SYNTHESIS OF 9-(*C*-5-HYDROXY-*C*-4-HYDROXY-METHYLCYCLOPENT-2-EN-*R*-1-YL)-9*H*-ADENINE [(±)-EPINOR-BCA][1]

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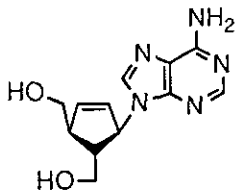
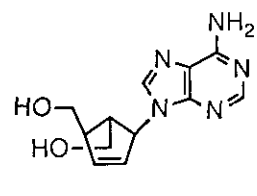
Abstract--9-(*c*-5-Hydroxy-*c*-4-hydroxymethylcyclopent-2-en-*r*-1-yl)-9*H*-adenine [(±)-Epinor-BCA] has been synthesized from the bicyclic hydroxy lactone (**2**) in eleven steps.

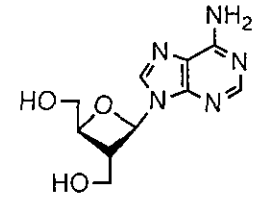
(1*R*, 4*S*, 5*R*)-9-[4, 5-Bis(hydroxymethyl)cyclopent-2-en-1-yl]-9*H*-adenine [(-)-(BCA)],[2] previously synthesized from (-)-Corey lactone in eleven steps,[3] has shown significant protection of MT-4 cells from the cytopathic effects of HIV-1 while (+)-BCA has not. The biological evaluations of all of the previously synthesized carbocyclic nucleoside analogues have been carried out with both enantiomers and, so far, only the enantiomers that are analogous to β-D-ribonucleosides have been found to exert the activity.[4] It is very interesting that (-)-BCA, having non-natural stereochemistry in the cyclopentenyl moiety, has exhibited the anti-viral activity. In (-)-BCA, an ethylene unit can be considered to mimic the oxygen atom



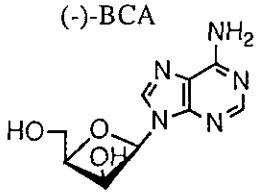
(-)-BCA



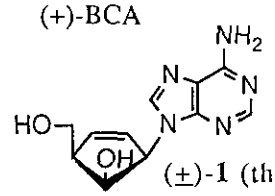
(+)-BCA



oxetanocin



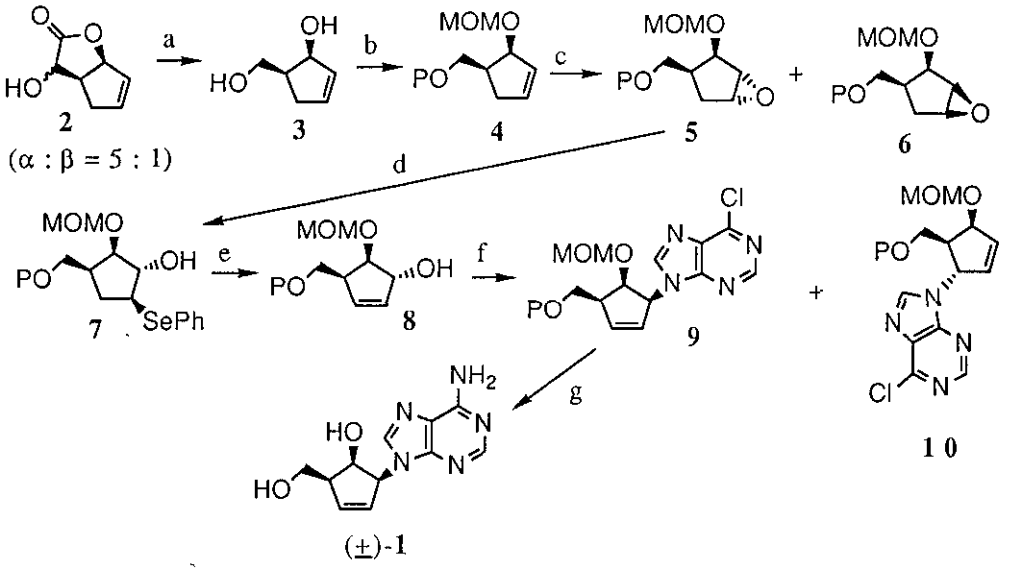
epinor-oxetanocin



(±)-**1** (this formula corresponds to the enantiomer having non-natural sugar moiety)

of oxetanose ring of oxetanocin, which has potent anti-HIV activity.[5] Recently epinor-oxetanocin was reported to show strong antiviral activity against HIV, the IC_{50} value of which was 0.54 μg/ml, while that of oxetanocin was 4.3 μg/ml.[6] This observation has led us to synthesize 9-(*c*-5-hydroxy-*c*-4-hydroxymethylcyclopent-2-en-*r*-1-yl)-9*H*-adenine [**1**: (±)-epinor-BCA]. It is because , if the ethylene unit in the enantiomer having non-natural sugar moiety of (±)-**1** could still mimic the oxygen atom in epinor-oxetanocin, one might expect the enhanced biological activity. We report here the synthesis of (±)-**1**.[7]

The starting material in the present synthesis was the bicyclic lactone (**2**) (α : β = 5 : 1), which was prepared in 65% yield by reaction of glyoxylic acid with cyclopentadiene in water.[8] Treatment of **2** with lithium aluminum hydride followed by oxidative cleavage and subsequent reduction gave the diol (**3**). Selective protection of the primary hydroxyl group as its *tert*-butyldiphenylsilyl ether and subsequent protection of the secondry hydroxyl group as its methoxymethyl ether provided the protected cyclopentene derivative (**4**). Epoxidation of **4** with *m*-CPBA proceeded in a stereoselective manner to give the epoxide (**5**) (94%)[9] along with its diastereomer (**6**) (6%).[10] Ring opening of the epoxide ring in **5** by phenylselenium anion



Scheme 2. P = $SiPh_2$-*t*-Bu. Reagents and conditions: a, i, $LiAlH_4$, Et_2O, ii, $NaIO_4$, CH_2Cl_2-H_2O, iii, $NaBH_4$, MeOH, 54%; b, i, *t*-BDPSCl, NEt_3, DMAP, CH_2Cl_2, ii, MOMCl, *i*-Pr_2NEt_3, CH_2Cl_2, 81%; c, *m*-CPBA, CH_2Cl_2, 94%; d, PhScScPh, $NaBH_4$, *n*-BuOH, reflux, 2 h; e, 30% H_2O_2, THF, 70% from **5**; f, 6-chloropurine, Ph_3P, DEAD, THF, -40 °C→room temperature, 10%; g, i, Bu_4NF, THF, ii, NH_3, MeOH, 80 °C (sealed tube), iii, conc. HCl, MeOH, reflux, 1 h, 64%.

generated from diphenyl diselenide and sodium borohydride[11] proceeded in a regioselective manner[12] to give the hydroxy selenide (7). Treatment of 7 with excess hydrogen peroxide gave the allylic alcohol (8).[13] The Mitsunobu reaction of 8 with 6-chloropurine gave the S_N2 product (9)[14] and S_N2' product (10)[15] in 10% and and 33% yields, respectively. The latter product (10) was apparently formed due to the steric hindrance of side chains on the cyclopentenol. The *cis* configuration between the methoxymethyl group and the purine base was evident from the upfield shift of methoxy (2.70 ppm) and methylene (4.26 ppm) groups of the methoxymethyl group due to shielding effect of the purine base. After desilylation of 9, the resultant alcohol was treated with ammonia in methanol, followed by deprotection of the methoxymethyl group to give the target compound [(±)-1: *mp* 226-229 °C (dec.)].[16] Evaluation of the biological potential of (±)-1 is under investigation.

ACKNOWLEDGMENT

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7. Since the enantiomer having natural sugar moiety is also expected to have some biological activity, we chose (±)-1 as the target molecule.
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9. **5**: 300 MHz ^{1}H-nmr ($CDCl_3$) δ: 1.03 (9H, s, *t*-Bu), 1.34 (1H, dd, *J* = 13.5 and 11 Hz, 5-H_a), 1.97 (1H, dd, *J* = 13.5 and 7.5 Hz, 5-H_b), 2.17 (1H, m, 4-H), 3 36 (3H, s, CH_3O), 3.52 and 3.53 (each 1H, AB type's d, *J* = 2 Hz, 1-H and 2-H), 3.61 (1H, dd, *J* = 10 and 6 Hz, CH_aOSi), 3.81 (1H, dd, *J* = 10 and 10 Hz, CH_bOSi), 4.24 (1H, d, *J* = 5 Hz, 3-H), 4.62 and 4.79 (each 1H, d, *J* = 6.6 Hz, OCH_2O), 7.39 (6H, m, Ph-H x 6), 7.64 (4H, m, Ph-H x 4).

10. **6**: 300 MHz ^{1}H-nmr ($CDCl_3$) δ: 1.04 (9H, s, *t*-Bu), 1.81 (1H, ddd, *J* = 15, 9, and 1.5 Hz, 5-H_a), 2.34 (1H, d, *J* = 15 Hz, 5-H_b), 2.34 (1H, m, 4-H), 3.28 (3H, s, CH_3O), 3.43 (1H, br s, 1-H or 2-H), 3.51 (1H dd, *J* = 2.5 and 1.5 Hz, 1-H or 2-H), 3.68 (1H, dd, *J* = 10 and 10 Hz, CH_aOSi), 3.86 (1H, dd, *J* = 10 and 5 Hz, CH_bOSi), 4.25 (1H, dd, *J* = 8 5 and 1.5 Hz, 3-H), 4 52 and 4.57 (each 1H, AB type's d, *J* = 7 Hz, OCH_2O), 7.38 (6H, m, Ph-H x 6), 7.65 (4H, m, Ph-H x 4).

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13. **8**: 300 MHz ^{1}H-nmr ($CDCl_3$) δ: 1.02 (9H, s, *t*-Bu), 2 99 (1H, m, 4-H), 3 41 (3H, s, CH_3O), 3.73 (1H, dd, *J* = 10 and 4 Hz, CH_aOSi), 3.79 (1H, dd, *J* = 10 and 6 Hz, CH_bOSi), 3.90 (1H, dd, *J* = 8 and 6 Hz, 5-H), 4.73 (2H, AB type's dd, *J* = 8 and 7 Hz, OCH_2O), 4.83 (1H, m, 1-H), 5.87 (1H, br d, *J* = 8 Hz, 3-H), 5.90 (1H, br d, *J* = 8 Hz, 2-H), 7.40 (6H, m, Ph-H x 6), 7.69 (4H, m, Ph-H x 4).

14. **9**: ^{1}H-nmr ($CDCl_3$) δ: 1.10 (9H, s, *t*-Bu), 2.70 (3H, s, CH_3O), 3.20 (1H, m, 4'-H), 3.77 (1H, dd, *J* =
10 and 2 Hz, 5'-H_a), 3.97 (1H, dd, *J* = 10 and 3.5 Hz, 5'-H_b), 4.07 and 4.26 (each 1H, d, *J* = 6.5 Hz, 4.67 (1H, dd, J = 6 and 6 Hz, 6'-H), 5 87 (1H, m, 1'-H), 5.88 and 6.23 (each 1H, m, 2'-H and 3'-H), 7.53 (10H, m, Ph_2Si), 8.04 and 8.74 (each 1H, s, purine-H x 2)

15. **10**: ^{1}H-nmr ($CDCl_3$) δ: 0.91 (9H, s, *t*-Bu), 2.65 (1H, dd, *J* = 14 and 6 5 Hz, 5'-H), 3.33 (3H, s, CH_3O), 3.90 (2H, m, CH_2OSi), 4.72 (2H, s, OCH_2O), 4.98 (1H, m, 4'-H), 5.67 (1H, m, 1'-H), 6.03 (1H, m, 3'-H), 6.37 (1H, m, 2'-H), 7.37 (10H, m, Ph_2Si), 8.02 and 8.63 (each 1H, s, purine-H x 2).

16. **1**: 300 MHz ^{1}H-nmr (CD_3OD) δ: 3.03 (1H, m, 4'-H), 3.82 (1H, dd, *J* = 9 and 6 Hz, 5'-H_a), 3.88 (1H, dd, *J* = 9 and 6.6 Hz, 5'-H_b), 4.68 (1H, dd, *J* = 5.5 and 5.5 Hz, 6'-H), 5 67 (1H, m, 1'-H), 5.95 (1H, m, 3'-H), 6.21 (1H, m, 2'-H), 8.01 and 8.23 (each 1H, s, purine-H x 2). High-resolution ms *m/z* Calcd for $C_{11}H_{13}N_2O_5$ (M^+): 247.1069. Found: 247.1055

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