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Preparation Involving a C4-C3 Ring Contraction in the Key Step of a Novel Cyclopropane Carbocyclic Nucleoside

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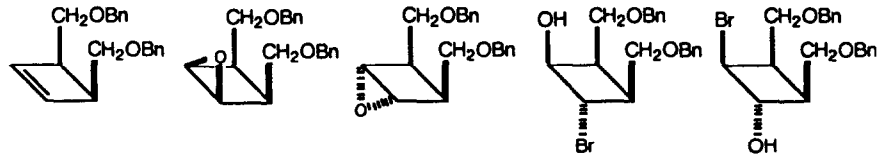
Abstract : Cis-3,4-bis(benzyloxymethyl)cyclobut-1-ene **1** mainly led to bromohydrin **5** with a cis relationship between bromine and the benzyloxymethyl groups. The stereospecific ring contraction of **5** afforded aldehyde **7** which could be converted into the nucleoside analogue **12**.

Several nucleoside analogues have shown anti-HIV activity and act as reverse transcriptase inhibitors.[1] A variety of cyclopentane and cyclobutane analogues have been synthesized and evaluated on the biological point of view. On the other hand only a few cyclopropane nucleoside analogues have been reported recently.[2] The purpose of this communication is to report the synthesis of the 1,2,3 trisubstituted nucleoside analogue **12** with three substituents on the same side of the cyclopropane ring.

We have pointed out, in a previous report,[3] that mixtures of epoxides **2** and **3** could be obtained by epoxidation of the corresponding cyclobutene compound **1**.



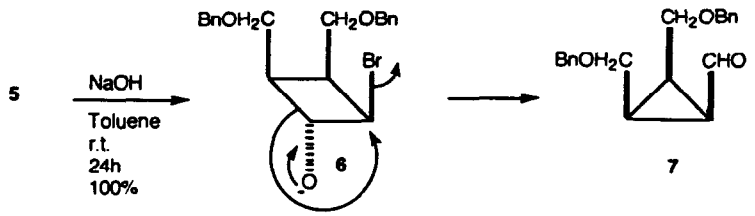
1 **2** **3** **4** **5**

Epoxide **2** was the predominant product (**2**/**3** = 72 : 28) when reaction was run with *meta*-chloroperbenzoic acid in 8.25 h, whereas the result was reversed with Payne's reagent (**2**/**3** = 28 : 72). However, in the latter case, the reaction was very slow and 7% of the starting material **1** was recovered after 7-8 days.[4] Both epoxides **2** and **3** gave the expected bromohydrins **4** and **5**, respectively, in high yield, by treatment with aqueous hydrobromic acid. Bromohydrin **4** is thus efficiently obtained but the preparation of the starting epoxide **3** for obtention of the other bromohydrin **5** is cumbersome.

Fortunately we have obtained a good result for preparation of this bromohydrin **5**, (**4**/**5** = 90 : 10 ; **4**+**5** : 75% yield), by the bromohydroxylation of **1** by the use of N-bromosuccinimide and moist dimethylsulfoxide.[5] (10°C then r.t. 23 h).

This result is in agreement with a mechanism proceeding via bromonium ion *syn* to the benzyloxymethyl substituents.[6] Both compounds **4** and **5** were separated by flash chromatography on silica gel.

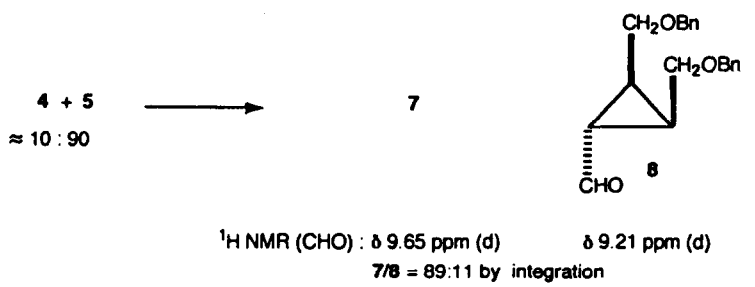
We were pleased to observe a quantitative and totally stereoselective C_4-C_3 ring contraction[7] when bromohydrin **5** was treated with crushed sodium hydroxide in suspension in dry toluene and under argon. The reaction led to aldehyde **7**.[8] A mechanistic hypothesis for obtention of the sole isomer **7** is proposed in



Scheme 1

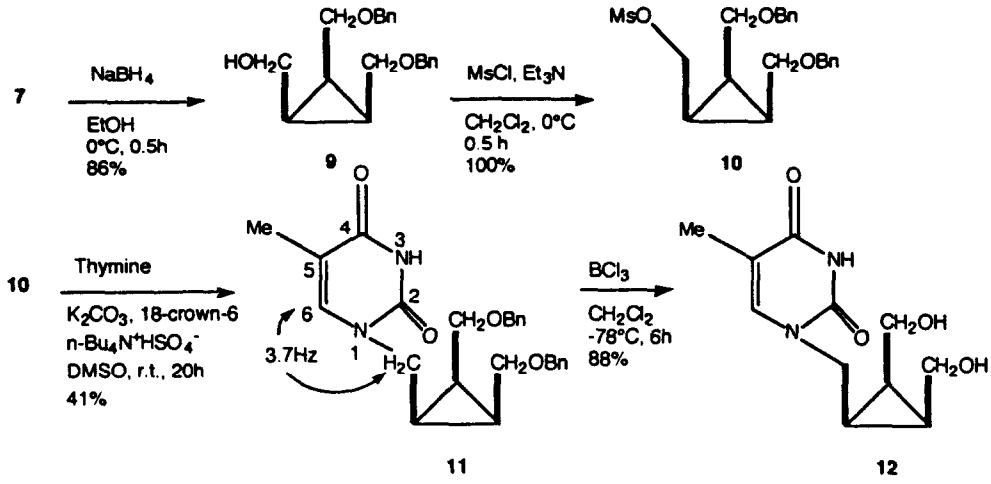
scheme 1. Configuration assignments are based on ^1H NMR NOE difference experiments (enhancements of 8.2% for H-1 upon saturation of H-3 and H-2 and of 5.4 and 4.8% for the aldehydic proton upon saturation of signals of CH_2 linked to the cyclopropane ring).

When the same ring contraction was run starting from the mixture of both products **4** and **5**, ^1H NMR showed that aldehydes **7** and **8** were formed together (Scheme 2). This result confirms the absence of **8** when starting from **5** only.



Scheme 2

Reduction of aldehyde **7** then mesylation of the resulting alcohol **9** led to compound **10** which was poorly stable and underwent thermal decomposition on warming (≈30°C). It was then immediatly submitted to the nucleophilic attack by thymine[2j] (scheme 3). Compound **11** was thus obtained. As expected the reaction proceeded exclusively through N_1 attack, as could be checked by measurement of a coupling constant between protons of CH_2 and C-6 on the coupled ^{13}C NMR spectrum. This coupling was suppressed upon the selective irradiation of these protons.



Scheme 3

Finally removal of the benzyl groups afforded the nucleoside analogue **12**.[9]

Preparative procedures

Preparation of **7** : Compound **5** (1.14 g, 2.9 mmol), in 5.9 mL of dry toluene was added dropwise under argon and with stirring to a suspension of freshly crushed NaOH (0.157 g, 3.93 mmol) in dry toluene (2.3 mL). Conversion was allowed to proceed at room temperature and monitored by TLC. NaOH (18 mg) was added after 19 h and conversion was complete after 5 h more. Dilution (AcOEt), washing (H_2O), drying ($MgSO_4$) of the organic phase and evaporation led to **7**. 100% yield (0.90 g, colorless oil).

Preparation of **11** : Thymine (1.12 g, 8.64 mmol), $nBu_4N^+HSO_4^-$ (0.605 g, 1.73 mmol), 18-crown-6 (0.970 g, 3.63 mmol) and K_2CO_3 (1.28 g, 8.99 mmol) were successively added under argon to a solution of freshly prepared **10** (1.35 g, 3.46 mmol) in dry DMSO solution (25.3 mL). Reaction mixture was stirred for 20 h at room temperature. Dilution (AcOEt), washing (H_2O), extraction (AcOEt), drying ($MgSO_4$) of the organic phase, evaporation and flash chromatography on silica gel (CH_2Cl_2/AcOEt) led to **11**. 41% yield (0.60 g, white foam).

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8) ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) 9.65 (d, 1H, CHO, J = 4.5 Hz) ; 7.35-7.25 (m, 10H, C_6H_5) ; 4.48 (m, 4H, benzylic (AB system) J = 11.9 Hz) ; 3.90 (dd, 2H, CH_2, J = 10.3, 6.4 Hz) ; 3.74 (dd, 2H, CH_2, J = 10.3, 7.4 Hz) ; 2.15 (td, 1H, H-1, J = 8.5, 4.5 Hz) ; 2.00 (m, 2H, H-2 and H-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 199.96 (C=O), 137.88 (s), 128.40 (d), 127.78 (d), 127.74 (d), 73.00 (t, two carbons), 64.11 (t, two carbons), 29.23 (d), 27.00 (d, two carbons).

9) ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm) 11.22 (br s, 1H, NH) ; 7.64 (s, 1H, H-6) ; 4.55 (t, 2H, OH, J = 4.9 Hz) ; 3.82 (d, 2H, CH_2-thymidyl, J = 6.9 Hz) ; 3.62 (m, 2H, CH_2OH) ; 3.50 (m, 2H, CH_2OH) ; 1.75 (s, 3H, CH_3) ; 1.29-1.14 (m, 3H, H-1', H-2', H-3'). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm) 164.24 (C=O), 151.05 (C=O), 141.49 (C-6), 108.25 (C-5), 56.44 (2 CH_2OH), 42.56 (CH_2-thymidyl), 20.84 (C-2', C-3'), 17.84 (C-1'), 12.03 (CH_3). Anal. calcd for $C_{11}H_{16}N_2O_4$: C, 54.99 ; H, 6.71 ; N, 11.66 ; found : C, 54.62 ; H, 6.84 ; N, 11.49. Mp 204-205°C (methanol).

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