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Synthesis of conformationally locked *C*-nucleosides having a 2,5-dioxabicyclo[2.2.1]heptane ring system

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Abstract

Some novel *C*-nucleosides having a 2,5-dioxabicyclo[2.2.1]heptane ring system were successfully synthesized via the coupling reaction of tetrahydrofurancarbaldehyde **1** with the lithium and the magnesium derivatives of aromatic heterocycles.

Keywords: nucleic acid analogues; bicyclic heterocyclic compounds; nitrogen heterocycles; Mitsunobu reactions.

Conformationally locked nucleosides constitute a class of molecules for antisense and antigene applications, which have been the focus of extensive work.[1] We have recently accomplished the first synthesis of 2′-*O*,4′-*C*-methyleneribonucleosides having a fixed N-form sugar conformation,[2] which were found to have potent RNA recognition ability when they were introduced into oligonucleotides.[3–7] On the other hand, natural and unnatural *C*-nucleosides have received a great deal of attention because of their potent biological activities, such as antiviral and antitumor activities.[8–10] Despite their importance, there is limited information available on the relationship between the conformation of *C*-nucleosides and their biological activities. Furthermore, *C*-nucleosides, unlike the natural nucleosides, can possess a great variety of heterocycles; therefore, the *C*-nucleoside analogues with fixed N-conformation are also of interest for antisense and antigene applications, along with their biological activities. Herein we report the first convenient synthesis of conformationally locked *C*-nucleosides having a 2,5-dioxabicyclo[2.2.1]heptane ring system.

The aldehyde **1** is used as a key building block for the synthesis of the bicyclic *C*-nucleosides. The synthetic route to **1** is shown in Scheme 1. Its synthesis started from 4-hydroxymethyl derivative **2**,[11] which was monosilylated by a *tert*-butyldiphenylsilyl group to afford **3** (70%).† Toluene-*p*-sulfonylation of **3** gave **4** (98%) and then acidic hydrolysis of **4** afforded diol **5** (77%). Because the reaction of diol **5** under the alkaline conditions was found to give the oxetane product **6** (43%) along with the desired product **7** (35%),[12] the C_3-hydroxy group was selectively protected according to the previously

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† The stereochemistry of **3**, **8** and **14** was confirmed by ^{1}H NMR and NOE measurements.

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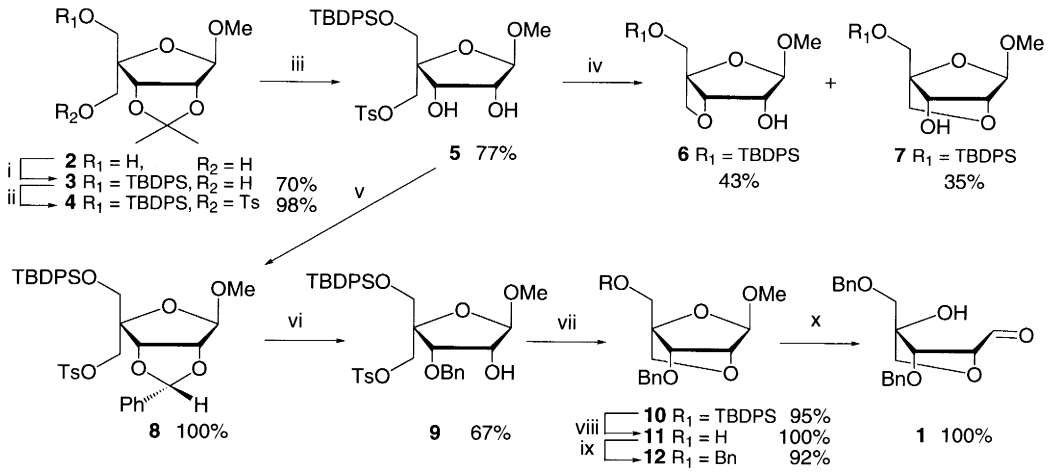
reported procedure.[2] The diol **5** was initially treated with benzaldehyde and zinc chloride to give 2,3-*O*-benzylidene derivative **8** (100%) as the sole diastereoisomer.† In the presence of titanium tetrachloride, 2,3-*O*-benzylidene **8** was treated with sodium cyanoborohydride in acetonitrile to afford 3-*O*-benzyl derivative **9** (67%) along with a 2-*O*-benzyl derivative (27%). Upon exposure of **9** to sodium hexamethyldisilazide in tetrahydrofuran, bicyclic methyl ribofuranoside **10** was obtained (95%). Deprotection at the 5-hydroxy group in **10** (**10**→**11**, 100%) followed by substitution by a benzyl group gave **12** (**11**→**12**, 92%), which was treated with 10% HCl to give the desired compound **1** successively (100%).‡ From analysis of the ^{1}H NMR spectrum, **1** was found to exist in an aldehyde form (not a hemiacetal form) because of the ring strain derived from the 2-*O*,4-*C*-methylene bridge.



Scheme 1. Reagents and conditions: (i) TBDPSCl (2.2 equiv.), Et_3N, CH_2Cl_2, rt; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (iii) CF_3COOH:THF:H_2O (14:8:3), rt; (iv) $(Me_3Si)_2NNa$ (10 equiv.), THF:benzene (5:2), rt; (v) PhCHO, $ZnCl_2$, rt; (vi) $NaBH_3CN$ (5 equiv.), $TiCl_4$ (5 equiv.), MeCN, rt; (vii) $(Me_3Si)_2NNa$, THF, rt; (viii) TBAF, THF, rt; (ix) BnBr, NaH, DMF, rt; (x) 10% HCl, THF, rt

Next, the aldehyde **1** was coupled with the magnesium and the lithium derivatives of some aromatic heterocycles as shown in Table 1. The magnesium derivative of 2-phenyl-5-oxazole gave the *S*-epimer of compound **13a** as a main product, while those of 2-pyridine, *N*-triisopropylsilyl-3-pyrrole and 2-*tert*-butyldiphenylsilyl-1-*N*,*N*-dimethylsulfamoyl-5-imidazole afforded the *R*-epimer of **13b**, **13c** and **13d**, respectively.§ This stereoselectivity may be explained by the *re*-face attack of nucleophiles on the carbonyl group of the chelation model,¶ as illustrated in Fig. 1. On the other hand, the lithium salts of heterocycles also gave the corresponding products; however, significant stereoselectivities were not observed.

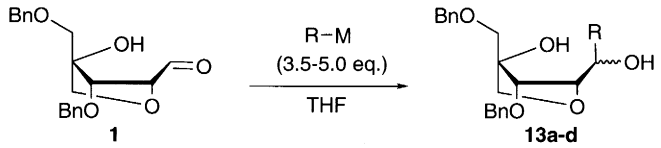
After separation of the *R*- and *S*-epimers of **13a**–**c** by silica gel column chromatography, these compounds were cyclized under typical Mitsunobu conditions.[15–17] As shown in Table 2, *S*-**13a** and *R*-**13b**, which were obtained as major products in the coupling reaction of **1** with magnesium salts, were treated with diethyl azodicarobxylate (DEAD) and triphenylphosphine (TPP) in tetrahydrofuran

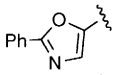
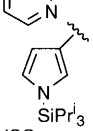
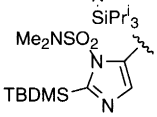
‡ Recently, the aldehyde **1** was alternatively prepared by Wengel et al.[13,14]

§ The stereochemistry of **13** was determined from the structure of their cyclization products **14**.

¶ A similar chelation model for 2,3,5-tri-*O*-benzyl-D-ribofuranose was reported by Yokoyama et al.[15]

Table 1
Coupling reaction of **1** with some aromatic heterocycles



R	M	Temp/°C	Time/h	Product	Yield (%)[a] (*R*/*S*)[b]	
	MgBr	20	18	**13a**	70	(8/92)
	Li	-78 → 30	2		82	(33/67)
	MgBr	20 → 50	3	**13b**	65	(85/15)
	Li	-78	3		56	(22/78)
	MgBr	20	2	**13c**	81	(98/2)
	Li	-78 → 20	2		56	(50/50)
	MgBr	20	2	**13d**	72	(90/10)
	Li	-78 → 20	2		80	(69/31)

a. Isolated yield of the mixture of *R*- and *S*-**13**. *b*. Determined by ^{1}H NMR measurements.

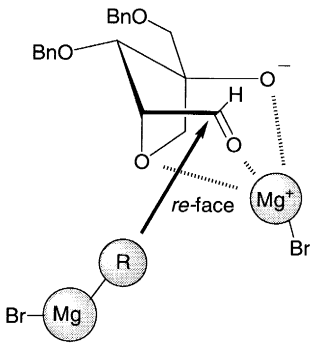


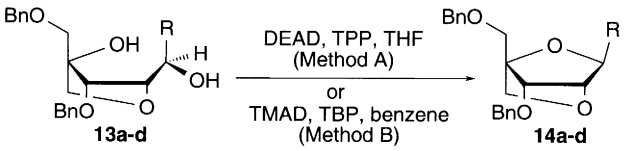
Fig. 1. Proposed chelation model

to give only bicyclic β-*C*-nucleosides **14a**,**b** in good yields,[‖] while *S*-**13c** gave the anomeric mixtures of **14c** (α:β=29:71). This is probably due to the partial S_N1-type reaction caused by the electron-donating feature of the *N*-silylated pyrrole ring. A mixture of *R*- and *S*-**13d** (*R*:*S*=90:10) was also employed for this ring-closure reaction by treatment with 1,1′-azobis(*N*,*N*-dimethylformamide) (TMAD) and tributylphosphine (TBP) in benzene to afford the desired product **14d** (α:β=10:90). α-Anomeric *C*-nucleosides were also obtained by using *R*-**13a**, *S*-**13b** and *S*-**13c** as shown in Table 3.[†]

Thus, we have successfully achieved the synthesis of conformationally locked *C*-nucleoside analogues

[‖] In the ^{1}H NMR spectra, β-**14** showed all singlet signals for $C_{1'}$-, $C_{2'}$- and $C_{3'}$-protons, which clearly indicate that the conformation of β-**14** is locked in N-form.[2] β-**14a**: ^{1}H NMR ($CDCl_3$) δ: 3.86 (2H, s), 4.12, 4.16 (2H, ABq, *J*=8 Hz), 4.35 (1H, s), 4.41 (1H, s), 4.62, 4.71 (2H, ABq, *J*=12 Hz), 4.62 (2H, s), 5.13 (1H, s), 7.02 (1H, s), 7.31–7.32 (10H, m), 7.43–7.46 (3H, m), 7.86 (2H, d, *J*=7 Hz). β-**14b**: ^{1}H NMR ($CDCl_3$) δ: 3.85 (2H, s), 4.02 (1H, s), 4.12, 4.13 (2H, ABq, *J*=8 Hz), 4.43, 4.58 (2H, ABq, *J*=12 Hz), 4.61 (1H, s), 4.66 (2H, s), 5.18 (1H, s), 7.14–7.36 (11H, m), 7.51 (1H, d, *J*=8 Hz), 7.65 (1H, ddd, *J*=2, 8, 8 Hz) 8.54 (1H, d, *J*=5 Hz).

Table 2
Synthesis of β-anomeric *C*-nucleosides

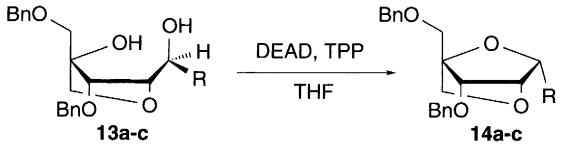


13a-d **14a-d**

Substrate	Method	Temp/°C	Time/h	Product	Isolated yield (%) (α/β)	
S-**13a**	A	0 → 20	6	**14a**	90	(0/100)
R-**13b**	A	0	3	**14b**	80	(0/100)
R-**13c**	A	20	12	**14c**	59[a]	(29/71)[b]
R-**13d** (*R*/*S*=90/10)	B	20	15	**14d**	90[a]	(10/90)[b]

a. Isolated yield of the anomeric mixture of **14**. *b*. Determined by ^{1}H NMR measurements.

Table 3
Synthesis of α-anomeric *C*-nucleosides



13a-c **14a-c**

Substrate	Temp/°C	Time/h	Product	Isolated yield (%) (α/β)	
R-**13a**	0	2	**14a**	72	(100/0)
S-**13b**	0 → 20	4	**14b**	64	(100/0)
S-**13c**	20	3	**14c**	86[a]	(78/22)[b]

See footnotes in Table 2.

14 through the coupling reaction of aldehyde **1** with the lithium and the magnesium derivatives of some aromatic heterocycles, and the subsequent Mitsunobu-type ring-closure reaction. Work on further chemical modification and some application of bicyclic *C*-nucleosides **14** is now in progress.

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