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Convenient Route to Both Enantiomers of a Highly Functionalized Trans-Disubstituted Cyclopentene. Synthesis of the Carbocyclic Core of the Nucleoside BCA

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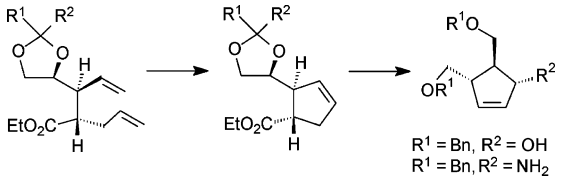
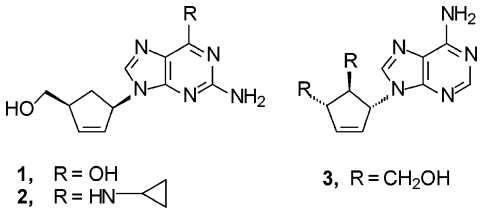


Synthesis of both enantiomers of a highly functionalized cyclopentenol derivative, versatile building block for a vast array of biologically active compounds, is described. The key steps involve stereocontrolled synthesis of a diene with two syn-disposed substituents from a (*R*)-(+)-glyceraldehyde derivative, ring-closing metathesis of this diene, and functional group manipulation of the resulting trans-disubstituted cyclopentene. One of the enantiomers of the cyclopentenol thus obtained has been converted to an amino cyclopentene, the carbocyclic core of the nucleoside (−)-BCA, a potent inhibitor of HIV reverse transcriptase.

Nucleosides[1] exhibit a wide range of biological activity. The metabolic instability of nucleosides caused by cleavage of glycosidic bonds by the enzymes phosphorylases has restricted their therapeutic application. The search for metabolically stable nucleosides with potent antitumor and antiviral activities led to several structural modifications. One such modification is replacement of the oxygen atom of the sugar ring by a methylene unit resulting in carbocyclic nucleosides. The carbocyclic nucleosides are highly resistant to phosphorylases with comparable biological activity to the parent nucloesides. With the outbreak of the AIDS epidemic, the search for new carbocyclic nucleoside analogues[2] intensified to a great extent. Several carbocyclic nucleosides[2a,b] such as carbovir **1**, abacavir **2**, and bis(hydroxymethyl)cyclopentenyl adenine (BCA) **3** have been found to be inhibitors of HIV, the causative agent of AIDS. Several approaches[3] to the synthesis of the carbocyclic core of the nucleosides **1** and **2** have been reported. However, there are only few reports[4] on the synthesis of BCA. We have initiated a program on the synthesis of carbocyclic nucleosides accomplishing a synthesis of (±)-cyclobut A[5] and (−)-carbovir.[6]



We next focused our attention on the synthesis of the carbocyclic moiety of BCA. While considering this synthesis, we were guided by our desire to design a synthesis of an enantiopure cyclopentene derivative that allows access not only to BCA but also to a vast array of vicinally substituted bioactive cyclopentanoids such as prostaglandins,[7] jasmones,[8] brefeldin,[9] etc. We visualized that the cyclopentenol **4** would be a versatile building block for entry into these classes of compounds. We herein report a stereocontrolled approach to the synthesis of both enantiomers of the highly functionalized cyclopentene derivative **4** and conversion of one of them to the amino cyclopentene **5**, an intermediate to (−)-BCA **3**.

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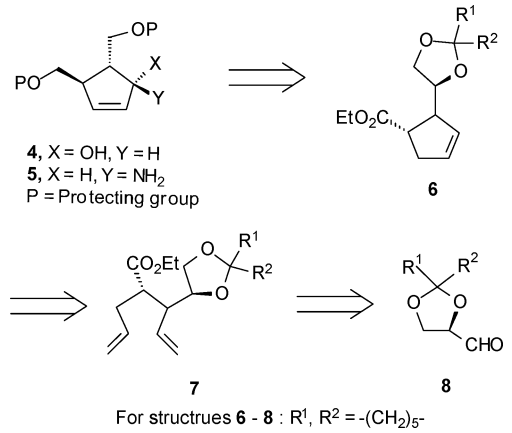
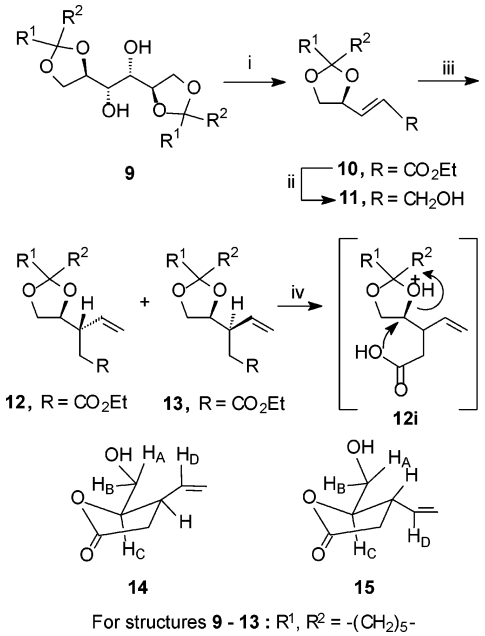
SCHEME 1



A retrosynthetic analysis (Scheme 1) dictated that the cyclopentenol **4** in principle could be obtained from the cyclopentene derivative **6** through functionalization. This should be available from ring-closing metathesis (RCM)[10] of the diene **7**. The diene **7** can be constructed from the glyceraldehyde derivative **8**. Sacrificing the chirality present in the ketal moiety at a suitable step in the synthetic sequence will ensure complete transfer of chirality from the C-2 center of the glyceraldehyde derivative **8** to the cyclopentenol **4**.

The synthesis begins with the unsaturated esters **12** and **13**. These were prepared from the protected D-mannitol derivative **9** (Scheme 2).[11] Wittig−Horner reaction of the in situ-generated aldehyde **8** from periodate cleavage of the diol **9** with triethyl phosphonoacetate afforded a mixture of the unsaturated ester **10** and its (*Z*)-isomer in a 4:1 ratio, which without separation was reduced with $LiAlH_4$ to give the alcohol **11** and its (*Z*)-isomer in a 4:1 ratio. Ortho ester Claisen rearrangement of this unsaturated alcohol mixture **11** gave a mixture of the unsaturated esters **12** and **13** in a ca. 1:1 ratio. Compounds **12** and **13** were separated by flash chromatography. For stereochemical assignment, the esters **12** and **13** were converted to the lactones **15** and **14**, respectively, through alkaline hydrolysis of the ester followed by acid-induced deketalization. Stereochemical assignment is based on comparison of the chemical shifts of H_A and H_C between the lactones **14** and **15**. The global energy minimum structure of the lactones as obtained by AM1 calculations[12] shows that in the lactone **14** in which the hydroxymethyl and the vinyl groups are cis to each other, H_A lies in the shielding cone of the vinyl group[13] and is shielded to δ 3.81 compared to H_A (δ 3.92) in the lactone **15**. Similarly, H_C, which is cis to the vinyl group in **15**, is shielded to δ 4.25 in **15** in comparison to that (δ 4.54) in the lactone **14**. A positive NOE (1%) between H_A and the vinylic proton H_D in the lactone **14** and that between H_C and the vinylic proton H_D in the lactone **15** also indicated the assigned structures. The inversion of configuration at C-2 of the esters **12** and **13** from **S** to **R** at C-5 during formation of the lactones **14** and **15** arises through intramolecular displacement of the protonated ketal oxygen in the intermediate **12i** by the carboxyl group. Thus, the unsaturated ester that produced the lactone **14** has the stereochemistry depicted in the structure **13**. The unsaturated ester giving the lactone **15** posseses the structure **12**. The absolute configuration at C-3 of the esters **12** and **13** was confirmed earlier as **S** and **R**, respectively, through transformation of the ester **13** to a cyclopentenol derivative of known absolute configuration.[6]

SCHEME 2[a]



[a] Reagents and conditions: (i) $NaIO_4$, MeCN/H_2O (3:2), K_2CO_3, $P(O)(OEt)_2CH_2CO_2Et$, 67%; (ii) $LiAlH_4$, Et_2O, −60 °C, 62%; (iii) $CH_3C(OEt)_3$, propionic acid, 140 °C, 6 h, 68%; (iv) KOH, EtOH−H_2O, 85 °C, 2 h, then 80% AcOH, 85 °C, 4 h, 61%.

With the unsaturated esters **12** and **13** ready in hand, we proceeded toward the synthesis of the diene **7** from alkylation of the enolate generated from the ester **13**. On the basis of Houk's model[14] for addition of electrophiles to C=C double bonds having an α-chiral center, we anticipated that allylation would take place from the side of the C-3 H to produce the diene **7** as the major product, which bears the required anti relationship between the ketal and the CO_2Et groups. Allylation of the lithium enolate of the ester **13** gave an inseparable mixture of the desired diene **(2*S*,3*S*,2′*S*)-7** and its **(2*R*,3*S*,2′*S*)**-diastereoisomer in a ca. 3:1 ratio. Allylation of the enolate of the ester **12** also produced an inseparable mixture of the **(2*R*,3*R*,2′*S*)**- and **(2*S*,3*R*,2′*S*)**-allylated products in an almost similar ratio (3:1). The relative orientation between the ketal and the CO_2Et moieties in the major

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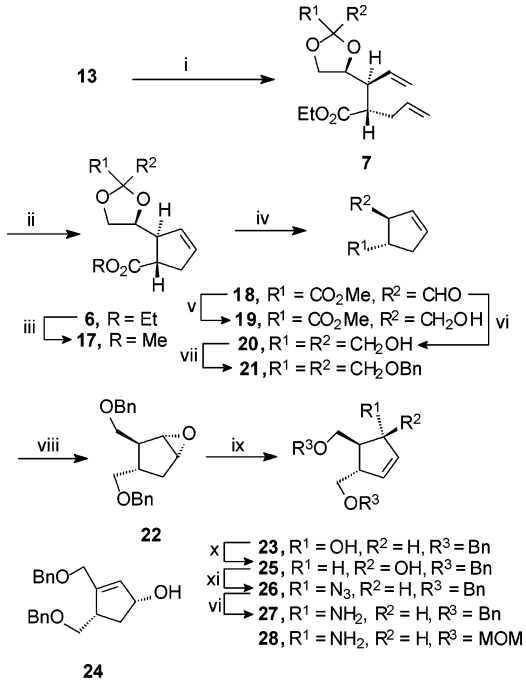
SCHEME 3[a]



[a] Reagents and conditions: (i) LDA, THF, $CH_2{=}CHCH_2Br$, HMPA, −78 °C−rt, 84%. (ii) **16**, C_6H_6, 60 °C, 20 h, 96%. (iii) NaOEt−EtOH, reflux, 10 h, then CH_2N_2, Et_2O, 84%. (iv) 75% AcOH, 18 h, then $NaIO_4$, MeOH−H_2O, rt, 1 h, 71%. (v) $NaBH_4$, MeOH, 55%. (vi) $LiAlH_4$, Et_2O, 0 °C−rt, 1 h, 68%. (vii) NaH, $PhCH_2Br$, THF, HMPA, reflux, 6 h, 75%. (viii) *m*-CPBA, CH_2Cl-CH_2Cl, 0 °C−rt, 5 h, 85%. (ix) PhSeSePh/$NaBH_4$, then 30% H_2O_2, 40%. (x) *p*-$NO_2C_6H_4COOH$, DEAD, PPh_3, C_6H_6, 78%, then KOH, EtOH−H_2O, reflux, 30 min, 91%. (xi) (a) MsCl, pyridine, 0 °C; (b) NaN_3, DMF, 100 °C.

isomer **7** could be established only after transformation of the mixture to the disubstituted cyclopentene **18** as shown in Scheme 3. RCM of the mixture of the diene **7** and its diastereoisomer with Grubbs' catalyst, Ph-CH=$Ru(PCy_3)_2Cl_2$ (**16**), in benzene at 60 °C proceeded smoothly to provide a mixture of the cyclopentene derivative **(1*S*,2*S*,2′*S*)-6** and its **(1*R*,2*S*,2′*S*)**-diastereoisomer in about the same ratio (3:1) in excellent yield. This mixture was equilibrated with 2% NaOEt in EtOH to produce a single cyclopentene derivative **17** after diazomethane treatment of the resulting carboxylic acid. The compound **17** was then converted to the hydroxy ester **19** through a three-step sequence involving acid-induced cleavage of the ketal, periodate cleavage of the resulting diol to the aldehyde **18**, and sodium borohydride reduction of the aldehyde **18** to the hydroxy ester **19**. After alkaline hydrolysis, **19** failed to provide any lactone. This confirmed the trans orientation of the vicinal substituents in the cyclopentenes **6**, **18**, and **19** and hence the syn relationship of the corresponding substituents in their precursor, diene **7**. After the trans orientation of the vicinal substituents was established, the cyclopentene **18** was reduced with $LiAlH_4$ to produce the diol **20**. The diol **20** was protected to give the dibenzyl ether **21**. For introduction of the hydroxyl group at the allylic position of the cyclopentene **21**, we decided to proceed through an epoxide elimination route. Epoxidation of the cyclopentene derivative **21** with mCPBA gave mainly the epoxide **22** with a trace amount of the other diastereoisomeric epoxide. Although the stereochemistry of the epoxide could not be ascertained at this stage, it may be speculated that the benzyloxy methyl group at the allylic position probably directed epoxidation from its opposite face due to steric reasons. An attempt to convert the epoxide **22** to the cyclopentenol **23** by using $LiNEt_2$[15] produced a complex mixture of products. Finally, we employed the procedure developed by Sharpless[16] for converting epoxide to allylic alcohol. Sequential treatment of the epoxide **22** with PhSeSePh−$NaBH_4$ and H_2O_2 (30%) afforded a mixture of the regioisomeric cyclopentenols **23** and **24**. Chromatographic purification of the mixture gave the desired cyclopentenol **23** in 40% yield and the isomeric cyclopentenol **24** in 20% yield. The cyclopentenol **23** was characterized by the appearance of two olefinic CH at δ 5.89 (1H, m) and 5.94 (1H, dd, J = 1.7 and 5.8 Hz). In contrast, the isomeric cyclopentenol **24** displayed only one olefinic CH as a singlet at δ 5.77. The cis stereochemical assignment of the C-1 OH group with C-4 benzyloxymethyl group was ascertained from NOE (0.5%) between C-1 and C-4 hydrogens. This also confirms the stereochemical assignment of the epoxide as depicted in the structure **22**. The cyclopentenol **23** obtained as above from the unsaturated ester **13** exhibits an optical rotation $[\alpha]_D = -41$ (*c* 0.2, $CHCl_3$). Application of the same protocol to unsaturated ester **12** afforded the enantiomer of the cyclopentenol derivative **23** with an optical rotation $[\alpha]_D = +40.25$ (*c* 0.4, $CHCl_3$).

Transformation of the cyclopentenol **23** to the amino cyclopentene **27** was achieved through standard protocol. Inversion of the stereochemistry of the C-1 OH group in **23** was accomplished by Mitsunobu reaction[17] to afford the cyclopentenol **25**. The cyclopentenol **25** was then converted to the azide **26** through the corresponding mesylate. Lithium aluminum hydride reduction of the azide **26** finally afforded the amino cyclopentene **27**. It is noteworthy that the MOM ether analogue **28** of the amino cyclopentene **27**, prepared by Tanaka et al.,[4c] has been converted to (−)-BCA. An analogue of the cyclopentenol **24** has also been converted to nucleosides.[18]

In conclusion, we have developed a route to the synthesis of trans vicinally disubstituted hydroxy- and amino cyclopentenes in enantiomerically pure form using an (*R*)-(+)-glyceraldehyde derivative as the chiral adjuvant.[19] The present approach provides access to both enantiomers of the cyclopentenyl derivatives from (*R*)-(+)-glyceraldehyde derivative. The key step involves ring-closing metathesis of a prebuilt diene carrying two anti-disposed substituents. Functional group manipulation in the cyclopentene obtained in this way finally led to the

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trans-disubstituted functionalized cyclopentene, the carbocyclic core of the nucleoside BCA.

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Supporting Information Available: Experimental procedures for all new compounds with microanalytical data, as well as copies of NMR (^{1}H, ^{13}C, and DEPT) for compounds **6**, **7**, **9**−**15**, and **17**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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