Nucleosides. Part 5.[1] Isolation and Characterization of the Stable Cyclic Adducts, (5*R*,6*S*)- and (5*S*,6*S*)-Bromo-*O*^{6},5′-cyclo-5,6-dihydrouridines in the Bromination of 2′,3′-*O*-Isopropylideneuridine with *N*-Bromosuccinimide

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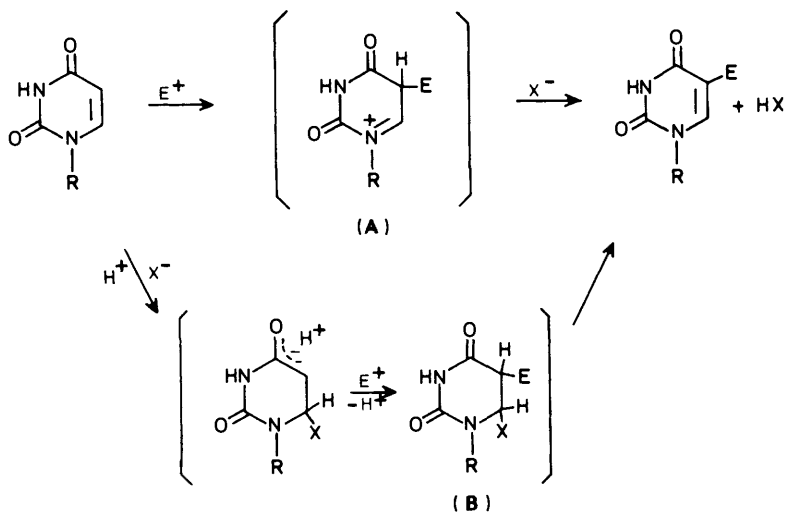
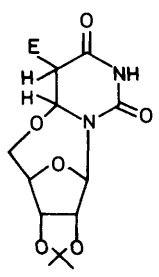
Bromination of 2′,3′-*O*-isopropylideneuridine (**1**) with *N*-bromosuccinimide in chloroform containing acetic acid gave two diastereoisomeric cyclic adducts, (5*R*,6*S*)- and (5*S*,6*S*)-bromo-*O*^{6},5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridines (**4a**) and (**4b**), whose structures were determined on the basis of their chemical reactivities and ^{1}H n.m.r. spectral results. The cyclic adducts (**4a**) and (**4b**) formed an equilibrium mixture under acidic conditions [(**4a**)/(**4b**) = 9:11], while under neutral and basic conditions both adducts were converted into 5-bromo-2′,3′-*O*-isopropylideneuridine (**2**).

Electrophilic substitution at the 5-position of uridines has been extensively investigated for the purpose of the synthesis of biologically active 5-substituted uridines.[2] Two types of mechanism have been proposed to explain the electrophilic substitution reaction (Scheme 1).[3] One is a mechanism analogous to that for aromatic electrophilic substitution, involving the transient formation of a σ complex (**A**) which could be stabilized by electron donation from the ring nitrogen (N-1). In another mechanism, nucleophilic addition at the 6-position occurs before electrophilic attack at the 5-position to give a 5,6-dihydro adduct (**B**) as a key intermediate. For example, bromination of uridines in aprotic solvents, *e.g.* acetic anhydride[4] and *N*,*N*-dimethylformamide (DMF),[5] probably occurs by the former mechanism and in aqueous[6] and alcoholic solution[7] the latter mechanism appears to prevail with the addition of an hydroxylic function (*e.g.* water or alcohol) to the 6-position followed by attack of a bromonium ion (Br^+) at the 5-position. For a reaction proceeding *via* the latter mechanism, a stable intermediate, a 5,6-dihydro adduct (**B**), has often been isolated.[8] On the other hand, previous studies have shown that electrophilic substitution, *e.g.* base-catalyzed hydroxymethylation and hydrogen exchange, at the 5-position of 2′,3′-*O*-isopropylideneuridine (**1**) proceeds by the latter mechanism and is remarkably accelerated by the intramolecular participation of a 5′-sugar hydroxy group.[9] However, the intermediacy of such an intramolecular cyclic adduct (**C**) for electrophilic substitution is less well established.[10,11]



Scheme 1.

In the course of our study[12] on the bromination† of 2′,3′-*O*-isopropylideneuridine (**1**), we found the formation of two



(**C**)

† The halogenation of uridine derivatives has been extensively investigated.[3] However, only few studies on the bromination of 2′,3′-*O*-isopropylideneuridine (**1**) have been undertaken.[12]

Table. Coupling constants for compounds (**5**), (**6a**),[a] and (**6b**)[a]

J(HH)/Hz	(**5**)[b]	(**6a**)/6*S*[c]	(**6b**)/6*R*[c]
5,5	17.1	17.1	17.7
5,6	9.0	8.9	4.9
	5.6	5.6	2.8
4′,5′	2.6	2.4	3.7
	0	0.7	3.7
5′,5′	12.8	13.0	—

[a] Cited from the data reported by Cadet *et al.*[15] [b] In $CDCl_3$. [c] In D_2O.

stable cyclic adducts, 5-bromo-O^6,5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridines (**4a**) and (**4b**) upon treatment of the uridine (**1**) with *N*-bromosuccinimide (NBS) in chloroform containing acetic acid. Here, we describe the isolation and structural elucidation of the cyclic adducts (**4a**) and (**4b**), and their chemical reactivities.

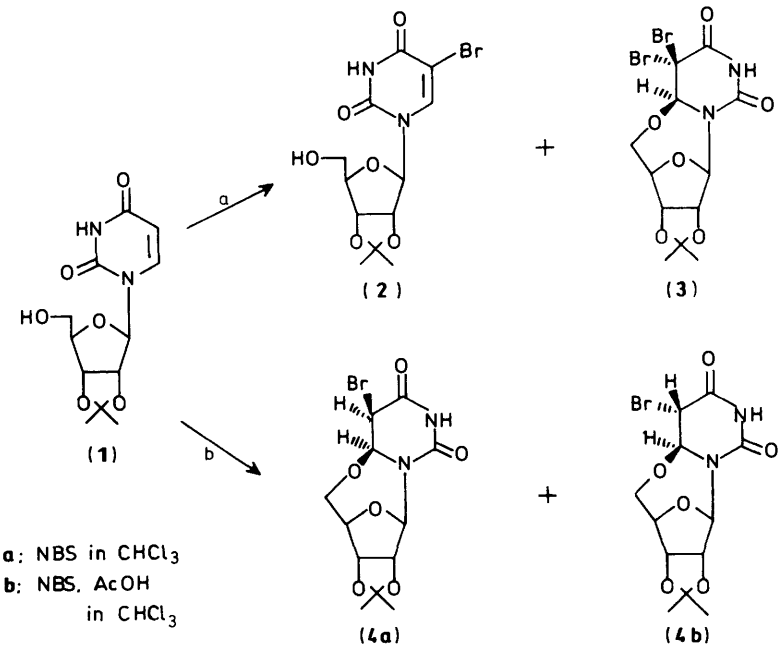
Results and Discussion

Treatment of 2′,3′-*O*-isopropylideneuridine (**1**) with an equimolar proportion of NBS in chloroform at 40 °C for 20 h gave 5-bromo-2′,3′-*O*-isopropylideneuridine (**2**) and 5,5-dibromo-O^6,5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridine (**3**) in 31 and 21% yield, respectively. The structures of (**2**) and (**3**) were confirmed by comparison with authentic samples.[12,13] In sharp contrast, bromination with NBS in chloroform containing acetic acid [chloroform–acetic acid, 10:1 (v/v)] gave a 1:1 mixture of two diastereoisomeric brominated compounds in 54% yield. Fractional recrystallization of the mixture from methanol allowed isolation of products (**4a**) {m.p. 213—215 °C, $[\alpha]_D$(MeOH) −78.8°} and (**4b**) {m.p. 232—235 °C, $[\alpha]_D$(MeOH) −49.5°}. Microanalytical results and spectral data for these indicated that they were two of four possible diastereoisomeric 5-bromo-O^6,5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridines, the absolute configurations of which were determined as (5*R*,6*S*)- and (5*S*,6*S*)- on the basis of the following facts.

The photo-debromination[14] of (**4a**) and (**4b**) by irradiation in DMF gave the same product, O^6,5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridine (**5**).[14] Irradiation of 5,5-dibromo-O^6,5′-cyclo-2′,3′-*O*-isopropylideneuridine (**3**) in DMF gave quantitatively a mixture of (**4a**) and (**4b**) in the ratio of 52:48. These results indicate that the C-6 of (**4a**) and (**4b**) adopts the same configuration. The configuration of (**5**) was reasonably deduced by a comparison of its ^{1}H n.m.r. spectrum with those of (6*S*)- and (6*R*)-O^6,5′-cyclo-2′-deoxy-5,6-dihydrouridines (**6a**) and (**6b**), the stereochemistry of which has been firmly established by Cadet *et al.*[15] As shown in the Table, the coupling constants of protons around the C-6 of (**5**) are closely similar to those of the 6*S*-isomer (**6a**). Therefore, all compounds (**4a**), (**4b**), (**5**), and (**3**)* have an *S*-configuration at the 6-position. Irradiation of the 6-H signal in a nuclear Overhauser effect (n.O.e.) experiment for (**4a**) and (**4b**) led to enhancement of the 5-H signal (25.5 and 5.8%, respectively), clearly indicating that the configuration of protons at C-5 and C-6 is *cis* for (**4a**) and *trans* for (**4b**). Both (**4a**) and (**4b**) were converted with ease into 5-bromo-2′,3′-*O*-isopropylideneuridine (**2**) upon warming in methanol. Half-lives for the consumption of (**4a**) and (**4b**) in methanol at 28 °C were 1.5 and 8 h, respectively. This result supports the view that the 5*R*,6*S*-isomer (**4a**) is able to adopt a more favourable configuration at the 5- and 6-positions than the 5*S*,6*S*-isomer (**4b**) and thus undergo *trans*-elimination: this is in agreement with the conclusion obtained above by the n.O.e. experiment.

In the bromination of the uridine (**1**), the β-O^6,5′-cyclic bond (*S*-configuration) formed at the 6-position exclusively to give the *cis*- and *trans*-cyclo adducts (**4a**) and (**4b**). This has an interesting mechanistic implication in comparison with the reaction of thymidine with *N*-iodosuccinimide[11] since the latter gives a mixture of two *trans*-addition products resulting from both α- and β-O^6,5′-cyclic bond formation.

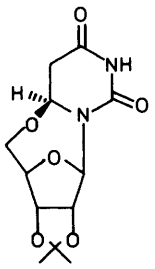
Two plausible mechanisms (paths a and b) for the formation



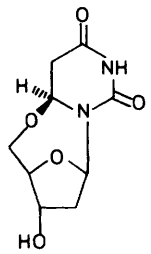
Scheme 2.

of (**4a**) and (**4b**) can be formulated as shown in Scheme 3. A mechanism initiated by addition of a bromine radical was omitted because the NBS–carboxylic acid system is used as

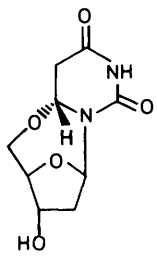
* The absolute configuration at the 6-position of (**3**) has been equivocal.[12]



(5)

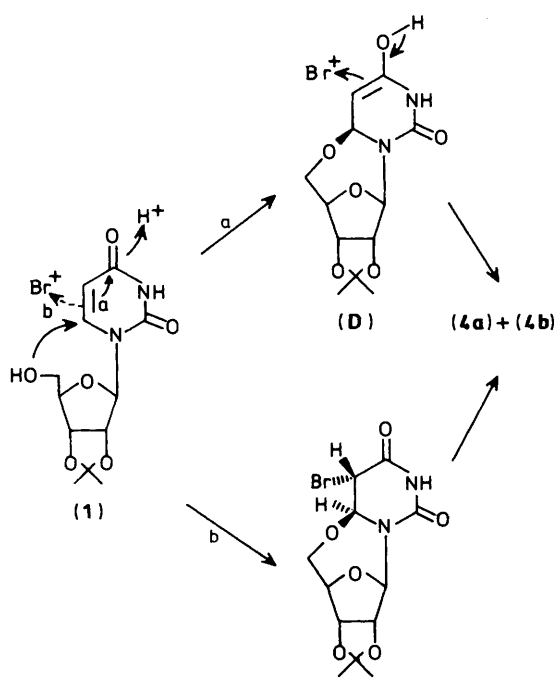


(6a)



(6b)

the source of bromonium ion.[16] Path a involves 1,4-addition initiated by protonation at the 4-carbonyl oxygen leading to an intermediate D. Path b involves concerted 1,2-*trans*-addition to give (**4b**) and its subsequent epimerisation to (**4a**). Path a seems to be a more favourable mechanism than path b, by which the concurrent formation of (**4a**) and (**4b**) is not reasonably explained (*vide infra*).



Scheme 3.

As described above (**4a**) and (**4b**) were slowly converted into the 5-bromouridine (**2**) in methanol at room temperature. Upon treatment of (**4a**) and (**4b**) with sodium methoxide in methanol or with 1M sodium hydroxide the 5-bromouridine (**2**) was immediately formed. 5-Halogeno-5,6-dihydro-2′,3′-*O*-isopropylidene-O^6,5′-cyclouridines (C: E = halogeno group, in Scheme 1) have been proposed[17] as possible intermediates in the ring contraction of 5-halogeno-2′,3′-*O*-isopropylideneuridines into the imidazole nucleoside by sodium hydroxide and in the formation of 2′,3′-*O*-isopropylidene-O^6,5′-cyclouridine by the reaction of 5-halogeno-2′,3′-*O*-isopropylideneuridines with sodium methoxide. The formation of the 5-bromouridine (**2**) from the cyclic adducts (**4a**) and (**4b**), corresponding to the proposed intermediate (**C**) in the above reactions, is contrary to our expectation.

On the other hand, the cyclic adducts (**4a**) and (**4b**) underwent slow interconversion under acidic conditions, *i.e.* independent treatment of (**4a**) and (**4b**) in chloroform containing a small amount of acetic acid at 60 °C gave an equilibrium mixture of (**4a**) and (**4b**) (9:11) after *ca.* 150 h. The slow interconversion of (**4a**) and (**4b**) under acidic conditions could occur *via* enolization and suggests that path a is more favourable than path b for the formation of (**4a**) and (**4b**) as mentioned previously.

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. ^{1}H N.m.r. spectra were determined with a JEOL TNM-GX270 n.m.r. spectrometer using tetramethylsilane as an internal standard. Chemical shifts are reported in p.p.m. (δ) and *J* values in Hz. Optical rotations were obtained with a JASCO DIP-4 automatic polarimeter. Mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV. Elemental analysis was carried out at the Microanalytical Laboratory of our University. Column chromatography was carried out on silica gel (Wako gel C-300).

Bromination of 2′,3′-O-*Isopropylideneuridine* (**1**) *with* N-*Bromosuccinimide* (*NBS*).—A suspension of 2′,3′-*O*-isopropylideneuridine (**1**) (244 mg, 0.86 mmol) and NBS (178 mg, 1 mmol) in $CHCl_3$ (10 ml) was heated at 40 °C for 20 h to afford three products and starting material on t.l.c. analysis. The resulting precipitate was filtered off and the filtrate diluted with $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$ and water, evaporated under reduced pressure, and the residue chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (50:1). The faster moving fraction gave 5,5-dibromo-O^6,5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridine (**3**) (78 mg, 21%), which was identical with an authentic sample.[12]

The later fraction gave 5-bromo-2′,3′-*O*-isopropylideneuridine (**2**) (98 mg, 31%), which was identical with an authentic sample.[13]

(5R,6S)-5-*Bromo*-O^6,5′-*cyclo*-5,6-*dihydro*-2′,3′-O-*isopropylideneuridine* (**4a**) *and* (5S,6S)-5-*Bromo*-O^6,5′-*cyclo*-5,6-*dihydro*-2′,3′-O-*isopropylideneuridine* (**4b**).—AcOH (1 ml) was added to a suspension of 2′,3′-*O*-isopropylideneuridine (**1**) (284 mg, 1 mmol) and NBS (214 mg, 1.2 mmol) in $CHCl_3$ (10 ml) and the mixture was stirred for 4 h at room temperature. The resulting precipitate was filtered off and the filtrate was diluted with $CHCl_3$. The solution was washed with a saturated aqueous $NaHCO_3$ and water and evaporated under reduced pressure to afford a 1:1 mixture of (**4a**) and (**4b**) (195 mg, 54%). Fractional recrystallization of the mixture from methanol gave (**4a**) (faster), m.p. 213—215 °C (Found: C, 39.8; H, 4.1; N, 7.7. $C_{12}H_{15}BrN_2O_6$ requires C, 39.69; H, 4.16; N, 7.71%); $\delta_H(CDCl_3)$ 7.47 (1 H, br, HN[3]), 6.19 (1 H, s, 1′-H), 5.07 (1 H, d, *J* 7.69 Hz, 6-H), 4.75 (1 H, d, *J* 5.99 Hz, 2′-H), 4.71 (1 H, d, *J* 5.99 Hz, 3′-H), 4.56 (1 H, d, *J* 2.56 Hz, 4′-H), 4.53 (1 H, d, *J* 7.69 Hz, 5-H), 4.15 (1 H, d, *J* 12.82 Hz, 5′-H), 3.78 (1 H, dd, *J* 12.82 and 2.56 Hz, 5′-H), 1.53 (3 H, s, CH_3), and 1.34 (3 H, s, CH_3); *m/z* 362 (M^+); $[\alpha]_D$ −78.8° (*c* 1 in CH_3OH).

The later fractional precipitate gave (**4b**), m.p. 232—235 °C (Found: C, 39.5; H, 4.05; N, 7.75. $C_{12}H_{15}BrN_2O_6$ requires C, 39.69; H, 4.16; N, 7.71%); $\delta_H(CDCl_3)$ 7.34 (1 H, br, HN[3]), 6.40 (1 H, s, 1′-H), 4.93—4.90 (2 H, m, 6-H and 2′-H), 4.80 (1 H, d, *J* 5.56 Hz, 3′-H), 4.51 (1 H, d, *J* 1.71 Hz, 4′-H), 4.49 (1 H, br, 5-H), 4.24 (1 H, d, *J* 12.83 Hz, 5′-H), 3.82 (1 H, dd, *J* 12.83 and 1.71 Hz, 5′-H), 1.53 (3 H, s, CH_3), and 1.35 (3 H, s, CH_3); *m/z* 362 (M^+); $[\alpha]_D$ −49.5° (*c* 1 in CH_3OH).

Isolation of (6S)-O[6],5′-*Cyclo*-5,6-*dihydro*-2′,3′-O-*isopropylideneuridine* (**5**) *by Irradiation of Compound* (**4a**).—A solution of compound (**4a**) (50.4 mg, 0.14 mmol) in DMF (100 ml) was irradiated for 24 h with a 400-W high-pressure mercury lamp under an N_2 stream. The mixture was evaporated under reduced pressure and the residue was chromatographed on a silica gel column eluting with $CHCl_3$–MeOH (10:1). The faster fractions gave compound (**5**) (30 mg, 76%), m.p. 174—177 °C [lit.,[14] m.p. 156—160 °C (decomp.)] (Found: C, 50.95; H, 5.75; N, 9.85. $C_{12}H_{16}N_2O_6$ requires C, 50.70; H, 5.67; N, 9.86%); $\delta_H(CDCl_3)$ 7.36 (1 H, br, HN[3]), 6.21 (1 H, s, 1′-H), 5.07 (1 H, dd, *J* 5.56 and 8.98 Hz, 6-H), 4.72 (2 H, s, 2′-H and 3′-H), 4.52 (1 H, d, *J* 2.57 Hz, 4′-H), 4.04 (1 H, d, *J* 12.82 Hz, 5′-H), 3.73 (1 H, dd, *J* 2.57 and 12.82 Hz, 5′-H), 2.98 (1 H, dd, *J* 5.56 and 17.09 Hz, 5-H), 2.76 (1 H, dd, *J* 8.98 and 17.09 Hz, 5-H), 1.53 (3 H, s, CH_3), and 1.34 (3 H, s, CH_3); *m/z* 284 (M^+); $[\alpha]_D$ −50.0° (*c* 1 in CH_3OH).

The later fractions gave 5-bromo-2′,3′-*O*-isopropylideneuridine (**2**) (8 mg, 16%), which is identical with an authentic sample.[13]

Irradiation of Compound (**4b**).—A solution of compound (**4b**) (3.5 mg, 0.0096 mmol) in DMF (10 ml) was irradiated for 18 h with a 400 W high-pressure mercury lamp under an N_2 stream. The mixture was evaporated under reduced pressure to give the residue, whose ^1H n.m.r. spectrum in $CDCl_3$ was completely identical with that of (6*S*)-*O*[6],5′-cyclo-5,6-dihydro-2′,3′-*O*-isopropylideneuridine (**5**) obtained above.

Irradiation of (6S)-5,5-*Dibromo*-O[6],5′-*cyclo*-5,6-*dihydro*-2′,3′-O-*isopropylideneuridine* (**3**).—A solution of compound (**3**) (5.1 mg, 0.012 mmol) in DMF (10 ml) was irradiated for 3 h with a 400-W high-pressure mercury lamp under an N_2 stream. The solvent was removed under reduced pressure to give a 52:48 mixture of (**4a**) and (**4b**), whose ratio was estimated by inspecting the ^1H n.m.r. spectrum of the mixture in $CDCl_3$.

Conversion of Compound (**4a**) *into Compound* (**2**) *in* CD_3OD *as Monitored by N.m.r.*—Compound (**4a**) (3.5 mg, 0.0097 mmol) was dissolved in CD_3OD (1 ml) in an n.m.r. tube with tetramethylsilane as an internal standard. The peak height of the 1′-H signal at 6.11 (**4a**) and the 6-H signal at 8.33 (**2**) were measured at 28 °C. The ratio of (**4a**):(**2**) reached 97.5:2.5 after 0.08 h, 63.5:36.5 after 1 h, 38.8:61.2 after 2 h, 27.7:72.3 after 2.75 h, 23.4:76.6 after 3.33 h, 15.1:84.9 after 4.33 h, and 6.0:94.0 after 6.5 h.

Conversion of Compound (**4b**) *into Compound* (**2**) *in* CD_3OD *as Monitored by N.m.r.*—Compound (**4b**) (3.5 mg, 0.0097 mmol) was dissolved in CD_3OD (1 ml) in an n.m.r. tube with tetramethylsilane as an internal standard. The peak height of the 1′-H signal at 6.27 (**4b**) and the 6-H signal at 8.33 (**2**) were measured at 28 °C. The ratio of (**4b**):(**2**) reached 91.7:8.3 after 0.5 h, 86.4:13.6 after 1.25 h, 80.9:19.1 after 2.17 h, 65.6:34.4 after 4 h, 63.5:36.5 after 5 h, 53.5:46.5 after 7 h, and 45.9:54.1 after 10 h.

Reaction of Compound (**4a**) *with* NaOMe.—A suspension of compound (**4a**) (100 mg, 0.28 mmol) in methanolic NaOMe [prepared from Na (6.4 mg, 0.28 mmol) in absolute MeOH (10 ml)] was refluxed for 5 min. The mixture was neutralized with Amberlite CG-50 (H^+) and evaporated under reduced pressure. Recrystallisation of the residue from EtOH gave compound (**2**) (90 mg, 90%), which is identical with the product prepared above.

Reaction of Compound (**4b**) *with* NaOMe.—A suspension of compound (**4b**) (100 mg, 0.28 mmol) in methanolic NaOMe [prepared from Na (6.4 mg, 0.28 mmol) in absolute MeOH (10 ml)] was refluxed for 5 min. The mixture was neutralized with Amberlite CG-50 (H^+) and evaporated under reduced pressure. Recrystallisation of the residue from EtOH gave compound (**2**) (94 mg, 94%), which is identical with the product prepared above.

Conversion of Compounds (**4a**) *and* (**4b**) *into Compound* (**2**) *in* 1M NaOH *Solution*.—Stirring of a solution of (**4a**) and (**4b**) (2 mg) in 1M aqueous NaOH (2 ml) at room temperature for 5 min resulted in formation of compound (**2**), which was confirmed by t.l.c. comparison with the product prepared above.

Epimerisation of Compounds (**4a**) *and* (**4b**) *in* $CDCl_3$ *in the Presence of* AcOH *as Monitored by N.m.r.*—Compound (**4a**) (*ca.* 1 mg) was dissolved in $CDCl_3$ (1 ml) in an n.m.r. tube with tetramethylsilane as an internal standard and AcOH (1 drop) was added to it. The peak height of the 1′-H signals at 6.19 (**4a**) and 6.40 (**4b**) were measured over a period of 168 h at 60 °C. The ratio of (**4a**):(**4b**) reached 91.5:8.5 after 6.7 h, 78.8:22.2 after 25.5 h, 66.3:33.7 after 44 h, 56.7:43.3 after 68 h, 50.9:49.1 after 91 h, 45.1:54.9 after 139 h, and 43.8:56.2 after 168 h.

Compound (**4b**) (*ca.* 1 mg) was dissolved in $CDCl_3$ (1 ml) in an n.m.r. tube with tetramethylsilane as an internal standard and AcOH (1 drop) was added. The peak height of the 1′-H signals at 6.40 (**4b**) and 6.19 (**4a**) were measured over a period of 188 h at 60 °C. The ratio of (**4b**):(**4a**) reached 98.3:1.7 after 1 h, 94.1:5.9 after 4 h, 90.8:9.2 after 8 h, 82.1:17.9 after 24 h, 73.0:27.0 after 47 h, 70.9:29.1 after 53.7 h, 65.5:34.5 after 71 h, 63.2:36.8 after 93 h, 60.6:39.4 after 117 h, and 56.6:43.4 after 188 h.

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