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SYNTHESIS OF (1*R*,4*S*,5*R*)-9-(4,5-BISHYDROXY-METHYLCYCLOPENT-2-EN-1-YL)-9*H*-ADENINE [(-)-BCA] AND SELECTIVE INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS[1]

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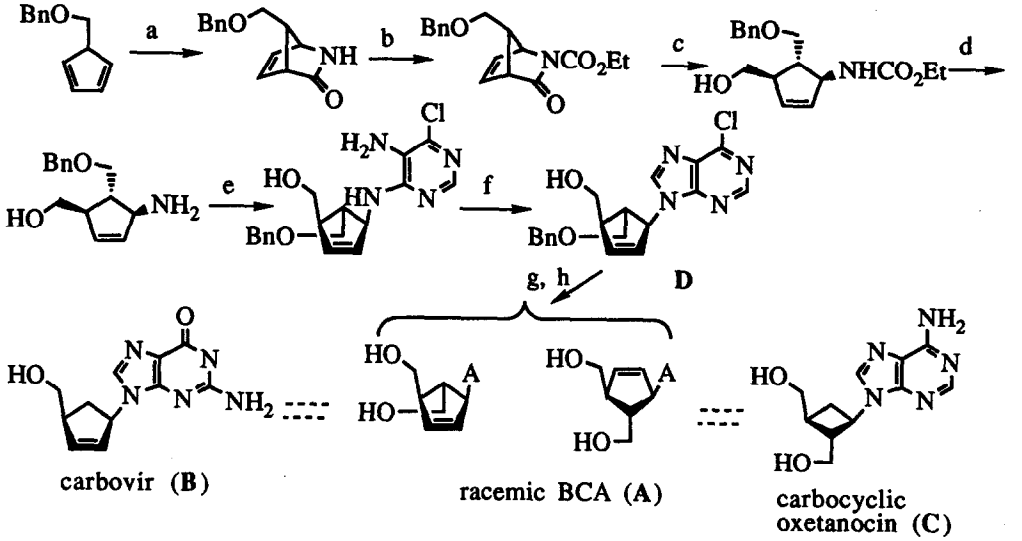
Summary: (1*R*,4*S*,5*R*)-9-(4,5-Bishydroxymethylcyclopent-2-en-1-yl)-9*H*-adenine [(-)-BCA] has been synthesized from (-)-Corey lactone in 11 steps and shown to have potent and selective effects against human immunodeficiency virus type 1. The result demonstrated that the potent-HIV activity of racemic BCA obtained in our previous work is expressed solely by the (1*R*,4*S*,5*R*)-(-)-isomer.

9-(*c*-4,*t*-5-Bishydroxymethylcyclopent-2-en-*r*-1-yl)-9*H*-adenine (BCA),[3,4] previously synthesized by the route shown in Scheme 1,[4,5] has showed significant protection of MT-4 cells from the cytopathic effects of HIV-1. The fact that signifi-

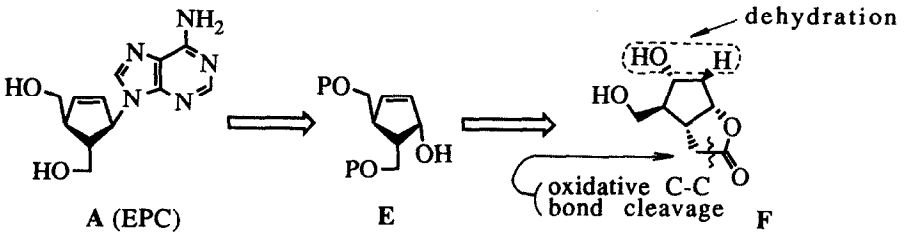


Scheme 1. A=9-adenyl. All formulae except the starting diene and BCA are expressed as if they have absolute structures analogous to that of carbovir and hence β-D-ribofuranosyl nucleosides. Reagents and conditions for steps (a-h) are described in reference 4 in detail.

cant antiviral effects observed at BCA concentrations that are approximately 200-fold below cytotoxic concentrations for the host cells has made BCA a high-priority candidate for further development as a potentially useful new antiviral drug for the treatment and prophylaxis of AIDS.[4]

BCA (**A**) has a hybrid structure between carbovir[6] and carbocyclic oxetanocin[7], both of which have significant anti-HIV activity. One enantiomer of A is regarded as a hydroxymethyl derivative of carbovir (B), while the other one as a homomethylene derivative of carbocyclic oxetanocin (C). Hence, there was possibility that, on this racemate (**A**), each or both of the enantiomers could exert the anti-HIV activity. In order to evaluate the activity of each enantiomer, we have separated the enantiomers of BCA by means of high-pressure chromatography of the diastereomers of [1*S*]-(-)-camphanic acid ester of the intermediate (**D**) obtained in our previous synthesis[4] (Scheme 1). As a result, it has been found that (-)-BCA is a potent inhibitor of HIV-1 while (+)-BCA is inactive. This paper reports the successful conversion of (-)-Corey lactone (the monobenzoyl ester: **1**) to one enantiomer of BCA in eleven steps, all in regio- and stereospecific manners, and its identification with (-)-BCA shown previously as a potent inhibitor of HIV-1.[2]

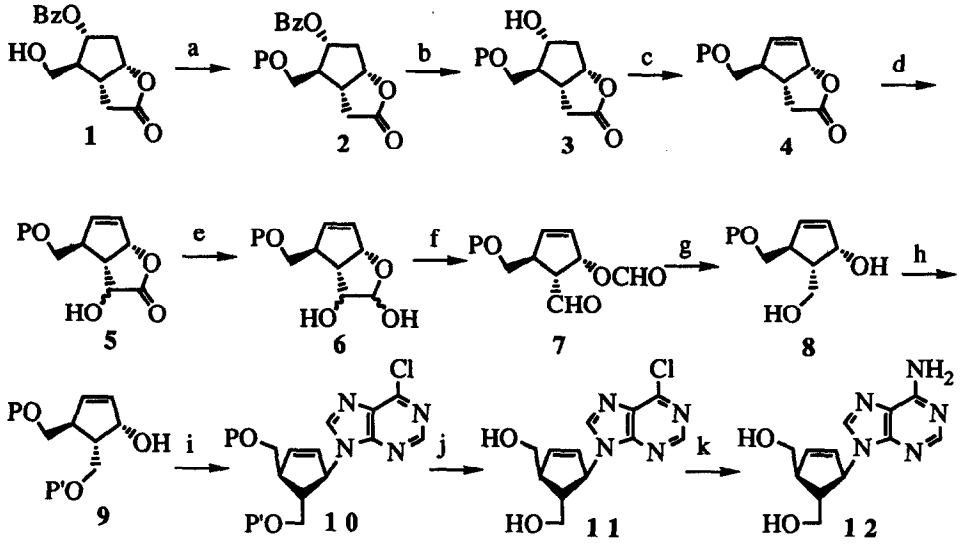
Based on the recent finding that Mitsunobu reaction of cyclopentanols and cyclopentenols with 6-chloropurine afforded the 9-substituted purine derivative with complete inversion,[8,9] the retrosynthetic route shown in Scheme 2 has been elaborated. Thus, the direct precursor of the target molecule (**A**) is the triol (**E**) which in turn would be synthesized from (-)-Corey lactone **F**.[10] For the conversion of **E** to **A**, the aforementioned Mitsunobu reaction with 6-chloropurine followed by amination would be the choice, while dehydration and one-carbon unit shorting in the lactone ring were planned from (-)-Corey lactone **F** to **E** .



Scheme 2. P = an appropriate protecting group. All formulae correspond to the absolute structures.

The monobenzoyl ester (**1**: $[\alpha]_D^{20}$ -79.5°) of (-)-Corey lactone was silylated to give **2**, which by basic hydrolysis to give the secondary alcohol (**3**). The phenylselenylation of **3** followed by oxidative deselenylation[11] afforded the cyclopentene (**4**) as a sole product. The fact that no isomer was formed in this case fits well, as expected, that only *trans* elimination is possible for the above dehydration (Note that the OH and methine proton attached to CH_2OSi of **3** are *cis*-relationship).

Introduction of hydroxyl group in the lactone ring at the active methylene carbon[12] followed by reduction gave the diol (**6**). Oxidative cleavage with subsequent reduction gave the diol (**8**). The silylation of the primary alcohol of **8** gave the disilylated monoalcohol (**9**). Thus, the appropriately protected triol (cf. **E** in Scheme 2) has now been synthesized as an enantiomerically pure compound (EPC). The Mitsunobu reaction of **9** with 6-chloropurine gave the 9-substituted purine (**10**) in 49% yield. As noted in our previous paper,[8] a small amount (12%) of 7-substituted purine was formed as the byproduct.[9] After desilylation of **10**, the diol (**11**) thus obtained was treated with ammonia to give the target molecule [**12**: mp 207-208 °C, $[\alpha]_D^{20}$ -29.0° (*c* 0.3 in MeOH)]. The specific rotation of **12** thus obtained was identical with that of (-)-BCA previously obtained by the optical resolution of (±)-BCA.[2]



Scheme 3. P = $SiPh_2$-*t*-Bu, P' = $SiMe_2$-*t*-Bu. Reagents and conditions: a, *t*-BDPSCl, imidazole, DMF, 100%; b, 1% NaOH-MeOH, 88%; c, i, *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, r. t., ii, 30% H_2O_2, 89%; d, i, KHMDS, THF, -78 °C, ii, MoOPH, 84%; e, $LiAlH_4$, Et_2O, 82%; f, $Pb(OAc)_4$, C_6H_6, r. t., 91%; g, $LiAlH_4$, Et_2O, 75%; h, *t*-BDMSCl, imidazole, DMF, 66%; i, 6-chloropurine, Ph_3P, DEAD, THF, -30 °C→0 °C, 48%; j, Bu_4NF, THF, 93%; k, NH_3, MeOH, 90 °C (sealed tube), 83%.

The biological evaluations of all of the previously synthesized carbocyclic nucleoside analogues have been carried out with mixtures of (+) and (-) enantiomers and, so far, only the enantiomers that are analogous to β-D-ribonucleosides have been found to exert the activity.[6] It is very interesting that (-)-BCA, having non-natural stereochemistry in the cyclopentenyl moiety, has exhibited the antiviral activity. This fact implies that (-)-BCA would not only be an attractive candidate for anti-HIV agent, but also provide a new tool for the clarification of differences between the biochemistry of the virus and the uninfected cells.

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