ORGANIC
LETTERS

2007
Vol. 9, No. 22
4443−4446

Studies on the Generation of Unnatural *C*-Nucleosides with 1-Alkynyl-2-deoxy-D-riboses

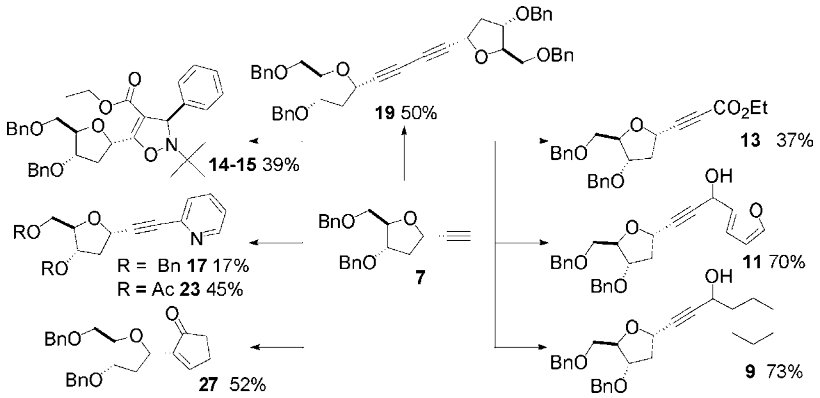
Mauro F. A. Adamo* and Roberto Pergoli

Centre for Synthesis and Chemical Biology (CSCB), Department of Pharmaceutical
and Medicinal Chemistry, The Royal College of Surgeons in Ireland,
123 St. Stephen's Green, Dublin 2, Dublin, Ireland

madamo@rcsi.ie

Received July 26, 2007

ABSTRACT



1-Alkynyl-2-deoxy-D-riboses 7 and 8 were independently synthesized and subsequently used to generate several novel *C*-nucleosides.

The discovery of new chemotherapeutic treatments for controlling microbial infections is an important topic in medicinal chemistry. Nucleosides and nucleoside biochemistry lie at the heart of life and life propagation, and therefore nucleoside analogues have attracted much attention as potential antimicrobial and antitumor agents. Many nucleosides of natural origin have been found to be bioactive. Bredinine[1] (Mizoribine) is an imidazole nucleoside antibiotic clinically used as an immunosuppressant;[2] Toyocamycin,[3] Mycalisin A,[4] and Thiosangivamycin[3] are three naturally occurring nucleosides exerting potent antiviral and antineoplastic activity; Pseudouridine,[5] Showdomycin,[6] Pyrazofurin,[7] and Tiazofurin[8] have been shown to possess a wide range of medicinal properties, including antibiotic, antiviral, and antitumor activity. *C*-Nucleosides belonging to the 2-deoxy-D-ribose series have been scarcely explored and at present no data are available on the biological activity of nucleosides of the α-anomeric series.[9] In recent times interest increased on the medicinal chemistry of alkynyl-substituted

---

(1) Mizuno, K.; Tsujino, M.; Takada, M.; Hayashi, K.; Atsumi, K.; Asano, K.; Matsuda, T. *J. Antibiot.* **1974**, *27*, 775.

(2) Amenmiya, H.; Itoh, H. In *Immunosuppressive Drugs*: *Developments in Anti-rejection Therapy*; Thompson, A. W., Starzt, T. E., Eds.; Edward Arnord: London, UK, 1993; p 161. Giruber, S. A. *Immunol. Rev.* **1992**, *129*, 5. Turka, L. A.; Dayton, J.; Sinclair, G.; Thomson, C. B.; Mitchell, B. S. *J. Clin. Invest.* **1991**, *87*, 940.

(3) Krawczyc, S. H.; Nassiri, M. R.; Kucera, L. S.; Kern, E. R.; Ptak, R. G.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1995**, *38*, 4106.

(4) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1985**, *29*, 3483.

(5) Buchanan, J. G.; Wightman, R. H. *Top. Antibiot. Chem.* **1982**, *6*, 229.

(6) Mubarak, A. M.; Brown, D. M. *Tetrahedron Lett.* **1981**, *22*, 683.

(7) Shaban, M. A. E.; Nasr, A. Z. *Adv. Heterocycl. Chem.* **1997**, *68*, 223.

(8) Sallam, M. A. E.; Luis, F. F.; Cassady, J. M. *Nucleosides Nucleotides* **1998**, *17*, 769.

(9) Adamo, M. F. A.; Adlington, R. M.; Baldwin, J. E.; Day, A. L. *Tetrahedron* **2004**, *60*, 841.

10.1021/ol701794u CCC: $37.00 © 2007 American Chemical Society
Published on Web 10/02/2007

nucleosides.[10,11] For instance, Matzuda described the synthesis of 3′-alkynyl cytosine and 3′-alkynyl uridine.[10] The presence of an additional electrophilic element (alkyne) imparted to these molecules a high antitumor activity. Additionally, 4′-alkynyl nucleosides have been prepared and found to be remarkably active against HIV.[11] The high activity displayed by 3′- and 4′-alkynyl nucleosides poses questions about the activity of other alkynyl nucleosides including 1-alkynyl nucleoside analogues. With this in mind, we set out to develop a synthetic route to families of *C*-nucleosides **1** and **2** (Figure 1) that (a) allows the inclusion of a wide variety of heterocyclic moieties, (b) allows the introduction of an alkynyl moiety at C-1′, and (c) allows the preparation of α and *β* *C*-nucleosides independently. We now report a preliminary account of the studies we have undertaken.

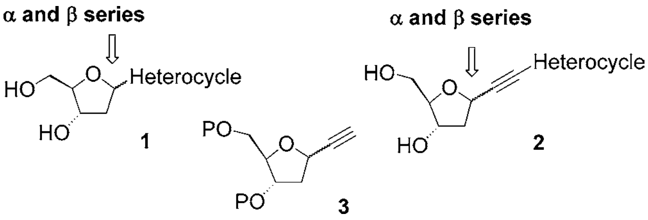
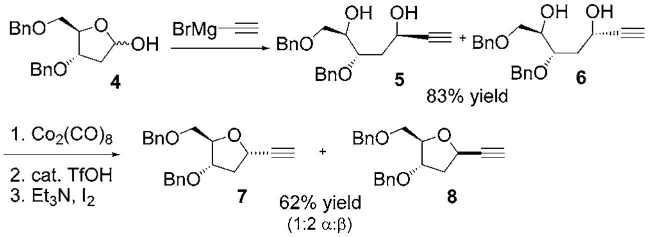


Figure 1. A family of 2-deoxyribose-based *C*-nucleosides.

A retrosynthetic analysis of *C*-nucleosides **1** and **2** identified 1-alkynyl-2-deoxy-D-ribose **3** as a key synthon for their preparation. For example, several compounds of general structure **1** could potentially be prepared from **3** by reacting the alkyne moiety in a cycloaddition reaction with various 1,3-dipoles. Alternatively, 1-alkynyl *C*-nucleosides of structure **2** could be obtained from **3** through a Sonogashira coupling or through a reaction with a suitable electrophile. A literature survey revealed that the preparation of 1-alkynyl-2-deoxy-D-riboses **7** and **8** has been reported.[12] In this report, **4** (Scheme 1) was converted to **7** and **8** by treatment with alkynylmagnesium bromide followed by intramolecular Nicholas reaction.

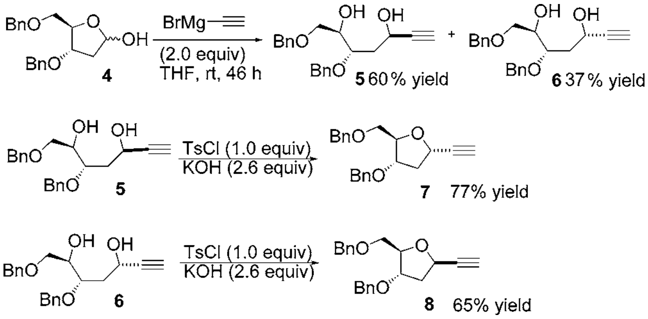
On the basis of this report, we have developed a more practical synthesis of compounds **7** and **8** that allowed their selective preparation independently (Scheme 2). In our synthesis, 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranose **4** was reacted with ethynylmagnesium bromide and the resulting diastereoisomeric diols **5** and **6** were subsequently separated by SiO_2 column chromatography. Diols **5** and **6** were then independently reacted with *p*-toluenesulfonyl chloride and base to obtain **7** and **8**, respectively, in stereospecific fashion.

Scheme 1. Inouye's Synthesis of Scaffolds **7** and **8**[12]



The stereochemistry at the anomeric position was assigned by NOE experiments: in the *β* anomer, positive NOE was observed between the anomeric H-5 and H-2; in the α anomer, positive NOE was observed between the anomeric H-5 and H-3 and between the anomeric H-5 and H-6.

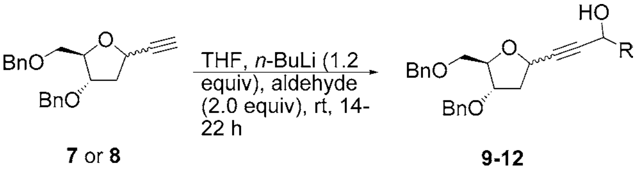
Scheme 2. Stereospecific Synthesis of **7** and **8**



This route offered the advantage of avoiding the use of highly sensitive $Co_2(CO)_8$ and rendered the preparation of **7** and **8** operationally simpler. Additionally, the chromatographic separation of **5** and **6** was easier compared to the separation of **7** from **8**. With compounds **7** and **8** in hand, we explored their potential for the preparation of *C*-nucleosides of structures **1** and **2**.

We began our studies by generating the lithium alkynoates of **7** and **8** (Scheme 3 and Table 1) and then reacting them with aromatic or aliphatic aldehydes. 2-Furaldehyde and cyclohexylcarboxaldehyde were selected as examples of an aromatic and an aliphatic aldehyde. We were delighted to observe that, in these experiments, propargylic alcohols **9**−**12** were obtained in high isolated yields (Scheme 3 and Table

Scheme 3. Preparation of Propargyl Alcohols **9**−**12**



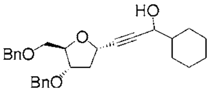
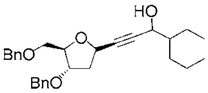
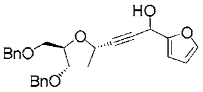
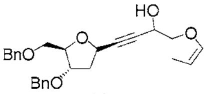
---

(10) Hattori, H.; Nozawa, E.; Iino, T.; Yoshimura, Y.; Shuto, S.; Shimamoto, Y.; Nomura, M.; Fukushima, M.; Tanaka, M.; Sasaki, T.; Matzuda, A. *J. Med. Chem.* **1998**, *41*, 2892.

(11) Ohrui, H.; Kohgo, S.; Kitano, K.; Sakata, S.; Kodama, E.; Yoshimura, K.; Matsuoka, M.; Shigeta, S.; Mitzuya, H. *J. Med. Chem.* **2000**, *43*, 4516.

(12) Masayoshi, T.; Morikawa, T.; Abe, H.; Inouye, M. *Org. Lett.* **2003**, *5*, 625.

Table 1. Isolated Yields of Propargyl Alcohols **9**−**12** (Scheme 3)

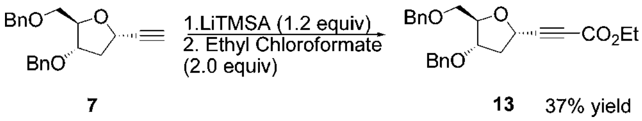
entry	starter	aldehyde	product	yield %[a]
1	**7**	Cyclohexyl	 **9**	73
2	**8**	Cyclohexyl	 **10**	72
3	**7**	2-furyl	 **11**	70
4	**8**	2-furyl	 **12**	54

[a] Isolated yields after flash chromatography.

1). Remarkably, in these reactions only one diastereoisomer was obtained.[13]

Lithiated **7** was also used as a starting material for the preparation of alkynyl ester **13** (Scheme 4). We were interested in attaching an electron-withdrawing group to the alkyne since, usually, electronic dissymmetry favors the reactivity of alkynes in 1,3-dipolar cycloadditions.[14]

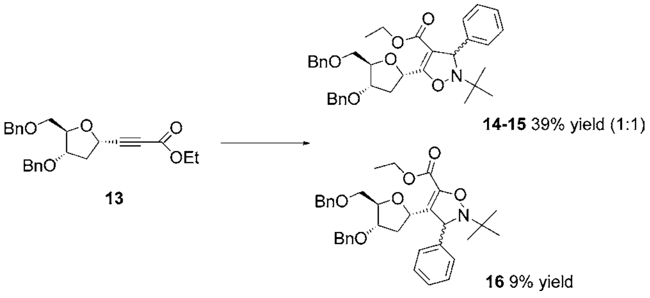
Scheme 4. Preparation of 1-Alkynyl Ester Deoxyribose **13**



Compound **13** was obtained in 37% isolated yield by reaction of **7** with lithium bis(trimethylsilyl)amide (LiTMSA) followed by treatment with ethyl chloroformate[15] (Scheme 4). To explore the potential of **13** for the generation of *C*-nucleosides, we have reacted **13** with phenyl *N*-*tert*-butylbenzyl nitrone (Scheme 5). Several reports described the 1,3-dipolar cycloaddition of nitrones to propargylic esters as proceeding with high levels of regio- and diastereoselectivity.

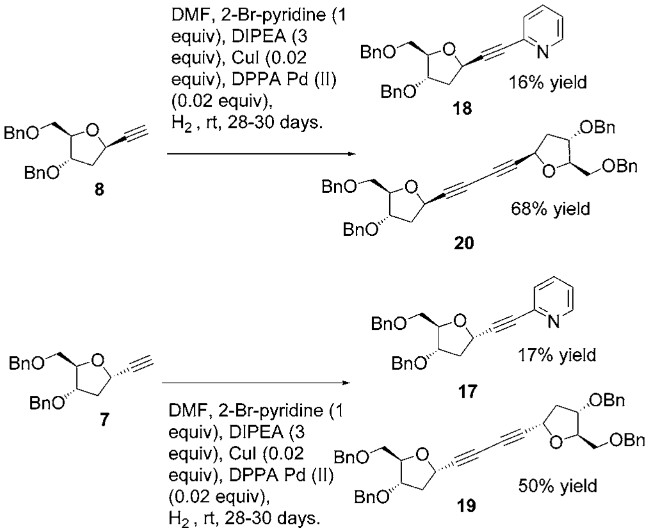
However, the reaction of **13** with *N*-*tert*-butylbenzyl nitrone yielded two diastereoisomeric isoxazolidines **14** and **15**[16] in a 1:1 ratio, together with a minor amount of regioisomer **16**.[16] Despite the poor yields, compounds **14**−**16** remain interesting for their potential medicinal properties.

Scheme 5. Reaction of 1-Alkynyl Ester **13** with Nitrones



The reactivity of **7** and **8** as alkyne components in the Sonogashira reaction was also studied. 2-Bromopyridine was selected as the arylbromide component and was reacted with **7** and **8** under standard Pd^0/Cu^I catalysis.[17] In these experiments, **17** and **18** were obtained in only 16−17% yields (Scheme 6).

Scheme 6. Preparation of 1-Alkynyl-*C*-nucleosides **17**−**20**



Compounds **19** and **20**, arising from an alkyne homocoupling process, were isolated as the principal products of the reaction.[18]

Several attempts were made to reduce the extent of formation of **19** and **20**. This included carrying out the reaction under nonoxidative atmosphere (hydrogen atmosphere),[18] or in the absence of copper cocatalyst,[18] or by using different ratios of Pd^0/Cu^I catalysts. To optimize the yield of **17** and **18** and reduce the long reaction time required, we

---

(13) Compounds **9**−**12** were obtained as colorless liquid. NOE were run in order to assign the absolute stereochemistry of **9**−**12**, but unfortunately these experiments were inconclusive.

(14) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Chapter 9, p 83. (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates*; VCH Publishers Inc.: New York, 1988.

(15) Uenishi, J.; Matsui, K.; Ohmiya, H. *J. Organomet. Chem.* **2002**, *653*, 141.

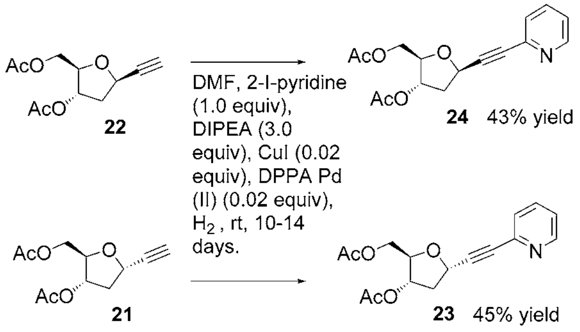
(16) Compounds **14**−**16** were obtained as colorless liquid. NOE experiments were run in order to assign the absolute stereochemistry of **14**−**16**, but unfortunately these experiments were inconclusive.

(17) Elangovan, A.; Wang, Y. H.; Ho, T. I. *Org. Lett.* **2003**, *5* (11), 1841.

(18) Lou, Y.; Gao, H.; Li, Y.; Huang, W.; Lu, W.; Zhang, Z. *Tetrahedron* **2006**, *62*, 2465.

have studied the effect of temperature, ratio of reagents, concentration of reactants, solvent, and aryl halide. In no case was an improvement of the yields of **17** and **18** noted. It was lately found that a more efficient Sonogashira coupling occurred by reaction of 1-alkynylsugars **21** and **22** and 2-iodopyridine (Scheme 7). Additionally, in these experiments no evidence for the formation of homocoupled compound was observed. Acetyl-protected alkynyl sugars **21** and **22** were opportunely prepared from **7** and **8** by means of debenzylation and subsequent acetylation.[19]

Scheme 7. Preparation of 1-Alkynyl-*C*-nucleosides **23** and **24**

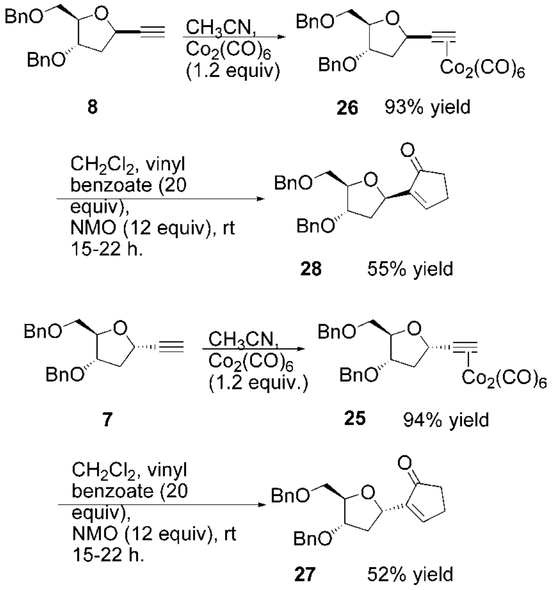


Alkynyl sugars **7** and **8** were also reacted with $Co_2(CO)_6$ to obtain the corresponding cobalt complexes **25** and **26** that are intermediates required for the Pauson−Khand reaction (Scheme 8).[20]

In this experiment, cobalt complexes **25** and **26** were obtained in high isolated yields. Compounds **25** and **26** were subsequently used to prepare cyclopentenones **27** and **28** by treatment with excess vinyl benzoate and *N*-methylmorpholine (NMO) (Scheme 8).

Considering the modular nature of this reaction, it is easy to envisage that several analogues could be prepared by means of variation of the alkene component.

Scheme 8. Preparation of *C*-Nucleosides **27** and **28**



In conclusion we have developed a practical synthesis of 1-alkynyl-2-deoxy-D-riboses **7** and **8** and we have studied their reactivity as starting materials for the generation of novel unnatural *C*-nucleosides. These studies identified the potential and limitation of **7** and **8** in synthesis and furnished several classes of novel *C*-nucleosides. Studies aimed at developing diversity orientated synthesis from **7** and **8** are in progress.

Acknowledgment. We would like to acknowledge the Irish Research Council for Science, Engineering and Technology (IRCSET) for a grant to R.P. and PTRLI cycle III for a grant to M.F.A.A.

Supporting Information Available: Procedures for the preparation and spectroscopic data of compounds **5**−**28** and NOE and $^1H-^1H$ cosy spectra of compounds **7** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701794U

---

(19) A full account for the preparation of **21**−**24** is reported in the Supporting Information together with their spectroscopic and analytical data.

(20) Rivero, M. R.; de la Rosa, J. C.; Carretero, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 14992. Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104.