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Stereoselective Synthesis of Alkynyl *C*-2-Deoxy-β-D-ribofuranosides via Intramolecular Nicholas Reaction: A Versatile Building Block for Nonnatural *C*-Nucleosides

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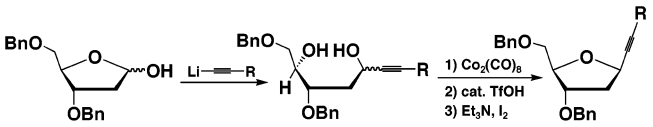
ABSTRACT



R = $SiMe_3$: $\beta/\alpha > 99$

The reaction of 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranose with various alkynyllithium reagents afforded diastereomeric mixtures of the corresponding ring-opened alkynyldiols. The resulting diastereomeric mixtures were successively treated with $Co_2(CO)_8$, a catalytic amount of TfOH, Et_3N, and iodine in one pot to give alkynyl *C*-3,5-di-*O*-benzyl-2-deoxy-β-D-ribofuranosides with high β-selectivities. The cobalt-mediated cyclization (intramolecular Nicholas reaction) is reversible; thus, thermodynamically more stable β-anomers were obtained preferentially. The alkynyl *C*-deoxyribofuranosides were converted to a variety of *C*-deoxyribofuranoside derivatives.

The significant and diverse pharmaceutical value of various *C*-glycosides has inspired investigations into developing new synthetic methods for their practical preparation.[1] Among the *C*-glycosides, alkynyl *C*-glycosides are attracting much attention because of the synthetic flexibility of the acetylenic function.[2] To the best of our knowledge, however, only one example of the synthesis of alkynyl *C*-2-deoxy-D-ribofuranosides has been reported, in which the weakly selective formation of the less important α-anomer was attained.[3] In our continuous studies on the development of synthetic receptors for nucleobases and its application to nonnatural oligonucleotides, we were confronted with difficulties in the preparation of alkynyl *C*-2-deoxy-β-D-ribofuranosides. Thus, we report herein a new approach for the stereoselective synthesis of the alkynyl *C*-deoxyribofuranosides.[4]

In the initial attempt for the synthesis of the furanosides, we examined the Mitsunobu cyclization of the alkynylated diol **2a**, which was prepared from 3,5-di-*O*-benzyl-

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(1) Recent books and reviews: (a) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*; Gordon and Breach: Amsterdam, 2001. (b) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (c) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. (d) Postema, M. H. D. *C-Glycoside Synthesis*; CRC: Boca Raton, FL, 1995. (e) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (f) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599.

(2) Recent reviews: (a) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665−2676. (b) Isobe, M. *J. Synth. Org. Chem., Jpn.* **1994**, *52*, 968−979. Some examples were also seen in ref 1.

(3) Wamhoff, H.; Warnecke, H. *ARKIVOC* (online computer file) **2001**, *2*, 1085−1090.

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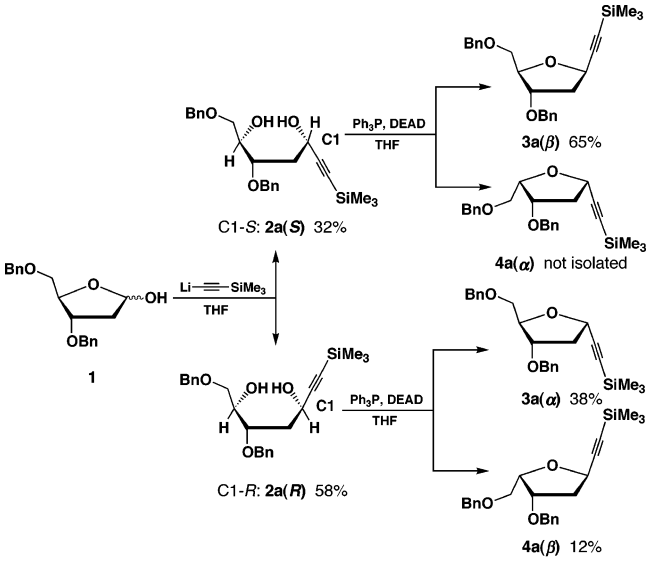
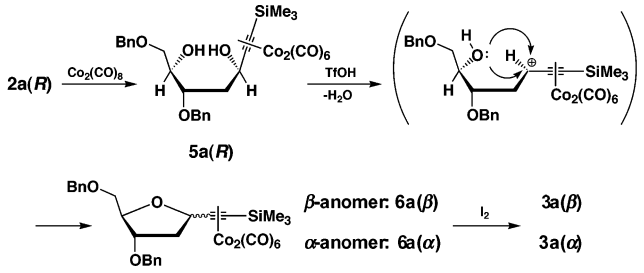
Scheme 1



2-deoxy-D-ribofuranose (**1**)[5] with (trimethylsilyl)ethynyllithium (Scheme 1). The diol **2a** was a mixture of two epimers (32 and 58%), and the ratio of the epimers was scarcely influenced by changing the reaction conditions. After treatment with standard Mitsunobu reagents (Ph_3P, DEAD),[6] **2a(*S*)** gave one cyclized product **3a(*β*)** and the other epimer **2a(*R*)** gave two cyclized products **3a(α)** and **4a(*β*)**.[7] The stereochemistry of the resulting furanosides was determined by NOE experiments[8] and derivatization of **3a(*β*)** to the known compound reported by Woerpel et al.,[5,8] while the C1 configurations of the starting diols **2a** were assigned on the basis of the stereochemistry of **3a** and **4a**, considering Mitsunobu inversion. The diol **2a(*S*)** was converted to the desired *β*-anomer **3a(*β*)** in 65% yield; on the other hand, α-anomer **3a(α)** and C4-inverted diastereomer **4a(*β*)**[9] were obtained from **2a(*R*)** in 38 and 12% yields, respectively. Unfortunately, Tsunoda modification[10] of the Mitsunobu reaction revealed no improvement of the product yield. Thus, the two-step reaction from **1** gave **3a(*β*)** in only 23% yield accompanied with troublesome separation of the diastereoisomers.

We thought that the useless diol **2a(*R*)** could be transformed to the desired **3a(*β*)** via an intramolecular Nicholas reaction.[11] Complexation of the alkynyl group of **2a(*R*)** with dicobalt octacarbonyl ($Co_2(CO)_8$) would afford **5a(*R*)**. In this complex, the $Co_2(CO)_6$-alkyne functionality stabilizes the adjacent sp^2-hybridized carbocation formed by treatment with acid, bringing about the loss of configuration at C1. The following nucleophilic attack of the C4-OH on the stablized carbocation may at least partly afford **6a(*β*)**. Treatment of **2a(*R*)** with 1.2 equiv of $Co_2(CO)_8$ in CH_2Cl_2 gave rise to the corresponding **5a(*R*)** in a quantitative yield. Cyclization of **5a(*R*)** to **6a** smoothly proceeded in the presence of 0.1 equiv of trifluoromethanesulfonic acid (TfOH) at 25 °C in CH_2Cl_2 (Scheme 2). Surprisingly, only one cyclized product

Scheme 2



6a(*β*) was obtained, which was determined to be the desired anomer after decomplexation with iodine to **3a(*β*)** in 93% overall yield. The reaction was also successful when the diastereomeric mixture of **2a** was used, and the reaction sequence of the complexation, cyclization, and decomplexation could be conducted in one pot. Indeed, a mixture of **2a(*S*)** and **2a(*R*)** was treated with $Co_2(CO)_8$, TfOH, Et_3N (for neutralization of TfOH), and iodine to yield **3a(*β*)** in 90% yield. In the conventional cyclization method utilizing TsCl and pyridine,[4a] **2a(*S*)** gave **3a(*β*)** and **4a(α)** in 51 and 8% yields, respectively, and **2a(*R*)** gave **3a(α)** and **4a(*β*)** in 59 and 7% yields, respectively.

This reaction sequence is applicable to a wide variety of alkynes. Thus, (trimethylsilyl)ethynyl, ethynyl, alkylethynyl, arylethynyl, heteroarylethynyl, and (allyloxymethyl)ethynyllithium or magnesium reagents could be used for the alkynylation. The complexation and following reactions afforded the corresponding alkynyl *C*-2-deoxy-D-ribofuranosides in high yields with high *β*-selectivities (Table 1).

Next, we tried to elucidate this high *β*-selectivity. The isolated **6a(α)** was subjected to the reaction conditions for

(4) On the other hand, various methods have been reported for the synthesis of alkynyl *C*-*β*-D-ribofuranosides: (a) Buchanan, J. G.; Edgar, A. R.; Power, M. J. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1943−1949. Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1191−1200. (b) Arakawa, K.; Miyasaka, T.; Hamamichi, N. *Chem. Lett.* **1976**, 1119−1122. Hamamichi, N.; Miyasaka, T.; Arakawa, K. *Chem. Pharm. Bull.* **1978**, *26*, 898−907. (c) De Las Heras, F. G.; Tam, S. Y.-K.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 84−90. Tam, S. Y.-K.; Klein, R. S.; De Las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854−4862. (d) Alonso, G.; Garcia-Lopez, M. T.; Garcia-Muñoz, G.; Madroñero, R. *An. Quim.* **1976**, *72*, 987−990. (e) Gupta, C. M.; Jones, G. H.; Moffatt, J. G. *J. Org. Chem.* **1976**, *41*, 3000−3009. (f) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501−2505. (g) Rycroft, A. D.; Singh, G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2667−2668. (h) Maqbool, Z.; Hasan, M.; Pott, K. T.; Malik, A.; Nizami, T. A.; Voelter, W. *Z. Naturforsch* **1997**, *52b*, 1383−1392.

(5) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208−12209. See Supporting Information of this paper.

(6) Reviews for Mitsunobu reaction: Mitsunobu, O. *Synthesis* **1981**, 1−28. Hughes, D. L. In *Organic Reaction*; Paquette, L. A., Ed.; John Wiley: New York, 1992; Vol. 42, pp 335−656.

(7) Weizman, H.; Tor, Y. *J. Am. Chem. Soc.* **2001**, *123*, 3375−3376.

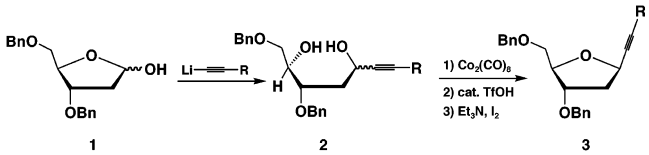
(8) See Supporting Information.

(9) This type of C4 inversion was also seen in the preparation of *C*-aryl ribofuranosides: Yokoyama, M.; Toyoshima, A.; Akiba, T.; Togo, H. *Chem. Lett.* **1994**, 265−268.

(10) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539−542. Itô, S.; Tsunoda, T. *Pure Appl. Chem.* **1994**, *66*, 2071−2074.

(11) Reviews for Nicholas reaction: (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214. (b) Smith, W. A.; Caple, R.; Smoliakova, I. P. *Chem. Rev.* **1994**, *94*, 2359−2382.

Table 1. Various Alkynylation and the Following Intramolecular Nicholas Reaction

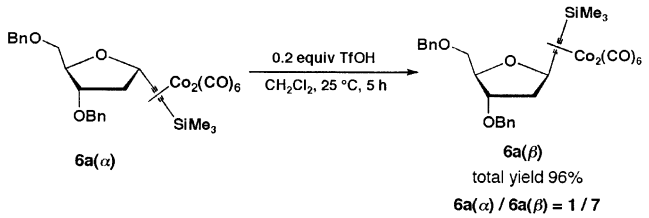


R	2	yield (%)	epimer ratio[a]	3	yield (%)	α:β[a]
$SiMe_3$	**2a**	90	36 (*S*):64 (*R*)	**3a**	90	1:99
H (BrMgC≡CH)	**2b**	83	34:66	**3b**	62	32:68
C_4H_9-*n*	**2c**	84	46:54	**3c**	62	8:92
Ph	**2d**	90	34:66	**3d**	99	12:88
2-pyrenyl	**2e**	90	34:66	**3e**	97	13:87
2-thienyl	**2f**	97	37:63	**3f**	78	10:90
$CH_2OCH_2CH{=}CH_2$	**2g**	89	39:61	**3g**	75	4:96

[a] Diastereomeric ratios were determined by isolated yields.

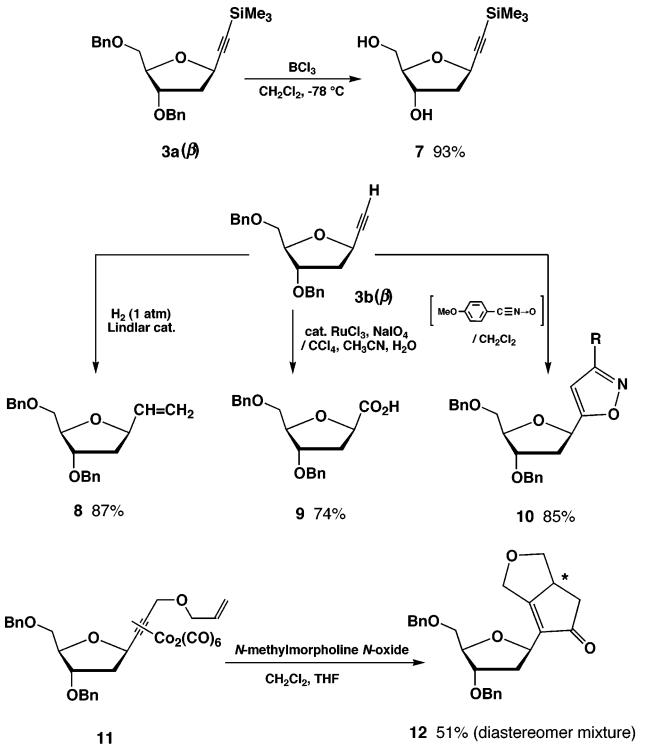
the cyclization (0.2 equiv of TfOH, 25 °C in CH_2Cl_2). The epimerization from **6a(α)** to **6a(*β*)** occurred, and the final ratio of **6a(α)** to **6a(*β*)** was found to be 1:7 (Scheme 3).[12] This ratio was slightly different from the value obtained by one-pot cyclization, indicating that further epimerization may proceed under the subsequent conditions for neutralization and decomplexation. This epimerization demonstrated that the *β*-anomer of the complex is thermodynamically more stable than the α-anomer, and both complexes were equilibrated under the acidic conditions.[13] The thermodynamic difference between **6a(α)** and **6a(*β*)** is still unknown and remains to be elucidated.

Scheme 3



The alkynyl *C*-deoxyfuranosides thus prepared have a wide flexibility for the synthesis of various classes of *C*-deoxyribofuranosides (Scheme 4). The (trimethysilyl)ethynyl moiety of **3a(*β*)** survived under the condition for the deprotection of the benzyl groups with BCl_3,[14] leaving unprotected (trimethylsilyl)ethynyl *C*-2-deoxyribofuranoside **7** in 93% yield. A parent ethynyl *C*-deoxyribofuranoside **3b(*β*)** was converted to vinyl *C*-2-deoxy-*β*-D-ribofuranoside **8** by Lindlar reduction and to *C*-carboxyl 2-deoxy-*β*-D-ribofuranoside **9** by oxidative cleavage of the acetylenic bond.[15] The latter product represents 2-deoxy-*β*-D-ribofuranoside with one carbon at the anomeric position. The acetylenic group can easily be transformed to various substituents with more than two carbon atoms. Thus, the reaction sequences described herein provide all kinds of building blocks covering most of *C*-2-deoxy-D-ribofuranoside. Furthermore, the acetylenic bond is a versatile precursor for the construction of various heterocycles, which was demonstrated by 1,3-dipolar cycloaddition[16] of **3b(*β*)** with nitrile *N*-oxide to afford *C*-isoxazolyl deoxyribofuranoside **10**. Alkynes possessing an external alkene moiety exhibit another notable extension of the reaction. The cobalt complex **11**, the precursor of **3g(*β*)**, was directly subjected to the conditions for Pauson−Khand reaction[17] to afford a novel bicyclic cyclopentenone-attached *C*-2-deoxy-D-ribofuranoside **12**. These types of *C*-nucleosides may be attracting much attention from the viewpoint of antiviral and antitumor drugs.[1a]

Scheme 4



In summary, we developed an effective method for the synthesis of various alkynyl *C*-2-deoxy-D-ribofuranosides with high *β*-selectivity. The reaction is applicable to a many kinds of alkynes, and the complexation, cyclization, and decomplexation steps can be conducted in one pot. We are currently investigating the utilization of the *C*-nucleosides

(12) Extra $Co_2(CO)_8$ (ca. 0.2 equiv) was added to preserve **6a** from decomposition.

(13) Isobe et al. reported similar phenomena in the cases of the cobalt complexes of the alkynyl *C*-pyranose ring: see ref 2.

(14) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923−1925.

(15) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(16) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Caramella, P., Grunanger, P., Eds.; Wiley & Sons: New York, 1984; Vol. 1, pp 322−356.

(17) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199−7205.

as building blocks in oligonucleotides and their application to the antisense DNA strategy.

Supporting Information Available: Experimental procedures and characterization data of all new compounds; NOESY spectra of **3a(*β*)**, **4a(*β*)**, **3a(α)**, and **4a(α)**; and ^{1}H NMR spectra of **5a(*R*)**, **5a(*S*)**, **6a(*β*)**, **6a(α)**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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