Tetrahedron 71 (2015) 5407–5413

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Construction of a chiral quaternary carbon center by a radical cyclization/ring-enlargement reaction: synthesis of 4α-azidoethyl carbocyclic ribose, a key unit for the synthesis of cyclic ADP-ribose derivatives of biological importance

Takatoshi Sato [a], Takayoshi Tsuzuki [a], Satoshi Takano [a], Kohtaro Kato [a], Hayato Fukuda [a], Mitsuhiro Arisawa [a,†], Satoshi Shuto [a,b,*]

[a] Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-ku, Sapporo 060-0812, Japan
[b] Center for Research and Education on Drug Discovery, Hokkaido University, Kita-ku, Sapporo 060-0812, Japan

ARTICLE INFO

Article history:
Received 16 February 2015
Received in revised form 22 May 2015
Accepted 24 May 2015
Available online 9 June 2015

Keywords:
Cyclic ADP-ribose
Radical reaction
Silicon tether
Quaternary carbon center
Carbocyclic ribose
Ring-enlargement

ABSTRACT

As a stable analog of the second messenger cyclic ADP-ribose (cADPR), we designed 4″-azidoethyl-cyclic ADP-carbocylic-ribose (N_3-cADPcR). For the synthesis of N_3-cADPcR, 1β-amino-2,3-*O*-isoproplylidene-4α-azidoethyl carbocyclic-ribose (**4**) having a chiral quaternary stereogenic center is required as the key unit. We successfully synthesized the desired unit **4** via construction of the quaternary stereogenic center by a radical cyclization/ring-enlargement reaction with a silicon-tethered substrate as the key step.

1. Introduction

Stereocontrolled construction of chiral quaternary carbon centers is a challenging issue in organic synthesis.[1] In our continuing medicinal chemical studies on cyclic ADP-ribose (cADPR, **1**, Fig. 1),[2] which is a Ca^{2+}-mobilizing second messenger,[3,4] we designed 4″α-azidoethyl-cADP-carbocyclic-ribose (N_3-cADPcR, **3**) having a chiral quaternary carbon center as a synthetic target. Here we describe the synthesis of 4α-azidoethyl carbocyclic-ribose **4** (Fig. 2), a key unit for the synthesis of N_3-cADPcR, in which the quaternary carbon center at the 4-position was effectively constructed by a radical cyclization/ring-enlargement reaction.[5]

Analogs of cADPR have been extensively designed and synthesized due to their potential usefulness for investigating the mechanism of cADPR-mediated Ca^{2+}release.[3,6,7] Because of its physiological importance, intensive studies of the signaling pathway that uses cADPR are needed, but the biological and chemical instability of cADPR due to its positively-charged N1-riboside structure[8] limits further studies of its physiological role. We previously designed and synthesized cyclic ADP-carbocyclic ribose (cADPcR, **2**),[2c] which is chemically and biologically stable

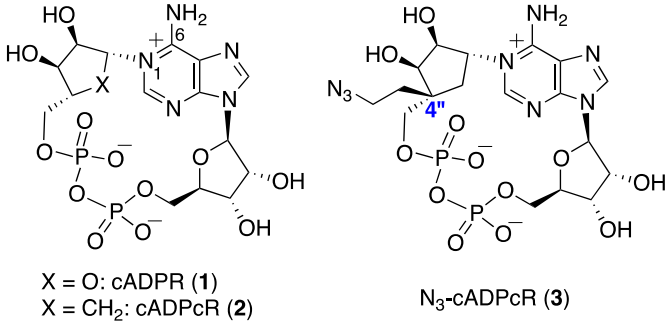

Fig. 1. cADPR (**1**), cADPcR (**2**), and N_3-cADPcR (**3**).

* Corresponding author. Tel./fax: +81 11 706 3769; e-mail address: shu@pharm.hokudai.ac.jp (S. Shuto).
† Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan.

http://dx.doi.org/10.1016/j.tet.2015.05.084
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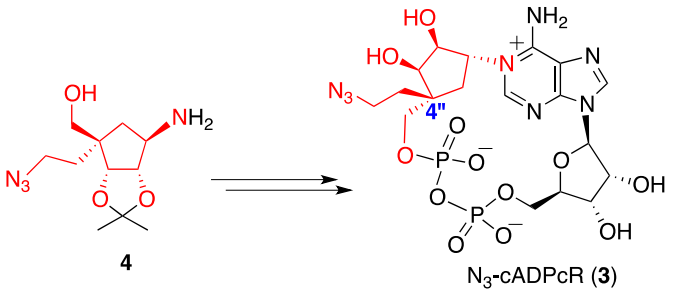


Fig. 2. Synthetic plan for N_3-cADPcR (**3**) with 4α-azidoethyl carbocyclic-ribose **4** as the key unit.

and effectively mobilizes Ca^{2+} in various biological systems.[2d,e] Therefore, cADPcR can be used as a lead structure for developing biological tools for investigating the cADPR-related Ca^{2+}-mobilizing signaling pathway.

Previous findings from structure–activity relationship (SAR) studies of cADPR revealed that the 6-NH_2 and pyrophosphate moieties are essential for its biological activity,[2b,6e] whereas the 3″-hydroxyl is not.[2e] Based on the structure–activity relationship findings and the three-dimensional structure of cADPcR predicted by NOE-based molecular dynamics study,[2g] we expected that the 4″α-position would not be important for recognition by the target biomolecules, because the position is rather distant from the essential 6-NH_2 and pyrophosphate moieties and near the unimportant 3″-hydroxyl in the three-dimensional cADPcR structure. Thus, we designed N_3-cADPcR (**3**) as a synthetic target, in which the azido group could be effectively used for conjugating various functional groups by a Hüisgen reaction to prepare useful biological tools.

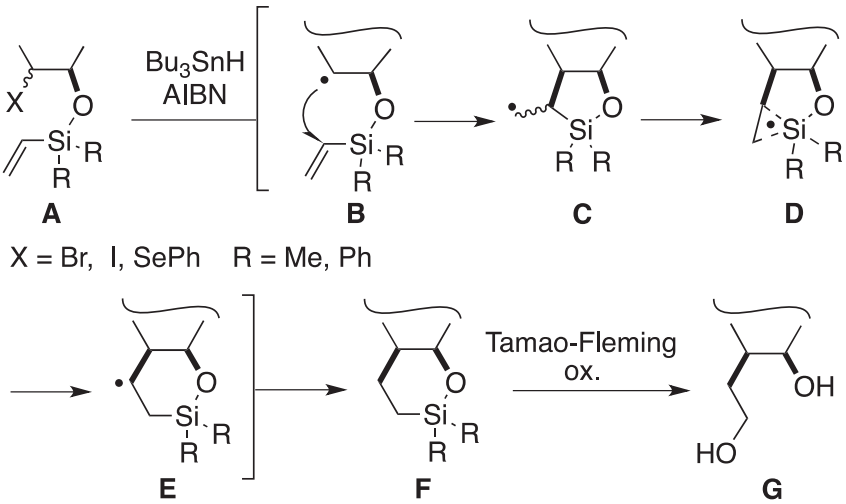
In the synthesis of N_3-cADPcR, the N1-carbocyclic adenosine structure would be constructed with 4α-azidoethyl carbocyclic ribose (**4**) as a key unit and the characteristic 18-membered cyclic pyrophosphate ring would be constructed by previously developed procedures.[2b,c] Thus, if the carbocyclic ribose unit **4** was available, synthesis of the target N_3-cADPcR could be achieved (Fig. 2). Therefore, we initiated our study for providing the key carbocyclic-ribose unit **4**, and in this report, we describe the details of the synthesis of **4** with a chiral quaternary carbon center.

2. Results and discussion

We previously developed a regio- and stereoselective method for introducing hydroxyethyl group at the β-position of a hydroxyl group in halohydrins or α-phenylselenoalkanols using an intramolecular radical cyclization reaction with a dimethyl- or diphenylvinylsilyl group as a temporary connecting radical-acceptor tether (Scheme 1).[5] In this reaction, the kinetically favored 5-*exo*-cyclized radical **C**, formed from the radical **B**, is rearranged into a more stable ring-enlarged radical **E** via pentavalent silicon radical **D**, which is subsequently trapped with Bu_3SnH to give **F**.[5b] Tamao-Fleming oxidation of the radical reaction product **F** allows us to stereoselectively introduce a hydroxyethyl group adjacent to the hydroxyl group.[5] We planned to construct the quaternary center at the 4-position of the carbocyclic-ribose unit **4** using this radical cyclization/ring-enlargement reaction.

Thus, we expected to obtain the carbocyclic amine **II** having the desired quaternary carbon center at the 4-position by the radical cyclization/ring-enlargement reaction and subsequent oxidation with the substrate **I** (Scheme 2). After various attempts to prepare substrate having the structure **I**, we reached substrates **11** and **12** for the radical reaction, which were synthesized from commercially available (1*R*)-2-azabicyclo[2.2.1]-hept-5-en-3-one (**5**) (Scheme 3). The bicyclic lactam **6**, prepared from **5** by a known procedure,[9] was converted to the aldehyde **8** via the alcohol **7**. Introduction of a phenylseleno group at the 4-position of **8** via its silyl enol ether gave **9**.[10] Reduction of the formyl group of **9** and subsequent protecting group manipulation gave **10**. Introduction of the silicon tether selectively at the 3-hydroxyl was unsuccessful. When **10** was treated with CH_2=CHSiPh2Cl, Et_3N, and DMAP in toluene, however, it afforded a mixture of the 2-*O*-tethered product **11** and the 3-*O*-tethered product **12** (99%) in a ratio of 1.4:1.

The key radical reaction was investigated next, and the results are summarized in Scheme 4. When a solution of Bu_3SnH and AIBN in benzene was added slowly to a solution of **11** and **12** (1.4:1), the reaction gave the cyclization product **13** with the desired quaternary stereogenic center as a major product (71%) along with the reduction product **14** (24%) with the unreacted 2-*O*-silyl group (entry 1). The stereochemistry of the products **13** and **14** was confirmed by NOE experiments (Fig. 3). Purified **11** or **12**[11] was then treated under the same radical reaction conditions. Thus, the reaction of 3-*O*-tethered **12** gave exclusively **13** (84%) (entry 2). Interestingly, when the 2-*O*-tethered **11** was subjected to the same



Scheme 1. Radical cyclization/ring-enlargement with a vinylsilyl group and subsequent oxidation to stereoselectively introduce a hydroxyethyl group.