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# 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

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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

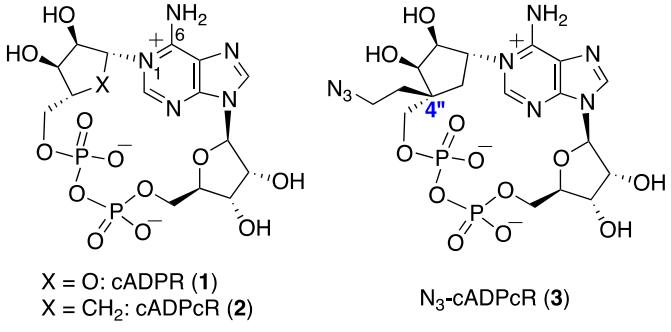


**Fig. 1.** cADPR (**1**), cADPcR (**2**), and $N_3$-cADPcR (**3**).

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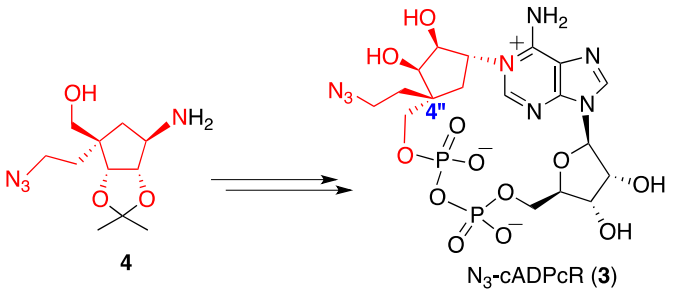



**Fig. 2.** Synthetic plan for $N_3$-cADPcR (**3**) with 4α-azidoethyl carbocyclic-ribose **4** as the key unit.

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.

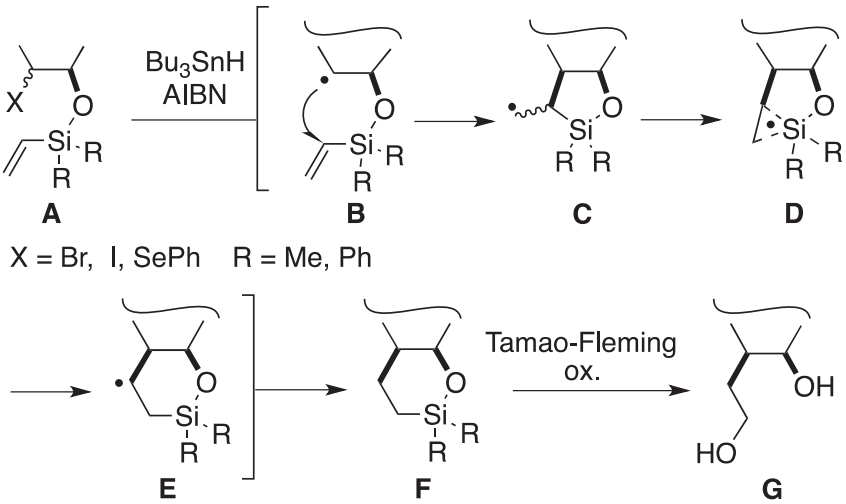
In the synthesis of $N_3$-cADPcR, the N1-carbocyclic adenosine structure would be constructed with 4α-azidoethyl carbocyclic ribose (**4**) as a key unit and the characteristic 18-membered cyclic pyrophosphate ring would be constructed by previously developed procedures.[2b,c] Thus, if the carbocyclic 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

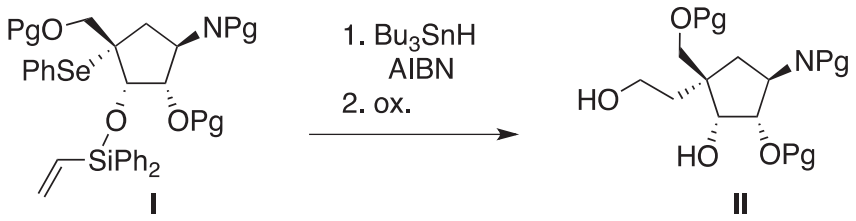
We previously developed a regio- and stereoselective method for introducing hydroxyethyl group at the β-position of a hydroxyl group in halohydrins or α-phenylselenoalkanols using an intramolecular radical cyclization reaction with a dimethyl- or diphenylvinylsilyl group as a temporary connecting radical-acceptor 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.

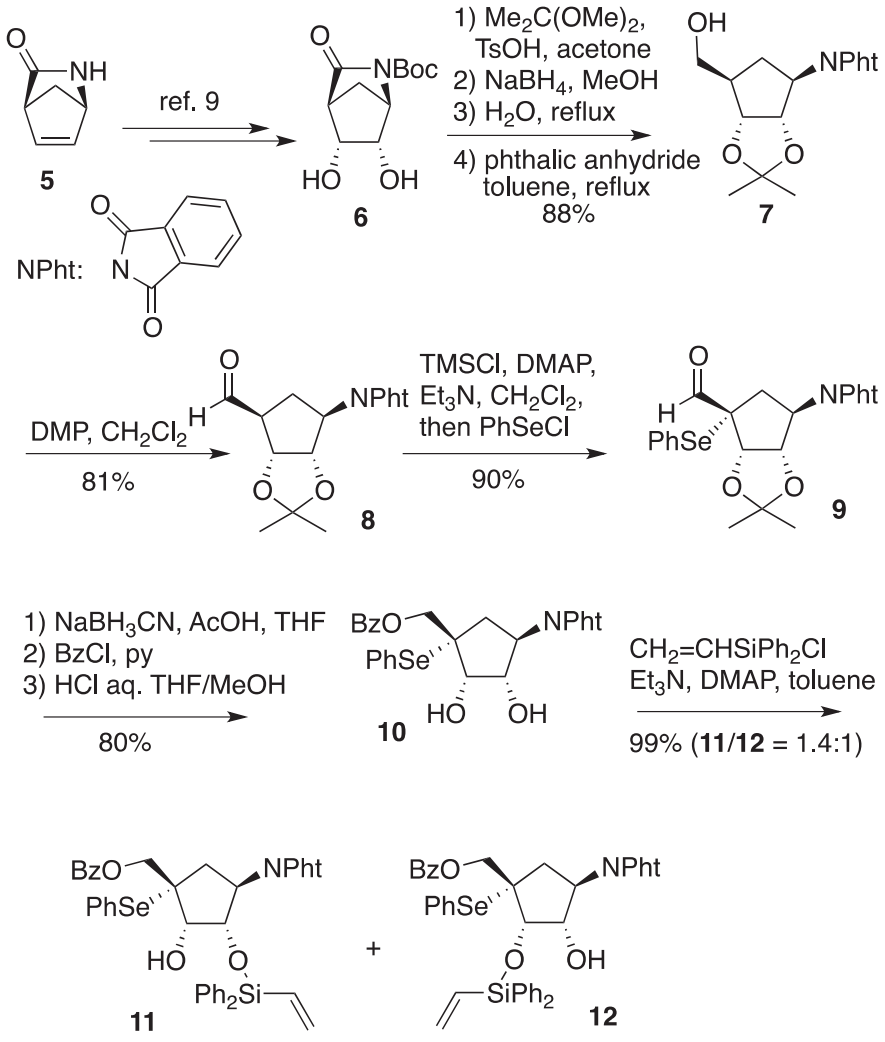
The key radical reaction was investigated next, and the results are summarized in Scheme 4. When a solution of $Bu_3SnH$ and AIBN in benzene was added slowly to a solution of **11** and **12** (1.4:1), the reaction gave the cyclization product **13** with the desired quaternary stereogenic center as 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.




**Scheme 2.** Plan for constructing the quaternary carbon center via the radical cyclization/ring-enlargement reaction.

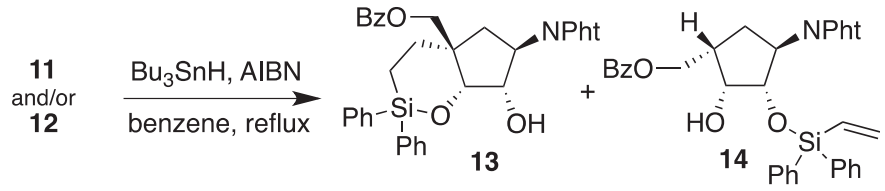



**Scheme 3.** Synthesis of the radical reaction substrates **11** and **12**.

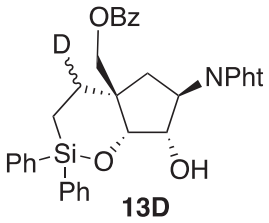
reaction, the desired cyclization product **13** was obtained as the major product with the reduction product **14** (34%). Thus, in this reaction, not only the 3-*O*-tethered **12**, but also the 2-*O*-tethered **11** unexpectedly worked as a substrate for the reaction forming the product **13** with the desired quaternary stereogenic center.

To investigate the reaction mechanism, we performed a deuterium-labeling reaction. When the mixture **11** and **12** (1.4:1) was treated with $Bu_3SnD$ instead of $Bu_3SnH$ under the same reaction conditions, cyclization product **13D**, in which the position β to the silicon was exclusively deuterated, was produced in 61% isolated yield. In addition, when the 2-*O*-tethered substrate **11** was heated under reflux in benzene, none of the migration product, i.e., the 3-*O*-tethered **12**, was formed. These results suggested that the desired cyclization product **13** formed via the *exo*-cyclization/ring-enlargement reaction from both **11** and **12**. In the case with the 2-*O*-tethered substrate **11**, migration of the silicon tether from the 2-hydroxyl to the 3-hydroxyl occurred, probably after the radical cyclization due to the steric demand of the cyclization product, as shown in Scheme 5. Thus, in accordance with previous cases, the *exo*-cyclization and subsequent ring-enlargement reaction effectively occurred in the radical reaction course to afford the desired product with the quaternary stereogenic center.

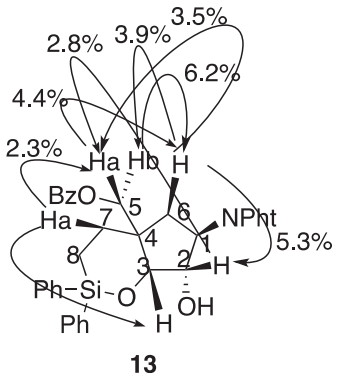
Thus, the stereogenic center was successfully constructed, and the product **13** was next converted into the carbocyclic-ribose unit




| entry | substrate | product (yield) 13 | 14 |
|---|---|---|---|
| 1 | **11** + **12** (1.4:1) | 71% | 24% |
| 2 | **12** | 84% | |
| 3 | **11** | 45% | 34% |




**Scheme 4.** Radical cyclization/ring-enlargement reaction of the substrate **11** and/or **12**.



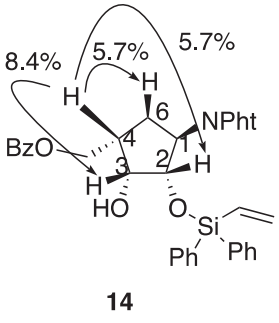
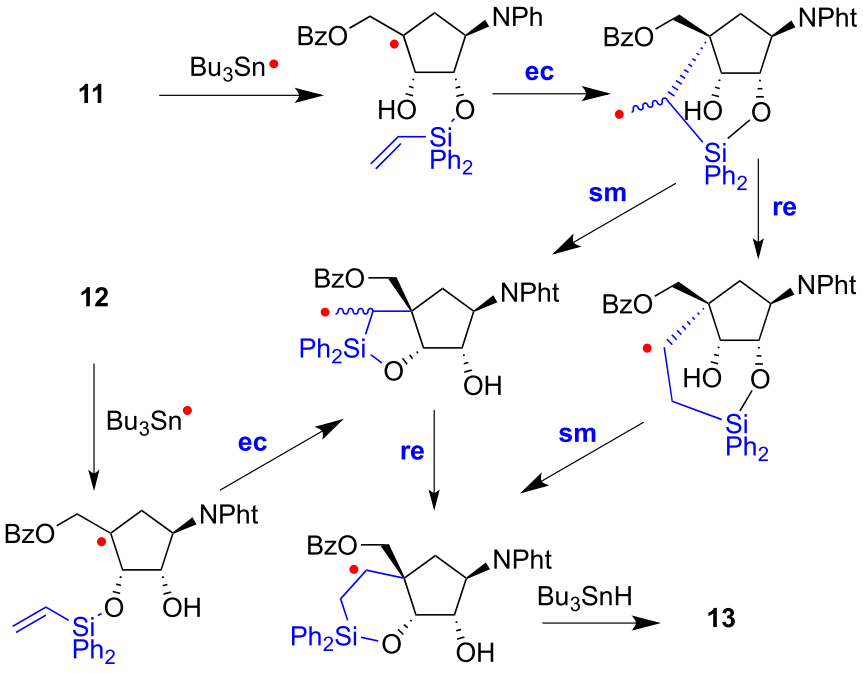



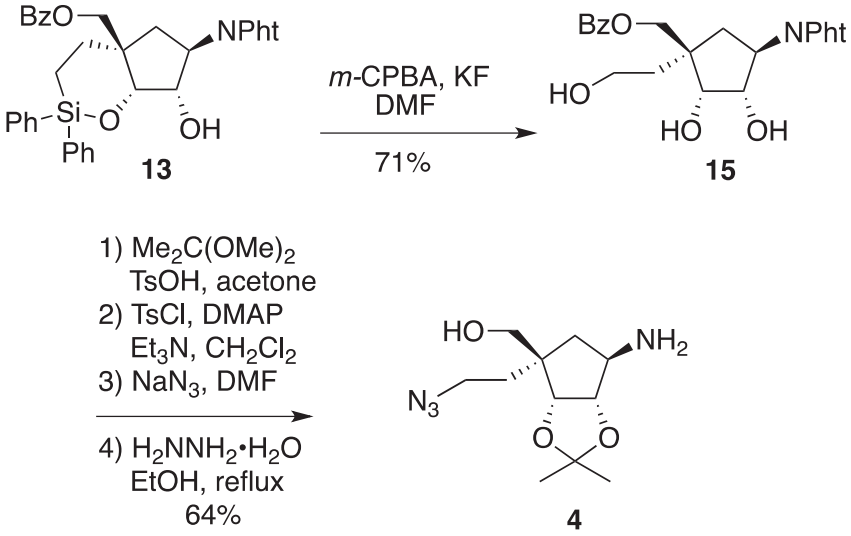

**Fig. 3.** NOE data of **13** and **14**.

**4**. When **13** was treated with *m*-CPBA and KF in DMF, oxidative cleavage of the oxasilacyclohexane ring proceeded to afford 4α-hydroxyethyl carbocyclic-ribose derivative **15** in 71% yield. Protecting the 2,3-*cis*-diol of **15** with an isopropylidene group and subsequent introduction of the azido group at the terminal position of the 4α-branched-chain, followed by removal of the phthaloyl group produced the desired 1β-amino-2,3-*O*-isopropyliden-4α-azidoethyl carbocyclic-ribose (**4**) (Scheme 6)..

In summary, we successfully prepared 4α-azidoethyl carbocyclic-ribose **4**, an essential unit for the synthesis of 4″α-azidoethyl-cyclic ADP-carbocyclic-ribose ($N_3$-cADPcR) of significant biological importance. For the synthesis of **4**, the key chiral quaternary stereogenic center was effectively constructed by a radical cyclization/ring-enlargement reaction with the silicon-tethered substrates. Synthesis of the target $N_3$-cADPcR (**3**) is now under investigation.




**Scheme 5.** The presumed radical reaction mechanism.




**Scheme 6.** Synthesis of 4α-azidoethyl carbocyclic-ribose **4**.

## 3. Experimental section

### 3.1. General methods and materials

$^1$H NMR spectra were recorded in $CDCl_3$ at ambient temperature unless otherwise noted, at 400 or 500 MHz, with TMS as an internal standard. $^{13}$C NMR spectra were recorded in $CDCl_3$ at ambient temperature at 100 or 125 MHz. Silica gel column chromatography was performed with silica gel 60 N (spherical, neutral, 63–210 μm, Kanto Chemical Co., Inc.). Flash column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm, Kanto Chemical Co., Inc.). Structures of synthesized compounds were confirmed by $^1$H NMR, $^{13}$C NMR, and HRMS spectra.

### 3.2. (1*R*,2*S*,3*R*,4*R*)-4-Hydroxymethyl-2,3-*O*-isopropylidenedioxy-1-phthaloylaminocyclopentane (7)

A mixture of **6** (2.01 g, 8.26 mmol), $Me_2C(OMe)_2$ (1.52 mL, 12.4 mmol), and TsOH•$H_2O$ (318 mg, 1.67 mmol) in acetone (82 mL) was stirred at room temperature for 1 h, then neutralized with saturated aqueous $NaHCO_3$ and concentrated. The residue was partitioned between AcOEt and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. A mixture of the residue and $NaBH_4$ (635 mg, 16.8 mmol) in MeOH (82 mL) was stirred at room temperature for 10 h, then neutralized with AcOH and evaporated. The residue was partitioned between AcOEt and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. A mixture of the residue in $H_2O$ (82 mL) was heated under reflux for 16 h and evaporated. A mixture of the residue and phthalic anhydride (1.19 g, 8.01 mmol) in toluene was heated under reflux for 12 h and evaporated. The residue was purified by column chromatography ($SiO_2$, AcOEt/hexane, 1:1–1:2) to give **7** (2.30 g, 7.25 mmol, four steps 88%) as a white amorphous powder: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.83–7.72 (4H, m), 5.07 (1H, dd, $J$=7.2 Hz, 5.9 Hz), 4.75–4.68 (1H, m), 4.62 (1H, dd, $J$=6.9 Hz, 5.9 Hz), 3.82–3.75 (2H, m), 2.41–2.32 (1H, m), 2.32 (1H, s), 2.20–2.15 (2H, m), 1.56 (3H, s),1.30 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.1, 134.1, 131.7, 123.2, 113.3, 81.9, 64.2, 55.2, 46.2, 31.3, 27.6, 25.2; HRMS (ESI) calcd for $C_{17}H_{19}O_5NNa$ 340.1177 $(M+Na)^+$, found 340.1155.

### 3.3. (1*R*,2*S*,3*R*,4*S*)-4-Formyl-2,3-*O*-isopropylidenedioxy-1-phthaloylaminocyclopentane (8)

A mixture of **7** (1.93 g, 6.08 mmol) and Dess-Martin periodinane (DMP, 3.20 g, 7.54 mmol) in $CH_2Cl_2$ (61 mL) was stirred at 0 °C for 30 min and then at room temperature for 1 h. After addition of aqueous saturated $Na_2S_2O_3$, the resulting mixture was partitioned between AcOEt and $H_2O$, and the organic layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, AcOEt/hexane, 1:2–2:3) to give **8** (1.55 g, 4.92 mmol, 81%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.84 (1H, s), 7.86–7.72 (4H, m), 5.28 (1H, dd, $J$=7.7 Hz, 3.6 Hz), 5.04 (1H, dd, $J$=6.3 Hz, 3.6 Hz), 4.78–4.73 (1H, m), 3.03–2.98 (1H, m), 2.48–2.42 (2H, m), 1.55 (3H, s), 1.34 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 200.4, 167.9, 134.2, 131.6, 123.4, 112.3, 83.2, 80.8, 58.2, 55.3, 29.1, 27.1, 24.7; HRMS (ESI) calcd for $C_{17}H_{17}O_5NNa$ 338.1014 $(M+Na)^+$, found 338.1004.

### 3.4. (1*R*,2*S*,3*R*,4*S*)-4-Formyl-2,3-*O*-isopropylidenedioxy-4-phenylseleno-1-phthaloylaminocyclopentane (9)

A mixture of **8** (1.25 g, 3.95 mmol), $Et_3N$ (0.94 mL, 6.7 mmol), and $Me_3SiCl$ (0.75 mL, 5.9 mmol) in $CH_2Cl_2$ (151 mL) was stirred at room temperature for 10 h, and then to which PhSeCl (774 mg, 4.04 mmol) was added. The resulting mixture was stirred at room temperature for 1 h and then partitioned between AcOEt and $H_2O$. The organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography (silica gel; hexane/AcOEt, 4:1–2:1) to give **9** (1.70 g, 3.61 mmol, two steps 90%) as white amorphous powder (α/β diastereomer ratio, about 45:1 on the $^1$H NMR): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.38 (1H, s, H-5), 7.77–7.24 (9H, m), 5.26 (1H, dd, $J$=6.3 Hz, 2.3 Hz), 5.24 (1H, d, $J$=6.3 Hz), 4.99 (1H, dd, $J$=7.5 Hz, 5.2 Hz, 2.3 Hz), 2.61 (1H, dd, $J$=14.3 Hz, 5.2 Hz), 2.47 (1H, H-6, $J$=14.3 Hz, 7.5 Hz), 1.68 (3H, s), 1.38 (3H, s); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 189.5, 168.0, 138.0, 134.2, 131.6, 129.6, 129.1, 125.3, 123.3, 113.4, 83.0, 81.3, 66.8, 54.8, 35.2, 25.7, 24.5; HRMS (ESI) calcd for $C_{16}H_{21}O_5NNaSe$ 494.0484 $(M+Na)^+$, found 494.0489.

### 3.5. (1*R*,2*S*,3*R*,4*S*)-4-Benzoyloxymethyl-2,3-*O*-isopropylidenedioxy-4-phenylseleno-1-phthaloylaminocyclopentane (10)

A mixture of **9** (1.60 g, 3.40 mmol, α/β diastereomer ratio, about 45:1), $NaBH_3CN$ (544 mg, 8.66 mmol), and AcOH (2.3 mL) in THF (34 mL) was stirred at room temperature for 24 h and then partitioned between AcOEt and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography (silica gel; hexane/AcOEt, 2:1) to give the 5-hydroxy reduction product (1.44 g, 3.05 mmol, 90%) as white amorphous, where the minor β-phenylseleno diastereomer was removed: A mixture of the obtained reduction product (406 mg, 0.859 mmol), BzCl (0.13 mL, 1.1 mmol) in pyridine (8.6 mL) was stirred at room temperature for 36 h and then evaporated. A mixture of the residue and aqueous HCl (1 M, 1.8 mL) in MeOH (24 mL) and THF (12 mL) was stirred at 50 °C for 10 h, and then partitioned between AcOEt and $H_2O$. The organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography (silica gel; hexane/AcOEt, 3:2–1:1) to give **10** (1.53 g, 80% from **9**) as white amorphous powder: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33–8.10 (14H, m), 4.99 (1H, ddd, *J*=10.8 Hz, 8.6 Hz, 5.9 Hz), 4.76 (1H, d, *J*=11.8 Hz), 4.70–4.67 (1H, m, H-2), 4.59–4.56 (1H, m, H-3), 4.47 (1H, d, H-5, *J*=11.8 Hz), 3.22 (1H, s, OH), 2.95 (1H, s, OH), 2.44 (1H, dd, *J*=13.9 Hz, 10.8 Hz), 1.81 (1H, dd, *J*=13.9 Hz, 8.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.0, 166.3, 138.0, 134.1, 133.2, 131.7, 129.8, 129.7, 129.6, 129.5, 128.5, 123.3, 73.9, 73.2, 67.3, 59.0, 55.9, 31.4; HRMS (ESI) calcd for $C_{27}H_{23}O_6NNaSe$ 560.0586 $(M+Na)^+$, found 560.0583.

### 3.6. (1*R*,2*S*,3*R*,4*S*)-4-Benzoyloxymethyl-2-diphenylvinylsiloxy-3-hydroxy-4-phenylseleno-1-phthaloylaminocyclopentane (11) and (1*R*,2*S*,3*R*,4*S*)-4-benzoyloxymethyl-3-diphenylvinylsiloxy-2-hydroxy-4-phenylselenyl-1-phthaloylaminocyclopentane (12)

A mixture of **10** (365 mg, 0.680 mmol), $Et_3N$ (110 μL, 0.81 mmol), DMAP (44 mg, 0.36 mmol), and diphenylvinylchlorosilane (185 mL, 0.82 mmol) in toluene (6.8 mL) was stirred at room temperature for 12 h, and then partitioned between AcOEt and $H_2O$. The organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography (silica gel; hexane/AcOEt, 2:1) to give a mixture of **11** and **12** (500 mg, 0.671 mmol, 99%, **11**/**12**=1.4:1.0) as white amorphous solid. The mixture (250 mg) was subjected to column chromatography again (silica gel; hexane/AcOEt, 4:1–2:1) to give pure **11** (58 mg) and **12** (35 mg) together with their mixture. **11**: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07–7.06 (24H, m), 6.40 (1H, dd, *J*=20.6 Hz, 15.5 Hz), 6.17 (1H, dd, *J*=15.5 Hz, 3.4 Hz), 5.93 (1H, dd, *J*=20.6 Hz, 3.4 Hz), 5.16 (1H, ddd, *J*=11.5 Hz, 8.0 Hz, 6.9 Hz), 5.11 (1H, dd, *J*=6.9 Hz, 6.9 Hz), 4.67 (1H, d, *J*=11.5 Hz), 4.51 (1H, dd, *J*=6.9 Hz, 6.9 Hz), 4.44 (1H, d, *J*=11.5 Hz), 3.41 (1H, d, *J*=6.9 Hz), 2.28 (1H, dd, *J*=13.7 Hz, 11.5 Hz), 1.76 (1H, dd, *J*=13.7 Hz, 8.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$); δ 167.9, 165.7, 138.6, 138.3, 135.1, 134.0, 133.0, 132.5, 131.8, 130.4, 130.4, 129.7, 129.5, 128.3, 128.0, 128.0, 123.2, 74.0, 74.0, 65.8, 59.3, 56.6, 29.9; HRMS (ESI) calcd for $C_{41}H_{35}O_6NNaSi$ 768.1295 $(M+Na)^+$, found 768.1291. **12**: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.94–7.28 (24H, m), 6.53 (1H, dd, *J*=20.6 Hz, 14.9 Hz), 6.28 (1H, dd, *J*=14.9 Hz, 3.4 Hz), 6.00 (1H, dd, *J*=20.6 Hz, 3.4 Hz), 5.13–5.09 (1H, m), 5.07 (1H, d, *J*=8.0 Hz), 4.51–4.49 (1H, m), 4.41 (2H, d, *J*=11.5 Hz), 3.17 (1H, d, *J*=8.6 Hz), 2.35 (1H, dd, *J*=14.4 Hz, 11.5 Hz), 1.55 (1H, dd, *J*=14.4 Hz, 8.6 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 167.6, 166.1, 138.5, 138.1, 134.9, 134.8, 133.7, 133.0, 132.3, 131.7, 130.2, 130.0, 129.7, 129.2, 129.2, 128.4, 127.9, 127.8, 123.0, 73.1, 72.8, 67.6, 57.9, 55.9, 31.4; HRMS (ESI) calcd for $C_{41}H_{35}O_6NNaSi$ 768.1297 $(M+Na)^+$, found 768.1296.

### 3.7. General procedure for the radical reactions

To a solution of substrate (37 mg, 0.050 mmol) in benzene (5 mL) at 80 °C, a solution of $Bu_3SnH$ (53 μL, 0.15 mmol) and AIBN (8 mg, 0.050 mmol) in benzene (2 mL) was added slowly over a 1 h period. The solvent was evaporated, and the residue was purified by silica gel column chromatography (silica gel; hexane/AcOEt, 9:1–4:1) to give **13**, or **13** and **14**, as white amorphous powder (yields are shown in Fig. 3). **13**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37–7.93 (19H, m), 5.01 (1H, ddd, *J*=10.4 Hz, 10.0 Hz, 5.0 Hz), 4.86 (1H, dd, *J*=10.4 Hz, 10.0 Hz, 9.5 Hz), 4.45 (1H, d, *J*=11.3 Hz), 4.36 (1H, d, *J*=5.0 Hz), 4.28 (1H, d, *J*=11.3 Hz), 2.98 (1H, d, *J*=10.4 Hz), 2.38 (1H, dd, *J*=13.6 Hz, 10.4 Hz), 2.27–2.22 (1H, m), 2.02 (1H, dd, *J*=13.6 Hz, 9.5 Hz), 1.99–1.95 (1H, m), 1.33–1.29 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.5, 166.4, 134.3, 134.0, 133.1, 133.0, 131.9, 130.7, 130.5, 129.7, 129.6, 128.4, 128.3, 128.2, 123.2, 75.9, 73.4, 69.6, 55.2, 43.8, 33.0, 28.1, 5.6; HRMS (ESI) calcd for $C_{35}H_{31}O_6NNaSi$ 612.1806 $(M+Na)^+$, found 612.1813; NOE irradiation of H-5a/observed at H-6b (4.4%), irradiation of H-5b/observed at H-6b (6.2%), irradiation of H-6b/observed at H-2 (5.3%), H-5a (3.5%), H-5b (3.9%), irradiation of H-2/observed at H-5a (2.8%), irradiation of H-7a/observed at H-3 (1.7%), H-5a (2.3%). **14**: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04–7.07 (19H, m), 6.35 (1H, dd, *J*=20.4 Hz, 15.0 Hz), 6.10 (1H, dd, *J*=15.0 Hz, 3.6 Hz), 5.79 (1H, dd, *J*=20.4 Hz, 3.6 Hz), 5.00 (1H, dd, *J*=7.7 Hz, 3.6 Hz), 4.91–4.85 (1H, H-1), 4.57 (1H, H-5, *J*=10.9 Hz, 8.6 Hz), 4.38 (1H, dd, *J*=10.9 Hz, 6.8 Hz), 4.19 (1H, dd, *J*=3.6 Hz, 3.6 Hz), 2.94–2.88 (1H, m), 2.77 (1H, s), 2.15 (1H, dd, *J*=13.6 Hz, 10.0 Hz), 2.00 (1H, ddd, *J*=13.6 Hz, 8.4 Hz, 5.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.9, 166.5, 137.9, 134.9, 134.8, 134.8, 133.6, 132.9, 132.5, 131.8, 130.3, 129.9, 129.6, 128.3, 127.9, 127.7, 127.7, 127.6, 123.0, 77.1, 73.2, 64.0, 54.5, 39.4, 29.1, 21.0; HRMS (ESI) calcd for $C_{35}H_{31}O_6NNaSi$ 612.1806 $(M+Na)^+$, found 612.1813; NOE irradiation of H-4/observed at H-6β (5.7%), H-3 (8.4%), H-2 (5.7%).

### 3.8. Deuterium labeling reaction

To a solution of a mixture of **11** and **12** (25 mg, 0.034 mmol, 1.4:1.0) in benzene (3.4 mL) at 80 °C, a solution of $Bu_3SnD$ (18 μL, 0.068 mmol) and AIBN (4 mg, 0.025 mmol) in benzene (1 mL) was added slowly over a 1 h period. The solvent was evaporated, and the residue was purified by silica gel column chromatography (silica gel; hexane/AcOEt, 9:1–3:1) to give **13D** (12 mg, 0.0208 mmol, 61%) as white amorphous powder: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93–7.37 (19H, m, Ar–H), 5.01 (1H, ddd, H-2, *J*=10.4 Hz, 10.0 Hz, 5.0 Hz), 4.86 (1H, dd, H-1, *J*=10.4 Hz, 10.0 Hz, 9.5 Hz), 4.45 (1H, d, H-5, *J*=11.3 Hz), 4.36 (1H, d, H-3, *J*=5.0 Hz), 4.28 (1H, d, H-5, *J*=11.3 Hz), 2.98 (1H, d, OH, *J*=10.4 Hz), 2.38 (1H, dd, H-6, *J*=13.6 Hz, 10.4 Hz), 2.24 (1H, dd, H-7, *J*=4.0 Hz, 8.6 Hz), 2.02 (1H, dd, H-6, *J*=13.6 Hz, 9.5 Hz), 1.30 (1H, dd, H-8, *J*=14.3 Hz, 4.0 Hz), 1.25 (1H, dd, H-8, *J*=14.3 Hz, 6.9 Hz); HRMS (ESI) calcd for $C_{35}H_{30}DO_6NNaSi$ 613.1874 $(M+Na)^+$, found 613.1876.

### 3.9. (1*R*,2*S*,3*R*,4*S*)-4-Benzoyloxymethyl-2,3-dihydroxy-4-(2-hydroxyethyl)-1-phthaloylaminocyclopentane (15)

A mixture of **13** (492 mg, 0.83 mmol), *m*-CPBA (585 mg, 3.34 mmol), and KF (194 mg, 3.3 mmol) in DMF (8.3 mL) was stirred at room temperature for 4 h, and then saturated aqueous $Na_2S_2O_3$ was added. The resulting mixture was partitioned between $CHCl_3$ and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. The residue was purified by column chromatography (silica gel; hexane/AcOEt, 1:1–1:2) to give **15** (252 mg, 0.59 mmol, 71%) as white amorphous powder: $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07–7.42 (9H, m), 4.92 (1H, ddd, *J*=9.1 Hz, 8.6 Hz, 5.0 Hz), 4.80 (1H, ddd, *J*=10.0 Hz, 10.0 Hz, 8.6 Hz), 4.56 (1H, d, *J*=11.3 Hz), 4.40 (1H, s), 4.40 (1H, d, *J*=11.3 Hz), 4.08 (1H, d,

$J$=5.0 Hz), 3.92 (1H, ddd, $J$=10.9 Hz, 10.4 Hz, 2.7 Hz), 3.83 (1H, ddd, $J$=10.9 Hz, 6.3 Hz, 4.5 Hz), 3.00 (1H, d, $J$=9.1 Hz), 2.64 (1H, s), 2.43 (1H, dd, $J$=13.6 Hz, 10.0 Hz), 2.25 (1H, ddd, $J$=15.0 Hz, 10.4 Hz, 4.5 Hz), 1.91–1.85 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 168.5, 166.5, 134.0, 133.2, 131.9, 129.8, 129.7, 128.5, 123.2, 74.1, 73.6, 68.0, 58.8, 54.8, 45.7, 35.0, 34.7; HRMS (ESI) calcd for $C_{23}H_{23}O_7NNa$ 448.1383 $(M+Na)^+$, found 448.1367.

### 3.10. (1*R*,2*S*,3*R*,4*S*)-1-Amino-4-(2-azidoethyl)-2,3-isopropylidenedioxy-4-hydroxymethylcyclopentane (4)

A mixture of **15** (33 mg, 0.077 mmol), $Me_2C(OMe)_2$ (10 μL, 0.085 mmol), and TsOH•$H_2O$ (1.4 mg, 7.4 μmol) in acetone (3.0 ml) was stirred at room temperature for 1 h, then neutralized with satd aqueous $NaHCO_3$ and evaporated. The residue was partitioned between AcOEt and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. A mixture of the residue, TsCl (18 mg, 0.097 mmol), DMAP (4.0 mg, 0.033 mmol), $Et_3N$ (21 μL, 0.15 mmol) in $CH_2Cl_2$ (1.0 mL) was stirred at room temperature for 1.5 h, and then neutralized with satd aqueous $NH_4Cl$ and concentrated. The resulting mixture was partitioned between AcOEt and $H_2O$, and the organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. A mixture of the residue and $NaN_3$ (8.6 mg, 0.132 mmol) in DMF (1.0 mL) was stirred at room temperature for 20 h, and then partitioned between AcOEt and $H_2O$. The organic layer was washed with brine, dried ($Na_2SO_4$), and evaporated. A mixture of the residue and $NH_2NH_2 \cdot H_2O$ (19 μL, 0.39 mmol) in EtOH (1.0 mL) was heated under reflux for 9 h, and then evaporated. The residue was purified by silica gel column chromatography (silica gel; $CHCl_3$/MeOH, 9:1–4:1) to give **4** (13 mg, 0.0492 mmol, 64%) as white amorphous powder: $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 4.40 (1H, d, $J$=5.4 Hz), 4.30 (1H, d, $J$=5.4 Hz), 3.46 (1H, d, $J$=10.9 Hz), 3.38 (1H, d, $J$=10.9 Hz), 3.36–3.30 (1H, m), 3.28–3.21 (1H, m), 3.17–3.20 (1H, m), 2.08 (1H, dd, $J$=14.6 Hz, 7.7 Hz), 1.76–1.61 (2H, m), 1.48 (1H, d, $J$=14.6 Hz), 1.33 (3H, s), 1.19 (3H, s); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 111.5, 89.0, 86.6, 68.3, 58.2, 51.0, 48.9, 42.5, 33.9, 26.9, 24.2; HRMS (ESI) calcd for $C_{11}H_{21}O_3N_4$ 257.1605 $(M+H)^+$, found 257.1608; IR ($CHCl_3$) $\nu_{max}$ 2096 $cm^{-1}$ ($N_3$).

## Supplementary data

Supplementary data ($^1$H NMR charts of compounds) related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.05.084.

## References and notes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10. When the phenylseleno group was introduced, a trace of the 4β-isomer was produced, and the 4α-product 8 was obtained in a pure form after silica gel column chromatography.
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