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Corey lactone as key precursor for a facile synthesis of novel 1,2,3-triazole carbocyclic nucleosides via Click Chemistry

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ABSTRACT

Corey lactone (**2**) and Click Chemistry allowed for an efficient and facile approach to the synthesis of novel 1,2,3-triazole carbocyclic nucleosides (**11** and **17**) in good overall yields.

Ribavirin (Fig. 1) was the first triazole nucleoside with a potent broad-spectrum antiviral[1] approved by the FDA for therapy against Hepatitis C Virus (HCV), and is currently being used clinically worldwide.[2] The discovery of Ribavirin in 1972[1a] sparked a new burst in research for the design and synthesis of novel triazole nucleosides,[3] resulting in some compounds with promising biological potential. For instance, recently reported ETCAR has exhibited cytostatic activity,[4] while TSAO has shown anti-HIV activity.[5]

Carbocyclic nucleosides (also named 'carbonucleosides' in short form) are compounds in which a methylene group has replaced the oxygen atom of the furanose ring. These compounds have potent metabolic stability because they are unaffected by phosphorylase and hydrolase enzymes that cleave the glycosidic bond of natural nucleosides.[6] For this reason, *1,2,3-triazole carbocyclic nucleosides* are peculiar compounds, and efforts by some research groups[7] have led to interesting biological agents. For instance, compound **A** has displayed activity against HIV-1[8] and compound **B** against Vaccinia Virus, SARSCoV, and Cowpox Virus.[9] Meanwhile, compound **C** has shown a specific inhibitory potential against Varicella Zoster Virus (TK+VZV).[10]

The emerging field of *Click Chemistry* (Pioneered by Huisgen[11] and brought back by Sharpless[12]), involving the Cu alkyne-azide cycloaddition (CuAAC), has become a powerful tool to obtain 1,2,3-triazoles which are well known as important biological agents.[13] In last decade the use of Click Chemistry was explored in the synthesis of 1,2,3-triazole nucleosides, nucleotides, and oligonucleotides.[14]

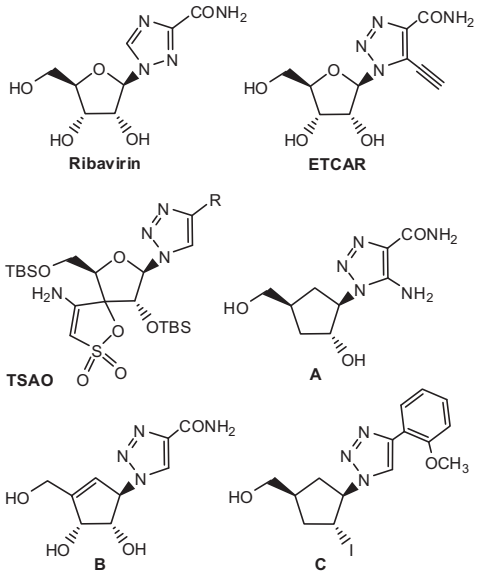

Figure 1. Representative bioactive triazole nucleosides and triazole carbocyclic nucleosides.

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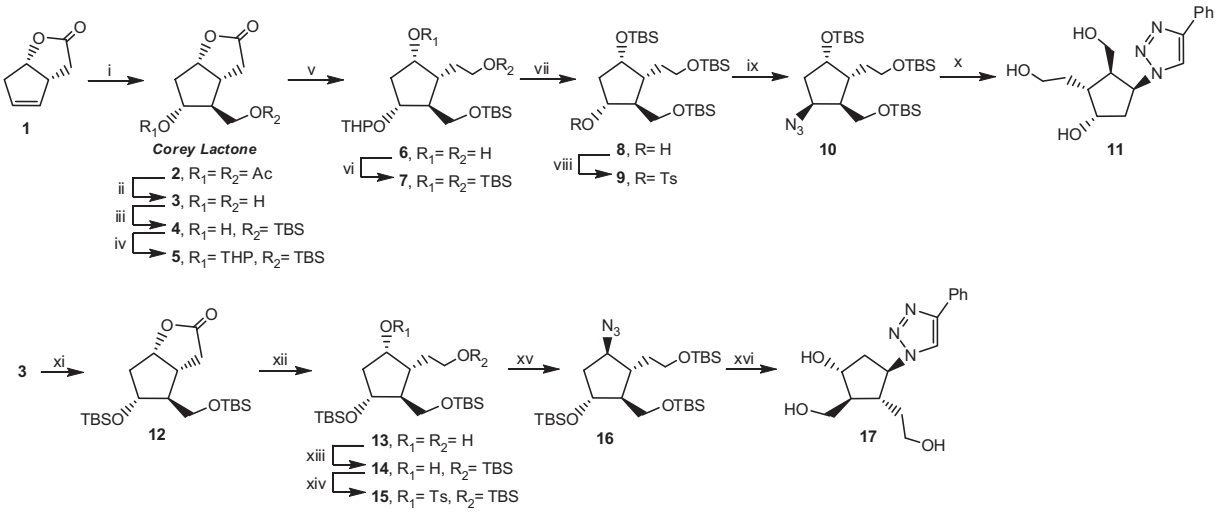

Scheme 1. Reagents and conditions: (i) paraformaldehyde, AcOH, H_2SO_4, 80 °C, 24 h, 70%; (ii) DBN, MeOH, rt, 12 h, 80%; (iii) TBSCl, Im, DMF, rt, 8 h, 75%; (iv) DHP, *p*-TsOH anh, DCM anhyd, rt, 1 h, 98%; (v) LAH, THF anhyd, rt, 4 h, 84%; (vi) TBSCl, Im, DMF, rt, 12 h, 88%; (vii) Me_2AlCl, DCM anhyd, rt, 3 h, 82%; (viii) TsCl, Py, rt, 24 h, 85%; (ix) NaN_3, DMF, MW, 150 °C, 15 min, 85%; (x) $CuSO_4{\cdot}5H_2O$, MeOH, 50 °C, 8 h, then, CuI, phenylacetylene, NaOH aq 0.5 M, 50 °C, overnight, 73%; (xi) TBSCl, Im, DMF, rt, 12 h, 90%; (xii) LAH, THF anhyd, rt, 4 h, 78%; (xiii) TBSCl, Im, DMF, rt, 8 h, 70%; (xiv) TsCl, Py, rt, 24 h, 80%; (xv) NaN_3, DMF, MW, 150 °C, 15 min, 80%; (xvi) $CuSO_4{\cdot}5H_2O$, MeOH, 50 °C, 8 h, then, CuI, phenylacetylene, NaOH aq 0.5 M, 50 °C, overnight, 70%.

Hence, in our pursuit of new strategies for producing 1,2,3-triazole carbocyclic nucleosides, we herein report a new simple route for the synthesis of novel α-D-2′-deoxy-homocarbanucleoside (**11**) and β-L-2′-deoxy analog (**17**) via Click Chemistry (Scheme 1). Furthermore, we propose *Corey lactone*[15] as the key precursor, being an excellent supplier of the required pseudosugar ring (cyclopentane) that allows for the high stereospecific configuration of all suitable functional groups.

The Corey lactone bis-acetate **2** was prepared in one step from commercially available unsaturated lactone **1** by stereospecific Prins Reaction according to the Tömösközi's method.[16] Structural confirmation for **2** was determined by 2D NMR techniques (COSY and HETCOR spectrum). This reaction led to a compound with four required and highly defined stereocenters along with two carbonyl functionalities. Transesterification of **2** by treatment with DBN in MeOH gave the corresponding Corey lactone diol (**3**) in 80% yield. Diol **3** became the key intermediate and provided two pathways for the synthesis of triazole carbocyclic nucleosides.

The strategic protection of hydroxyl groups with *tert*-butyldimethylsilyl chloride (TBSCl) played an important role in the synthesis. The conversions of alcohols (**3**, **6**, and **13**) to silyl ethers (**4**, **7**, **12**, and **14**) were achieved using TBS and imidazole (Im) in dry DMF with good yields (75, 88, 90, and 70%, respectively). The use of TBS allowed for the selective protection of primary over secondary alcohols. On the other hand, acid-catalyzed protection of hydroxyl lactone **4** with dihydropyrane (DHP) in the presence of *p*-TsOH catalyst afforded the tetrahydropyranyl (THP) ether **5** in excellent yield (98%) within 1 h. Lactones **5** and **12** were reduced by employing $LiAlH_4$ in dry THF, furnishing the corresponding dioles **6** and **13** in 84% and 78% yields, respectively. Selective deprotection of THP ether **7** was attained by employing dimethyl aluminum chloride (Me_2AlCl) according to Shibasaki's method.[17] Alcohol **8** was isolated in 82% yield.

For introduction of the azide group into a pseudosugar ring (**8** and **14**), we tested some methods for the one-pot conversion of alcohols to azides, including the procedures by Gómez-Vidal and Silverman (DPPA, DEAD, THF, 0 °C —Mitsunobu Reaction—),[18] Thompson et al. (DPPA, DBU, toluene, rt),[19] Mizuno and Shioiri (*p*-NO_2DPPA, DBU, toluene, rt),[20] and Gouin-Kovensky (NaN_3, PPh_3, CBr_4, DMF, rt).[21] Unfortunately the aforementioned methods were unsuccessful. Therefore, we decided to use the tosyl-azidation procedure. Alcohols **8** and **14** were treated with *p*-toluenesulfonyl chloride (TsCl) in pyridine (Py). Crude tosylates[22] were successfully purified by column chromatography to obtain the corresponding tosylates **9** and **15** (in 85% and 80% yields, respectively). Replacement of the tosyl group (**9** and **15**) by introduction of an azide group (NaN_3 in dry DMF) was possible with a microwave-assisted reaction (150 °C, 15 min) leading to compounds **10** and **16** (in 75% and 80% yields, respectively). On the other hand, there were not any reactions at room temperature, and sluggish reactions were observed (~60%) when using conventional heating (100 °C, 24 h). Since temperature seemed to be the main limiting factor in the aforementioned methods;[18–21] Shioiri's method was carried out with MW (150 °C, 15 min), resulting in a complete reaction (67% yield). Purification of tosylates was crucial; reaction with crude tosylates gave low yields (>30%).

Recently our collaborative research group reported a novel method for triazole formation through Click Chemistry.[23] Deprotection of silyl protecting groups and CuAAC of substrates **10** and **16** were subjected to a one-pot system. Firstly, silyl ethers (**10** and **16**) were treated with $CuSO_4{\cdot}5H_2O$ in methanol at 50 °C until total deprotection of silyl groups was observed (monitored by TLC). Then, CuI, phenylacetylene and NaOH aq 0.5 M were added and the mixture reactions were stirred at 60–65 °C overnight. The corresponding 1,2,3-triazole carbocyclic nucleosides **11** and **17** were achieved in good yields (73% and 70% respectively). The regiochemistry and structure of the target compounds (**11** and **17**) were assigned by 1D and 2D NMR techniques (^1H, ^{13}C, DEPT, COSY, HETCOR and NOESY experiments).

In summary, we have developed the first approach to the synthesis of 1,2,3-triazole carbocyclic nucleosides (α-D-2′-deoxy-homocarbanucleoside **11** and β-L-2′-deoxy analog **17**) from Corey lactone.

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Supplementary data

Supplementary data (including experimental procedures, characterization data of all compounds and copies of ^{13}C, ^{1}H, DEPT, COSY, HETCOR and NOESY spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.069.

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