A NOVEL AND EFFICIENT SYNTHESIS OF 9-(*c*-4, *t*-5-BISHYDROXYMETHYLCYCLOPENT-2-EN-*r*-1-YL)-9*H*-ADENINE (BCA) HAVING ANTI-HIV ACTIVITY FROM NORBORNADIENE[1]

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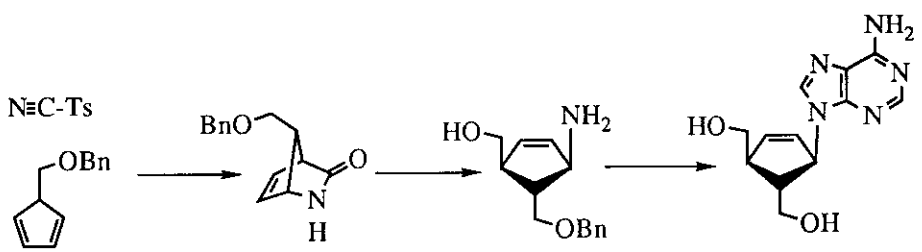
Abstract—9-(*c*-4, *t*-5-Bishydroxymethylcyclopent-2-en-*r*-1-yl)-9*H*-adenine (BCA: **1**), a novel carbocyclic nucleoside having significant anti-HIV activity, has been synthesized from norbornadiene.

In the search for therapeutic agents against AIDS (acquired immunodeficiency syndrome), much attention has been focused on the preparation of analogues of natural nucleosides as antimetabolites.[2] Previously, we synthesized 9-(*c*-4, *t*-5-bishydroxymethylcyclopent-2-en-*r*-1-yl)-9*H*-adenine (BCA : **1**) from the hetero Diels—Alder adduct (**3**) *via* the cyclopentenylamine (**2**) as the key intermediate and

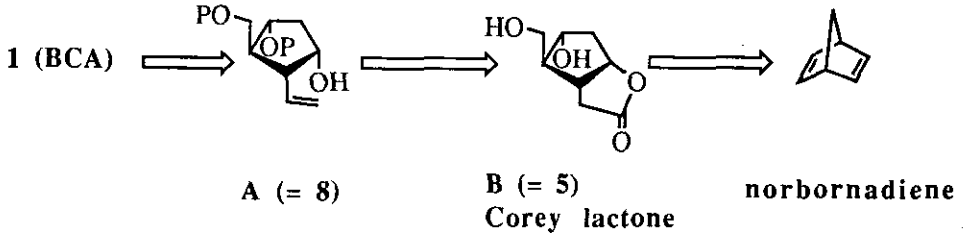


3 **2** **1 (BCA)**

Scheme 1

found significant anti-HIV activity.[3] Furthermore, our recent success in the separation of the optical isomers of BCA has demonstrated that the potent anti-HIV activity of racemic BCA is expressed solely by the (—)-enantiomer.[4] While determination of the absolute structure of (—)-BCA is in progress, it is an urgent need to elaborate a new and practical synthetic method of BCA from readily available materials. Two requisites for such synthetic plan are 1) the method should be extendible to the synthesis of both of the enantiomers of BCA and 2) incorporation of adenine should be achieved readily in a highly regio- and stereoselective manner. This paper reports a novel and efficient synthesis of BCA from norbornadiene through racemic Corey lactone. Two reactions, introduction of 6-chloropurine into a cyclopentanol by Mitsunobu reaction and transformation of the cyclopentanol to a cyclopentene by *o*-nitrophenyl selenocyanate—tributylphosphine, are included as the key steps.

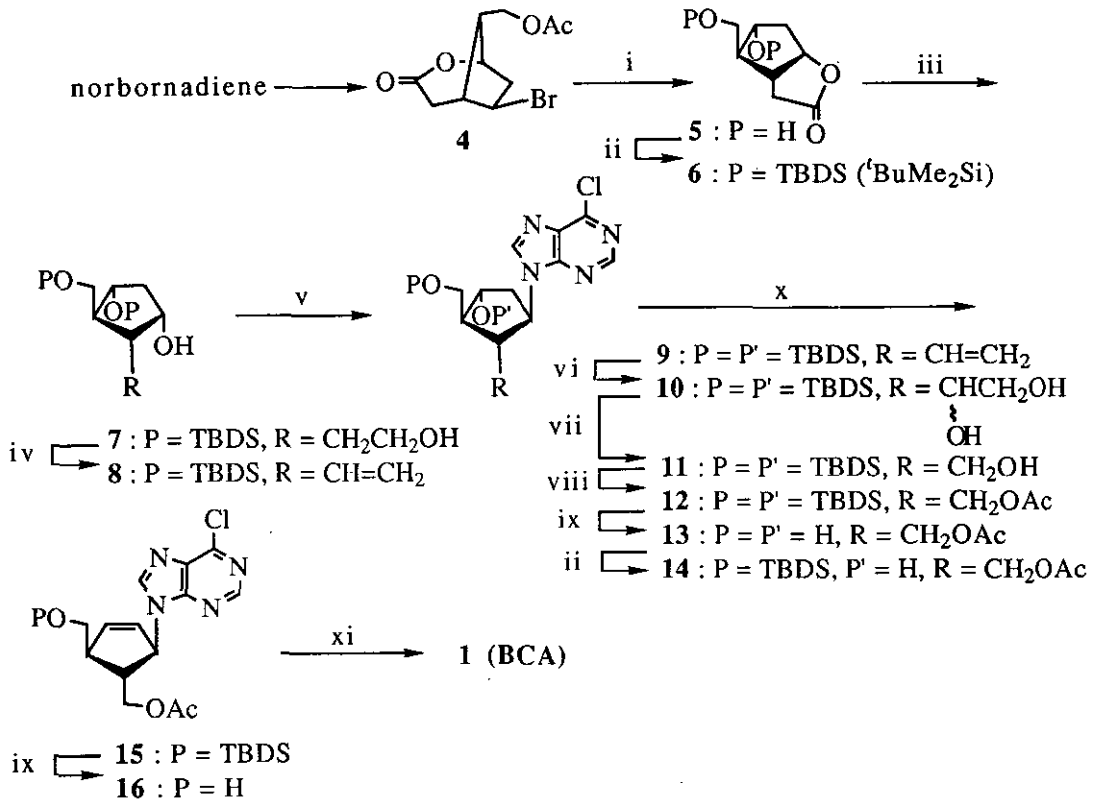
Our synthetic plan is shown by retrosynthesis shown in Scheme 2. We considered that a key precursor (**A**) for the synthesis of **1** could be synthesized stereoselectively from Corey lactone [**B** (=**5**)].



Scheme 2

Corey lactone (**5**) was obtained from the ring transformation of the bicyclic lactone (**4**) prepared from norbornadiene by a modification of the Corey's method.[5] Thus, heating of **4** in water gave **5** in quantitative yield. After protection of **5** with *tert*-butyldimethylsilyl (TBDS) group, compound (**6**) was reduced with $LiAlH_4$ to give the diol (**7**) in 58% yield. Olefination of **7** to the key intermediate (**8**) was achieved by treatment with *o*-nitrophenyl selenocyanate—tributylphosphine followed by oxidation with hydrogen peroxide.[6] When **8** was condensed with 6-chloropurine by an

application of Mitsunobu reaction,[7] the carbocyclic nucleoside (**9**) was obtained in 65% yield, together with a small amount (9%) of the 7-substituted purine derivative. In order to shorten one carbon unit from the vinyl group, **9** was subjected successively to the dihydroxylation with osmium tetroxide—4-methylmorpholine *N*-oxide, oxidative cleavage with sodium periodate, and reduction with sodium borohydride to give the alcohol (**11**) in 84% overall yield. After acetylation, two silyl groups of **12**



Scheme 3 Reagents and conditions : i, H_2O, reflux; ii, $^tBuMe_2SiCl$, imidazole, DMF; iii, LAH, ether, 0 °C; iv, a, *o*-nitrophenyl selenocyanate/tributylphosphine(Bu_3P), tetrahydrofuran(THF), 0 °C, b, H_2O_2; v, 6-chloropurine, diethyl azodicarboxylate/ triphenylphosphine, THF, room temperature; vi, osmium tetroxide/4-methylmorpholine *N*-oxide, acetone; vii, a, $NaIO_4$, MeOH—H_2O (3:1), b, $NaBH_4$, MeOH; viii, acetic anhydride, pyridine; ix, tetra-*n*-butylammonium fluoride ($^nBu_4NF$), THF; x, a, *o*-nitrophenyl selenocyanate/Bu_3P, THF, room temperature, b, H_2O_2; xi, NH_3, MeOH, 90 °C (sealed tube)

were removed by treatment with tetra-*n*-butylammonium fluoride to give the diol (**13**), whose primary hydroxy group was selectively protected again with TBDS group. The cyclopentene ring formation in **14** thus obtained was carried out by treatment with *o*-nitrophenyl selenocyanate—tributylphosphine and subsequent oxidation with hydrogen peroxide to give **15** in 77% yield. Finally, removal of the silyl group of **15** followed by treatment with ammonia gave desired compound (**1**), mp 179 — 180 °C (lit.,[3] mp 179 — 180 °C).

The present method for the synthesis of **1** has the following two advantages: 1) the method may be applied for an enantioselective synthesis of **1** by using both enantiomers[5] of Corey lactone and 2) the method may have wide applicability for the synthesis of various analogues of **1**.

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