a** (790 mg, 2.02 mmol), adenine (500 mg, 4.05 mmol), K_2CO_3 (577 mg, 4.05 mmol) and 18-crown-6 (540 mg, 2.02 mmol) in DMF (8.6 mL) at 110°C for 15h. ^1H NMR showed a 50 : 50 ratio of **8a/8b**. Chromatography on silica gel (107 g, cyclohexane/AcOEt 5 : 1 then 4 : 1) successively led to **A** (**8a** or **8b**) (37 mg, 5.8%) then to **8a+8b** in the 50 : 50 ratio (colorless oil, 307 mg, 48.1%). **A** (**8a** or **8b**) : ^1H NMR δ 7.35-7.23 (m, 10H, Ph), 4.56 (s, 2H, benzylic), 4.53 (s, 2H, benzylic), 3.59 (dd, 1H, H-2, $J_{H\text{-}2/H\text{-}2bis}$ = 9.6 Hz, $J_{H\text{-}2/H\text{-}1}$ = 3.1 Hz), 3.45 (dd, 1H, H-2bis, $J_{H\text{-}2bis/H\text{-}2}$ = 9.6 Hz, $J_{H\text{-}2bis/H\text{-}1}$ = 7.7 Hz), 3.40 (dd, 1H, H-4', $J_{H\text{-}4'/H\text{-}4'bis}$ = 10.2 Hz, $J_{H\text{-}4'/H\text{-}2'}$ = 6.6 Hz), 3.28 (dd, 1H, H-4'bis, $J_{H\text{-}4'bis/H\text{-}4'}$ = 10.2 Hz, $J_{H\text{-}4'bis/H\text{-}2'}$ = 6.9 Hz), 3.22 (m, 1H, H-1, $J_{H\text{-}1/H\text{-}2}$ = 3.1 Hz), 2.44 (br s, 1H, OH), 1.17 (m, 1H, H-2'), 0.81 (m, 1H, H-1'), 0.53-0.49 (m, 1H, H-3'), 0.47-0.43 (m, 1H, H-3'bis); ^{13}C NMR δ 138.44 (s, Ph), 137.98 (s, Ph), 128.39 (d, Ph), 128.29 (d, Ph), 127.73 (d, Ph), 127.67 (d, Ph), 127.64 (d, Ph), 127.53 (d, Ph), 74.07 (C-2), 73.79 (C-1), 73.32 (benzylic $\underline{C}H_2$), 73.23 (C-4'), 72.38 (benzylic $\underline{C}H_2$), 19.61 (C-1'), 16.15 (C-2'), 7.38 (C-3'); IR (film) cm^{-1} 3401, 2859, 1454, 1361, 1274, 1095, 1027, 738, 698; MS m/z (rel. intensity) 221 [$(M\text{-}CH_2Ph)^+$, 0.4], 203 [$(M\text{-}CH_2Ph\text{-}H_2O)^+$, 1], 191(4), 115 (3), 107 (8), 105 (4), 92 (13), 91 (100), 83 (4), 65 (3); HR-MS calcd for ($C_{20}H_{24}O_3\text{-}CH_2Ph$) : 221.1178. Found : 221.1172; calcd for ($C_{20}H_{24}O_3\text{-}CH_2Ph\text{-}H_2O$) : 203.1072. Found : 203.1067. **B** (**8b** or **8a**) : ^1H NMR (partially described from the mixture) δ 7.37-7.26 (m, 10H, Ph), 4.57 (s, 2H, benzylic), 4.51 (s, 1H, benzylic), 4.50 (s, 1H, benzylic), 3.64 (dd, 1H, H-2, J = 9.8, 3.0 Hz), 3.45 (m, 1H, H-2bis), 3.36-3.26 (m, 3H, H-1, H-4' and H-4'bis), 1.09 (m, 1H, H-2'), 0.81 (m, 1H, H-1'), 0.69 (m, 1H, H-3'), 0.54-0.50 (m, 1H, H-

3'bis); ^{13}C NMR (partially described) δ 137.92 (s, Ph), 128.31 (d, Ph), 127.69 (d, Ph), 127.48 (d, Ph), 127.47 (d, Ph), 74.18 (C-2), 73.47 (C-1), 73.30 (benzylic $\underline{C}H_2$), 73.21 (C-4'), 72.40 (benzylic $\underline{C}H_2$), 19.47 (C-1'), 15.44 (C-2'), 8.04 (C-3').

Acetylation of **A** (**8a** or **8b**) (30 mg, 0.1 mmol) in CH_2Cl_2 solution (0.3 mL) at 0°C was carried out by successively adding 4-DMAP (1.2 mg, 0.01 mmol), Et_3N (27 µL, 0.19 mmol) and Ac_2O (18 µL, dropwise). After 1h stirring at room temperature, the reaction mixture was cooled to 0°C and MeOH was added. Dilution (CH_2Cl_2), washing (successively with 5% $KHSO_4$, H_2O, 5% $NaHCO_3$ then H_2O), drying ($MgSO_4$) and evaporation led to acetate **A'** (**9a** or **9b**) as a colorless oil (34 mg, 100%). ^1H NMR δ 7.36-7.24 (m, 10H, Ph), 4.60-4.47 (m, 5H, H-1 and benzylic), 3.61 (d, 2H, H-2 and H-2bis, J = 4.9 Hz), 3.33 (m, 2H, H-4' and H-4'bis), 2.05 (s, 3H, CH_3), 1.27 (m, 1H, H-2'), 1.02 (m, 1H, H-1'), 0.59-0.50 (m, 2H, H-3' and H-3'bis); ^{13}C NMR δ 170.65 ($\underline{C}$=O), 138.48 (s, Ph), 138.04 (s, Ph), 128.33 (d, Ph), 128.28 (d, Ph), 127.61 (d, Ph), 127.59 (d, Ph), 127.49 (d, Ph), 127.44 (d, Ph), 75.70 (C-1), 73.07 (t), 72.92 (t), 72.13 (t), 71.28 (t), 21.14 (q), 17.99 (d), 16.64 (d), 8.04 (C-3'); IR (film) cm^{-1} 1735, 1371, 1240, 1097, 736, 698. Acetylation of the **8a+8b** mixture led to the spectral data for **B'** (**9b** or **9a**). ^1H NMR δ 7.36-7.24 (m, 10H, Ph), 4.60-4.47 (m, 5H, H-1 and benzylic), 3.62 (m, 2H, H-2 and H-2bis), 3.34 (m, 2H, H-4' and H-4'bis), 2.07 (s, 3H, CH_3), 1.11-1.07 (m, 1H, H-2'), 1.05-0.97 (m, 1H, H-1'), 0.73 (m, 1H, H-3'), 0.59-0.48 (m, 1H, H-3'bis); ^{13}C NMR (partially described) δ 170.65 ($\underline{C}$=O), 138.39 (s, Ph), 138.07 (s, Ph), 128.34 (d, Ph), 127.52 (d, Ph), 75.59 (C-1), 73.08 (t), 72.93 (t), 72.45 (t), 71.42 (t), 21.21 (q), 17.93 (d), 16.44 (d), 8.80 (C-3').

7-endo-Bromo-6-*exo*-*tert*-butyldimethylsilyloxy-2-oxo-3-oxabicyclo[3.2.0]heptane **13** and the [4,4'-$^2H_2$] derivative **13'**

t-$BuMe_2SiCl$ (2.58 g, 16.8 mmol) and imidazole (2.40 g, 34.9 mmol) were added to a solution of **12**[5] (2.90 g, 14.0 mmol) in DMF (59 mL) under argon. The reaction mixture was stirred for 62h at room temperature then H_2O (120 mL) was added. Extraction with AcOEt (6 x 85 mL), drying ($MgSO_4$), evaporation and chromatography on silica gel (220 g, cyclohexane/AcOEt 6 : 1) led to **13** as white crystals (4.27 g, 95%). M.p. 70-71°C (petroleum); ^1H NMR δ 4.41 (dd, 1H, H-7, $J_{H\text{-}7/H\text{-}1}$ = 9.7 Hz, $J_{H\text{-}7/H\text{-}6}$ = 6.5 Hz), 4.35 (dd, 1H, H-4, $J_{H\text{-}4/H\text{-}4'}$ = 9.7 Hz, $J_{H\text{-}4/H\text{-}5}$ = 5.6 Hz), 4.31 (s, 1H, H-4'), 4.28 (m, 1H, H-6, $J_{H\text{-}6/H\text{-}5}$ = 5.0 Hz, $J_{H\text{-}6/H\text{-}7}$ = 6.5 Hz), 3.35 (ddd, 1H, H-1, $J_{H\text{-}1/H\text{-}7}$ = 9.7 Hz, $J_{H\text{-}1/H\text{-}5}$ = 7.7 Hz, $J_{H\text{-}1/H\text{-}6}$ = 1.3 Hz), 2.99 (m, 1H, H-5), 0.90 (s, 9H, $C(CH_3)_3$), 0.14 (s, 3H, $Si(CH_3)_2$), 0.11 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR δ 173.63 ($\underline{C}$=O), 80.39 (d), 70.64 ($\underline{C}H_2$), 47.79 (d), 44.77 (d), 37.64 (d), 25.60 ($C(\underline{C}H_3)_3$), 17.79 ($\underline{C}(CH_3)_3$), -4.24 ($Si(\underline{C}H_3)_2$), -4.83 ($Si(\underline{C}H_3)_2$); IR (film) cm^{-1} 1766, 1255, 1157, 833, 777, 669. Anal. Calcd for $C_{12}H_{21}O_3SiBr$: C, 44.86; H, 6.59; Br, 24.87. Found : C, 44.58; H, 6.81; Br, 24.81. The reaction in the same experimental conditions from **12'** led to **13'** : ^1H NMR δ 4.41 (dd, 1H, H-7, J = 9.7, 6.5 Hz), 4.28 (dd, 1H, H-6), 3.35 (dd, 1H, H-1), 2.99 (dd, 1H, H-5, J = 7.7, 5.0 Hz), 0.90 (s, 9H, $C(CH_3)_3$), 0.14 (s, 3H, $Si(CH_3)_2$), 0.11 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR δ 173.63 ($\underline{C}$=O), 80.39 (d), 71.42-69.75 (m, $\underline{C}D_2$), 47.79 (d), 44.77 (m), 37.64 (d), 25.60 ($C(\underline{C}H_3)_3$), 17.79 ($\underline{C}(CH_3)_3$), -4.24 ($Si(\underline{C}H_3)_2$), -4.83 ($Si(\underline{C}H_3)_2$).

Reduction of **13**, obtention of **14** and **15**

A solution of **13** (200 mg, 0.62 mmol) in THF (4.4 mL) was added dropwise under argon to a cooled solution (0°C) of $LiAlH_4$ (100 mg, 2.49 mmol) in THF (2 mL). After 3.5h stirring at room temperature, the reaction mixture was cooled to 0°C, then 2M KOH (0.65 mL) was added dropwise. After 20-30 min stirring, Et_2O was added. Filtration, several washings of the solid phase with Et_2O, evaporation of filtrate, adding of CH_2Cl_2, drying ($MgSO_4$) and another evaporation led to **14** (186 mg, 92%); ^1H NMR δ 4.31-4.27 (m, 1H, H-1 or H-2), 4.27-4.23 (m, 1H, H-2 or H-1), 3.91 (m, 2H, $C\underline{H}_2OH$), 3.82 (m, 2H, $C\underline{H}_2OH$), 2.92 (br s, 1H, OH), 2.72 (m, 1H, H-3 or H-4), 2.54 (br s, 1H, OH), 2.46 (m, 1H, H-4 or H-3), 0.89 (s, 9H, $C(CH_3)_3$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$). In another experiment a solution of **13** (137 mg, 0.42 mmol) in

THF (1.7 mL) was added dropwise under argon to a solution of $LiEt_3BH$ (0.84 mL of a 1M solution in THF, 0.84 mmol) in THF (1.7 mL). After 24h stirring at room temperature then 21h at reflux, the reaction mixture was cooled to 0°C. KOH (200 µL of a 2M solution) then H_2O (2 mL) were added. Evaporation, adding of CH_2Cl_2, washing (brine), drying ($MgSO_4$), another evaporation then chromatography on silica gel (13 g, CH_2Cl_2/AcOEt 5 : 1 then 3 : 1) led to 100 mg of a **14+15** mixture in the 44 : 56 ratio, respectively. A part of this mixture (87 mg) was treated again with the same reagent (0.28 mL, 0.28 mmol) in THF (1.5 mL) for 3 days at reflux. The reaction led to 81 mg of crude product. The ^1H NMR ratio of **14/15** was 16 : 84, respectively. ^1H NMR δ 5.32 (s, 1H, H-2), 4.14 (dd, 1H, H-4, $J_{H\text{-}4/H\text{-}4'}$ = 8.9 Hz, $J_{H\text{-}4/H\text{-}5}$ = 3.9 Hz), 3.82 (d, 1H, H-4', $J_{H\text{-}4'/H\text{-}4}$ = 8.9 Hz), 3.74 (d, 2H, H-7 and H-7', J = 7.9 Hz), 1.86 (m, 1H, H-5), 1.80 (dd, 1H, H-1, J = 8.4, 6.9 Hz), 1.29 (br s, 1H, OH), 1.26-1.18 (m, 1H, H-6), 0.90 (s, 9H, $C(CH_3)_3$), 0.12 (s, 3H, $Si(CH_3)_2$), 0.11 (s, 3H, $Si(CH_3)_2$); ^{13}C NMR δ 97.88 (C-2), 66.44 (C-4), 57.56 (C-7), 28.59 (C-1), 25.75 ($C(\underline{C}H_3)_3$), 21.34 (C-6), 19.94 (C-5), 17.97 ($C(\underline{C}H_3)_3$), -4.25 ($Si(\underline{C}H_3)_2$), -4.99 ($Si(\underline{C}H_3)_2$).

[4,4'-$^2H_2$]-6-*exo*-*tert*-Butyldimethylsilyloxy-2-oxo-3-oxabicyclo[3.2.0]heptane **16'**

AIBN (27 mg, 0.16 mmol) was added to a solution of **13'** (4.25 g, 13.1 mmol) in toluene (53 mL) under argon then *n*-Bu_3SnH (6.34 mL, 22.9 mmol) was added dropwise with stirring. The reaction was allowed to proceed for 7h at room temperature, then evaporation and chromatography on silica gel (cyclohexane then cyclohexane/AcOEt 11 : 1) led to **16'** as white crystals (2.93 g, 91%). **16** : m.p. 65-66°C (pentane); ^1H NMR δ 4.34-4.27 (m, 3H, H-4, H-4' and H-6), 3.04 (m, 2H, H-1 and H-5), 2.53 (m, 1H, H-7), 2.42 (m, 1H, H-7'), 0.88 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 179.88 ($\underline{C}$=O), 71.33 (C-4), 70.96 (C-6), 46.86 (d), 35.54 (C-7), 31.06 (d), 25.66 ($C(\underline{C}H_3)_3$), 17.87 ($\underline{C}(CH_3)_3$), -4.85 ($Si(\underline{C}H_3)_2$); IR (film) cm^{-1} 1781, 1371, 1257, 1170, 1153, 1133, 1120, 881, 844, 775. Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.46; H, 9.15; Si, 11.59. Found : C, 59.11; H, 9.16; Si, 11.80. **16'** : ^1H NMR δ 4.34-4.27 (m, 1H, H-6), 3.04 (m, 2H, H-1 and H-5), 2.53 (m, 1H, H-7), 2.42 (m, 1H, H-7'), 0.88 (s, 9H, $C(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 179.88 ($\underline{C}$=O), 71.32-71.23 (m, $\underline{C}D_2$), 70.96 (C-6), 46.86 (m), 35.54 (C-7), 31.06 (d), 25.66 ($C(\underline{C}H_3)_3$), 17.87 ($\underline{C}(CH_3)_3$), -4.85 ($Si(\underline{C}H_3)_2$).

trans-3-Hydroxymethyl-*trans*-2-([6,6'-$^2H_2$]-hydroxymethyl)-1-*tert*-butyldimethylsilyloxy-cyclobutane **17'**

Reduction of **16'** (2.75 g, 11.2 mmol) with $LiAlH_4$ (2.25 g, 56.3 mmol) in THF (116 mL) for 4h at room temperature, practically in the same experimental conditions as for reduction of **13**, led to **17'** (colorless oil, 2.79 g, 100%). **17** : ^1H NMR δ 4.06 (m, 1H, H-1), 3.73 (m, 3H, H-6, H-6' and OH), 3.67 (m, 3H, H-5, H-5' and OH), 2.54 (m, 1H, H-2), 2.45 (m, 1H, H-3), 1.97 (m, 1H, H-4), 1.87 (m, 1H, H-4', $J_{H\text{-}4'/H\text{-}4}$ = 11.3 Hz, $J_{H\text{-}4'/H\text{-}1}$ = 7.7 Hz), 0.87 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 67.08 (C-1), 63.20 (C-5), 60.70 (C-6), 48.88 (d), 32.37 (C-4), 30.83 (d), 25.77 ($C(\underline{C}H_3)_3$), 18.00 ($\underline{C}(CH_3)_3$), -4.81 ($Si(\underline{C}H_3)_2$), -4.83 ($Si(\underline{C}H_3)_2$); IR (film) cm^{-1} 3338, 1253, 1132, 1029, 867, 836, 777. **17'** : ^1H NMR δ 4.06 (m, 1H, H-1), 3.75-3.67 (m, 2H, H-5 and H-5'), 3.17 (br s, 2H, OH), 2.54 (dd, 1H, H-2), 2.45 (m, 1H, H-3), 1.97 (m, 1H, H-4), 1.87 (m, 1H, H-4'), 0.87 (s, 9H, $C(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 67.08 (C-1), 63.20 (C-5), 60.85-59.93 (m, $\underline{C}D_2$), 48.88 (m), 32.37 (C-4), 30.83 (d), 25.77 ($C(\underline{C}H_3)_3$), 18.00 ($\underline{C}(CH_3)_3$), -4.81 ($Si(\underline{C}H_3)_2$), -4.83 ($Si(\underline{C}H_3)_2$).

trans-3-Benzyloxymethyl-*trans*-2-([6,6'-$^2H_2$]-benzyloxymethyl)-1-*tert*-butyldimethyl-silyloxycyclobutane **19'**

NaH (60% dispersion in mineral oil, 1.34 g, 33.4 mmol) was added portionwise to a solution of **17'** (2.77 g, 11.1 mmol) in DMF (27.7 mL), under argon, at 0°C, with stirring. Benzyl bromide (3.25 mL, 26.8 mmol) was added dropwise to this mixture, then the reaction was allowed to proceed for 5h at room temperature. MeOH in excess was then added at 0°C and, after 1h stirring at room temperature, evaporation, adding of

AcOEt, washing (water (2 x 14 mL) then brine (14 mL)), drying ($MgSO_4$) and another evaporation led to the crude product. Chromatography on silica gel (285 g, cyclohexane/AcOEt 50 : 1 -> 30 : 1) gave **19'** as a colorless oil (3.83 g, 80%). **19** : ^1H NMR δ 7.37-7.23 (m, 10H, Ph), 4.50-4.39 (m, 4H, benzylic), 4.18 (m, 1H, H-1), 3.59-3.53 (m, 2H, H-6 and H-5), 3.52-3.46 (m, 2H, H-6' and H-5'), 2.63 (m, 1H, H-2), 2.47 (m, 1H, H-3), 2.09 (m, 1H, H-4, $J_{H\text{-}4/H\text{-}4'}$ = 10.9 Hz, $J_{H\text{-}4/H\text{-}1}$ = 7.4 Hz), 1.96 (m, 1H, H-4'), 0.85 (s, 9H, $C(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 138.65 (s, Ph), 138.58 (s, Ph), 128.28 (d, Ph), 128.24 (d, Ph), 127.76 (d, Ph), 127.69 (d, Ph), 127.47 (d, Ph), 127.40 (d, Ph), 72.94 (benzylic C), 72.92 (benzylic C), 71.04 (CH_2OBn), 68.98 (CH_2OBn), 68.27 (C-1), 47.36 (d), 33.61 (C-4), 28.93 (d), 25.85 ($C(CH_3)_3$), 18.09 ($C(CH_3)_3$), -4.78 ($Si(CH_3)_2$); IR (film) cm^{-1} 1251, 1132, 1091, 836, 777, 734, 696. **19'** : ^1H NMR δ 7.37-7.23 (m, 10H, Ph), 4.50-4.39 (m, 4H, benzylic), 4.18 (m, 1H, H-1), 3.58 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.3 Hz, $J_{H\text{-}5/H\text{-}3}$ = 6.4 Hz), 3.49 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.3 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.9 Hz), 2.63 (dd, 1H, H-2), 2.47 (m, 1H, H-3), 2.09 (m, 1H, H-4), 1.96 (m, 1H, H-4'), 0.85 (s, 9H, $C(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR δ 138.65 (s, Ph), 138.58 (s, Ph), 128.28 (d, Ph), 128.24 (d, Ph), 127.76 (d, Ph), 127.69 (d, Ph), 127.47 (d, Ph), 127.40 (d, Ph), 72.94 (benzylic C), 72.92 (benzylic C), 71.04 (CH_2OBn), 68.99-68.62 (m, CD_2), 68.27 (C-1), 47.36 (m), 33.61 (C-4), 28.93 (d), 25.85 ($C(CH_3)_3$), 18.09 ($C(CH_3)_3$), -4,78 ($Si(CH_3)_2$).

trans-3-Benzyloxymethyl-*trans*-2-([6,6'-$^2H_2$]-benzyloxymethyl)-1-hydroxycyclobutane **2a'** and the corresponding mesylate **5a'**

n-Bu_4NF (1M solution in THF, 1.29 mL, 1.29 mmol) was added dropwise to a solution of **19'** (184 mg, 0.43 mmol) in THF (2 mL). After 23h stirring at room temperature, evaporation, then chromatography on silica gel (32 g, cyclohexane/AcOEt 3 : 1 then 2 : 1) led to **5a'** as a colorless oil (120 mg, 89%). ^1H NMR δ 7.35-7.26 (m, 10H, Ph), 4.47 (m, 2H, benzylic, AB system, J = 12.0 Hz), 4.43 (s, 2H, benzylic), 4.20 (m, 1H, H-1), 3.52 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.3 Hz, $J_{H\text{-}5/H\text{-}3}$ = 6.4 Hz), 3.47 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.3 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.0 Hz), 2.58 (dd, 1H, H-2), 2.54-2.46 (m, 1H, H-3), 2.15 (m, 1H, H-4), 1.97 (m, 1H, H-4'), 1.77 (br s, 1H, OH); ^{13}C NMR δ 138.39 (s, Ph), 138.38 (s, Ph), 128.35 (d, Ph), 128.33 (d, Ph), 127.72 (d, Ph), 127.59 (d, Ph), 127.57 (d, Ph), 127.52 (d, Ph), 73.09 (benzylic C), 73.04 (benzylic C), 70.80 (CH_2OBn), 69.78-69.01 (m, CD_2), 69.18 (C-1), 47.46 (m), 32.54 (C-4), 28.59 (d). Mesylation of **2a'** in the same experimental conditions as for **2a** led to **5a'**. ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 5.00 (m, 1H, H-1), 4.44 (m, 2H, benzylic, AB system, J = 11.8 Hz), 4.43 (s, 2H, benzylic), 3.51 (m, 2H, H-5 and H-5'), 2.97 (dd, 1H, H-2, J = 9.8, 7.4 Hz), 2.92 (s, 3H, CH_3), 2.61 (m, 1H, H-3), 2.34 (m, 2H, H-4 and H-4'); ^{13}C NMR δ 138.06 (s, Ph), 138.00 (s, Ph), 128.41 (d, Ph), 128.37 (d, Ph), 128.20 (d, Ph), 127.90 (d, Ph), 127.72 (d, Ph), 127.69 (d, Ph), 75.96 (C-1), 73.25 (benzylic C), 73.18 (benzylic C), 69.54 (CH_2OBn), 68.05-67.10 (m, CD_2), 44.93 (m), 38.09 (CH_3), 30.83 (C-4), 29.63 (d).

cis-2,3-Bis(benzyloxymethyl)-1-oxocyclobutane **20**

DMSO (367 µL, 5.12 mmol) was added dropwise to a solution of oxalyl chloride (204 µL, 2.29 mmol) in CH_2Cl_2 (5.3 mL), at -78°C, under argon. The mixture was stirred for 10 min at the same temperature then **2a** (650 mg, 2.08 mmol) in CH_2Cl_2 (2.2 mL) was introduced dropwise (40 min). Stirring was pursued for 40 min more at -78°C, then Et_3N (1.5 mL, 10.6 mmol) was added dropwise. After 0.5h at -78°C, the reaction mixture was slowly warmed up to room temperature (1h). Adding of water (6.2 mL), decantation, extraction (CH_2Cl_2, 3 x 3 mL), washing of the combined organic phases with 10% HCl (8.5 mL), drying ($MgSO_4$) and evaporation gave 646 mg (100%) of the **20+21** mixture in the 95 : 5 ratio (^1H NMR). As chromatography on silica gel led to epimerization, this mixture was used without purification in the following step. **20** : ^1H NMR δ 7.36-7.26 (m, 10H, Ph), 4.46 (s, 2H, benzylic), 4.43 (m, 2H, benzylic, AB system, J = 12.3 Hz), 3.79 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.4 Hz, $J_{H\text{-}5/H\text{-}3}$ = 5.9 Hz), 3.72 (m, 2H, H-6 and H-6'), 3.65 (m, 2H, H-2 and H-5'), 3.13 (ddd, 1H, H-4, J = 18.9, 10.8, 3.4 Hz), 2.86 (m, 1H, H-4'), 2.83 (m, 1H, H-3).

Reduction of the **20+21** mixture with $NaBD_4$

$NaBD_4$ (134 mg, 3.12 mmol) was added portionwise with stirring to a solution of **20+21** (**20/21** = 95 : 5, 646 mg, 2.08 mmol) in EtOH (8.6 mL). After 25 min at room temperature, the reaction mixture was cooled to 0°C and 1.8 mL of 1M HCl then 0.5 mL of 6M HCl were added dropwise. Evaporation, extraction (CH_2Cl_2, 5 x 13 mL), drying of the combined organic phases ($MgSO_4$) and another evaporation led to a mixture of **2b"+2a"** together with a small amount of **22** (**2b"/2a"+22** = 61 : 39 by ^1H NMR). Chromatography on silica gel (51 g, cyclohexane/AcOEt 5 : 1 then 3 : 1) successively led to **2b"** (350 mg, 53.7%) then to **2a"** (174 mg, 26.7%). **2b"** : ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 4.47 (d, 1H, benzylic, J = 11.8 Hz), 4.42 (s, 2H, benzylic), 4.39 (d, 1H, benzylic, J = 11.8 Hz), 3.86 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.7 Hz, $J_{H\text{-}5/H\text{-}3}$ = 5.4 Hz), 3.79 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.7 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 4.9 Hz), 3.56 (dd, 1H, H-6, $J_{H\text{-}6/H\text{-}6'}$ = 9.3 Hz, $J_{H\text{-}6/H\text{-}2}$ = 7.8 Hz), 3.48 (dd, 1H, H-6', $J_{H\text{-}6'/H\text{-}6}$ = 9.3 Hz, $J_{H\text{-}6'/H\text{-}2}$ = 4.9 Hz), 3.24 (s, 1H, OH), 2.81 (m, 1H, H-3), 2.42 (m, 2H, H-4 and H-4'), 1.81 (m, 1H, H-2); ^{13}C NMR δ 138.17 (s, Ph), 137.77 (s, Ph), 128.45 (d, Ph), 128.39 (d, Ph), 127.90 (d, Ph), 127.82 (d, Ph), 127.79 (d, Ph), 127.69 (d, Ph), 73.42 (t), 73.08 (t), 70.55 (t), 67.75 (t), 66.04 (t, C-1), 42.56 (d), 35.47 (C-4), 29.48 (d). **2a"** : ^1H NMR δ 7.35-7.26 (m, 10H, Ph), 4.47 (m, 2H, benzylic, AB system, J = 12.0 Hz), 4.43 (s, 2H, benzylic), 3.61 (dd, 1H, H-6, $J_{H\text{-}6/H\text{-}6'}$ = 9.6 Hz, $J_{H\text{-}6/H\text{-}2}$ = 6.9 Hz), 3.57-3.51 (m, 2H, H-6' and H-5), 3.47 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.3 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.0 Hz), 2.59 (m, 1H, H-2), 2.54-2.46 (m, 1H, H-3), 2.15 (dd, 1H, H-4, $J_{H\text{-}4/H\text{-}4'}$ = 11.8 Hz, $J_{H\text{-}4/H\text{-}3}$ = 2.0 Hz), 1.97 (dd, 1H, H-4', $J_{H\text{-}4'/H\text{-}4}$ = 11.8 Hz, $J_{H\text{-}4'/H\text{-}3}$ = 9.4 Hz), 1.77 (s, 1H, OH); ^{13}C NMR δ 138.39 (s, Ph), 138.88 (s, Ph), 128.35 (d, Ph), 128.33 (d, Ph), 127.72 (d, Ph), 127.59 (d, Ph), 127.57 (d, Ph), 127.52 (d, Ph), 73.09 (t), 73.04 (t), 70.80 (t), 69.35 (t), 68.69 (t, C-1), 47.36 (d), 32.54 (C-4), 28.59 (d).

Mitsunobu reaction, preparation of **23**, **2a"** and **5a"**

PPh_3 (820 mg, 3.09 mmol) and PhCOOH (263 mg, 2.32 mmol) were added to a solution of **2b"** (485 mg, 1.55 mmol) in THF (8.5 mL). The stirred mixture was cooled to 0°C and DEAD (492 µL, 3.09 mmol) was added dropwise. The reaction mixture was stirred for 6 days at room temperature. Evaporation, adding of CH_2Cl_2 (10 mL), washing (sat. $NaHCO_3$ (2 mL) then brine (10 mL)), drying ($MgSO_4$) and another evaporation led to the crude product that was chromatographed on silica gel (100 g, cyclohexane/AcOEt 20 : 1 then 12 : 1). **23** was thus obtained as a colorless oil (717 mg, 80%). ^1H NMR δ 8.04 (m, 2H, Ph), 7.55 (m, 1H, Ph), 7.43 (m, 2H, Ph), 7.37-7.26 (m, 10H, Ph), 4.47 (s, 2H, benzylic), 4.46 (m, 2H, benzylic, AB system, J = 11.8 Hz), 3.74-3.66 (m, 2H, H-6 and H-6'), 3.65 (dd, 1H, H-5, $J_{H\text{-}5/H\text{-}5'}$ = 9.3 Hz, $J_{H\text{-}5/H\text{-}3}$ = 6.0 Hz), 3.58 (dd, 1H, H-5', $J_{H\text{-}5'/H\text{-}5}$ = 9.3 Hz, $J_{H\text{-}5'/H\text{-}3}$ = 6.4 Hz), 2.97 (m, 1H, H-2), 2.67 (m, 1H, H-3), 2.39 (dd, 1H, H-4, $J_{H\text{-}4/H\text{-}4'}$ = 11.8 Hz, $J_{H\text{-}4/H\text{-}3}$ = 2.5 Hz), 2.25 (dd, 1H, H-4', $J_{H\text{-}4'/H\text{-}4}$ = 11.8 Hz, $J_{H\text{-}4'/H\text{-}3}$ = 9.8 Hz). A solution of 15% NaOH (1.05 mL, 3.95 mmol) was added dropwise to a solution of **23** (505 mg, 1.21 mmol) in MeOH (9 mL). The reaction mixture was stirred for 17h at room temperature. Evaporation, adding of brine (20 mL), extraction (CH_2Cl_2, 4 x 10 mL), washing (brine, 30 mL), drying ($MgSO_4$) and another evaporation yielded **2a"** (369 mg, 97%). Its spectral data are given above. Mesylation of **2a"** in the same experimental conditions as for **2a** led to **5a"**. ^1H NMR δ 7.37-7.26 (m, 10H, Ph), 4.44 (m, 2H, benzylic, AB system, J = 11.8 Hz), 4.43 (s, 2H, benzylic), 3.62 (d, 2H, H-6 and H-6', J = 6.7 Hz), 3.51 (m, 2H, H-5 and H-5'), 2.97 (m, 1H, H-2), 2.92 (s, 3H, CH_3), 2.61 (m, 1H, H-3), 2.34 (m, 2H, H-4 and H-4').

Preparation of **8a'+8b'** and of **8a"+8b"**

The mixtures of **8a'+8b'** and of **8a"+8b"** were obtained from **5a'** and **5a"**, respectively, in the same experimental conditions as in the reaction from **5a**. **A'** (**8a'** or **8b'**) ^1H NMR δ 7.35-7.23 (m, 10H, Ph), 4.56 (s, 2H, benzylic), 4.53 (s, 2H, benzylic), 3.40 (dd, 1H, H-4', $J_{H\text{-}4'/H\text{-}4'bis}$ = 10.2 Hz, $J_{H\text{-}4'/H\text{-}2'}$ = 6.6 Hz), 3.28 (dd, 1H, H-4'bis, $J_{H\text{-}4'bis/H\text{-}4'}$ = 10.2 Hz, $J_{H\text{-}4'bis/H\text{-}2'}$ = 6.9 Hz), 3.22 (d, 1H, H-1, $J_{H\text{-}1/H\text{-}1'}$ = 8.4 Hz), 2.44 (br s, 1H, OH), 1.17 (m, 1H, H-2'), 0.81 (m, 1H, H-1'), 0.53-0.49 (m, 1H, H-3'), 0.47-0.43 (m, 1H, H-3'bis). **B'**

(**8b'** or **8a'**) (partially described) ^{1}H NMR δ 7.37-7.26 (m, 10H, Ph), 4.57 (s, 2H, benzylic), 4.51 (s, 1H, benzylic), 4.50 (s, 1H, benzylic), 3.36-3.26 (m, 3H, H-1, H-4' and H-4'bis), 1.09 (m, 1H, H-2'), 0.81 (m, 1H, H-1'), 0.69 (m, 1H, H-3'), 0.54-0.50 (m, 1H, H-3'bis). **A"** (**8a"** or **8b"**) : ^{1}H NMR δ 7.35-7.23 (m, 10H, Ph), 4.56 (s, 2H, benzylic), 4.53 (s, 2H, benzylic), 3.59 (dd, 1H, H-2, $J_{H\text{-}2/H\text{-}2bis}$ = 9.6 Hz, $J_{H\text{-}2/H\text{-}1}$ = 3.1 Hz), 3.45 (dd, 1H, H-2bis, $J_{H\text{-}2bis/H\text{-}2}$ = 9.6 Hz, $J_{H\text{-}2bis/H\text{-}1}$ = 7.7 Hz), 3.40 (dd, 1H, H-4', $J_{H\text{-}4'/H\text{-}4'bis}$ = 10.2 Hz, $J_{H\text{-}4'/H\text{-}2'}$ = 6.6 Hz), 3.28 (dd, 1H, H-4'bis, $J_{H\text{-}4'bis/H\text{-}4'}$ = 10.2 Hz, $J_{H\text{-}4'bis/H\text{-}2'}$ = 6.9 Hz), 3.22 (m, 1H, H-1), 2.44 (br s, 1H, OH), 1.17 (m, 1H, H-2'), 0.53-0.49 (m, 1H, H-3'), 0.45 (dd, 1H, H-3'bis). **B"** (**8b"** or **8a"**) : ^{1}H NMR δ 7.37-7.26 (m, 10H, Ph), 4.57 (s, 2H, benzylic), 4.51 (s, 1H, benzylic), 4.50 (s, 1H, benzylic), 3.64 (dd, 1H, H-2, $J_{H\text{-}2/H\text{-}2bis}$ = 9.8 Hz, $J_{H\text{-}2/H\text{-}1}$ = 3.0 Hz), 3.45 (m, 1H, H-2bis), 3.36-3.26 (m, 3H, H-1, H-4' and H-4'bis), 2.35 (br s, 1H, OH), 1.09 (m, 1H, H-2'), 0.69 (dd, 1H, H-3', $J_{H\text{-}3'/H\text{-}3'bis}$ = 8.4 Hz, $J_{H\text{-}3'/H\text{-}2'}$ = 4.9 Hz), 0.54-0.50 (m, 1H, H-3'bis).

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