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A Remarkably Simple Chemicoenzymatic Approach to Structurally Complex Bicyclo[3.1.0]hexane Carbocyclic Nucleosides

Hyung R. Moon, Harry Ford, Jr., and Victor E. Marquez*,†

Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, FCRDC, Frederick, Maryland 21702-1201

marquezv@dc37a.nci.nih.gov

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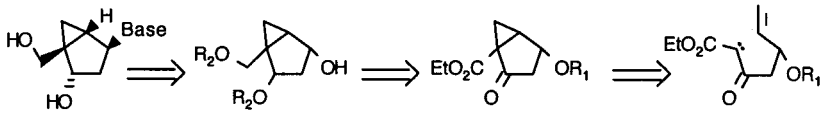
ABSTRACT



Intramolecular cyclopropanation of a carbene engendered from the corresponding diazo β-ketoester produced the desired bicyclo[3.1.0]-hexane pseudosugar. Purine nucleosides obtained via Mitsunobu coupling were resolved with adenosine deaminase. The requisite β-ketoester was assembled in one step from ethyl acetoacetate and acrolein.

Over the past several years, our laboratory, in collaboration with other investigators, has undertaken a systematic study of the role of the sugar ring in the process of recognition and binding of nucleosides, nucleotides, and oligonucleotides to their target enzymes.[1,2] The emerging picture from these studies shows that the majority of enzymes appear to have strict conformational requirements for substrate binding with the furanose ring in a well-defined shape. In particular, methanocarba nucleosides built on a rigid bicyclo[3.1.0]-hexane template have been instrumental in defining the role of sugar puckering in nucleosides and nucleotides by stabilizing the active receptor-bound conformation and thereby identifying the biologically favored sugar conformer.[1] The two principal conformational parameters controlled by the bicyclo[3.1.0]hexane template are the ring pucker, defined by the phase angle of pseudorotation P (0°−360°, Figure 1), and the deviation from planarity indicated by the maximum out-of-plane pucker ν_{max} ($\nu_{max} = \nu_2/\cos P$).[3] The value of P depends on the five endocyclic torsion angles $\nu_0-\nu_4$ (the fused cyclopropane ring being excluded) according to the following relationship: $\tan P = (\nu_4 + \nu_1) - (\nu_3 + \nu_0)/2\nu_2 (\sin 36° + \sin 72°)$.[3] By convention, a phase angle

† Fax: 301-846-6033.

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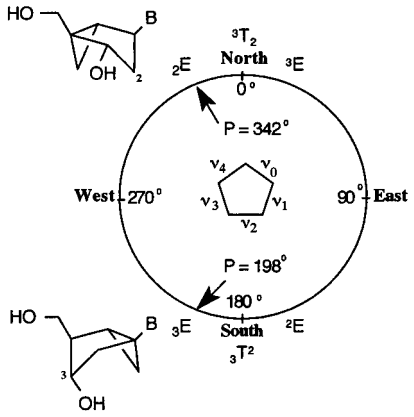
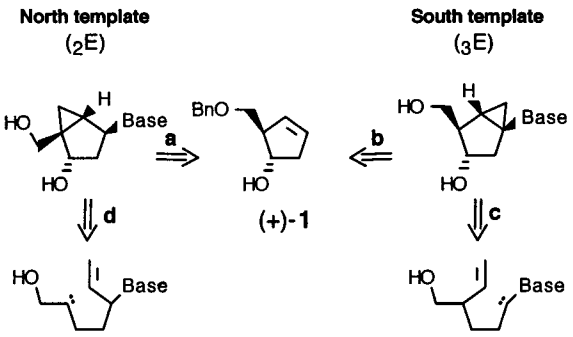


Figure 1. Fixed location of the bicyclo[3.1.0]hexane templates in the pseudorotational cycle.

$P = 0°$ is set to correspond to an absolute North conformation of the cyclopentane ring in a symmetrical twist form. $^3T_2$. and a phase angle $P = 180°$ corresponds to the antipodal South conformation, $_3T^2$.[3] By virtue of its rigid pseudoboat conformation,[1] the bicyclo[3.1.0]hexane system is able to lock the conformation of the cyclopentane ring into envelope conformations $_2E$ (North) and $_3E$ (South) that are within the normal range of North ($_2E \rightarrow {}^3T_2 \rightarrow {}^3E$, $P = 0° \pm 18°$) and South ($^2E \rightarrow {}_3T^2 \rightarrow {}_3E$, $P = 180° \pm 18°$) conformations observed for the majority of conventional nucleosides either in solution or in the solid state (Figure 1).[3]

The synthetic approach to these conformationally locked carbocyclic nucleosides is not simple and relies on the availability of the chiral synthon (1*S*,2*R*)-2-[(benzyloxy)-methyl]cyclopent-3-enol [(+)-**1**],[4] which we have successfully converted into all nucleobase families of locked bicyclo[3.1.0]hexane North ($_2E$) and South ($_3E$) nucleosides (Scheme 1, routes a and b).[5]

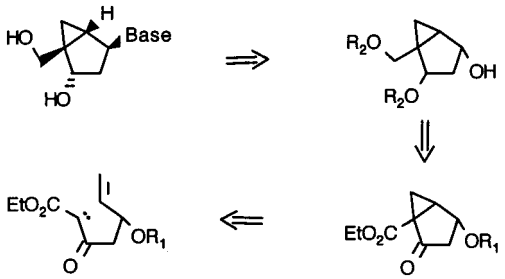
Scheme 1



Since the availability of (+)-**1** is a limiting factor, our plan was to design the simplest chemical approach possible to the requisite racemic bicyclo[3.1.0]hexane system and rely on a practical and efficient enzymatic step for final chiral resolution. On the basis of the fact that the majority of active antiviral nucleosides have a locked North conformation,[1] we decided to test the validity of our chemicoenzymatic approach with the conformationally rigid purine nucleosides, (N)-(+)-methanocarba-G (**15**)[1b] and (N)-(−)-methanocarba-A (**20**),[1b] in which only the enantiomerically equivalent β-D-nucleosides are expected to be recognized as substrates of the enzyme adenosine deaminase (ADA).[6]

We have recently reported on the use of an olefin ketocarbene cycloaddition to effectively generate a bicyclo[3.1.0]-hexane platform to synthesize a conformationally locked South nucleoside (Scheme 1, route c).[7] Herein, we wish to report a diametrically opposed approach to a North platform outlined in retrosynthetic fashion in Scheme 2. The most attractive feature of this approach is that we can build a rather complex molecular scaffold with remarkable diastereoselectivity using very simple starting materials and reagents.

Scheme 2



As shown in Scheme 3, a solution of LDA treated with ethyl acetoacetate and reacted with acrolein gave a 53% yield of a keto−enol mixture of racemic ethyl 5-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-3-oxohetp-6-enoate [(±)-**3a**,**b**] after protection of the alcohol as a silyl ether. Following diazo transfer with tosyl azide, the β-keto ester was converted to the diazo compound (±)-**4** in nearly quantitative yield (99%). Metal-catalyzed thermolysis of (±)-**4**, which presumably proceeds via a carbenoid intermediate,[8] gave a mixture of (±)-**5** (61%) and its diastereoisomer (±)-**6** (23%). The identity of (±)-**5** was unequivocally confirmed after tandem reductions with sodium borohydride and lithium aluminum hydride (LAH) gave diol (±)-**8** in 79% yield (Scheme 4). Benzylation of (±)-**8** followed by removal of the silyl ether

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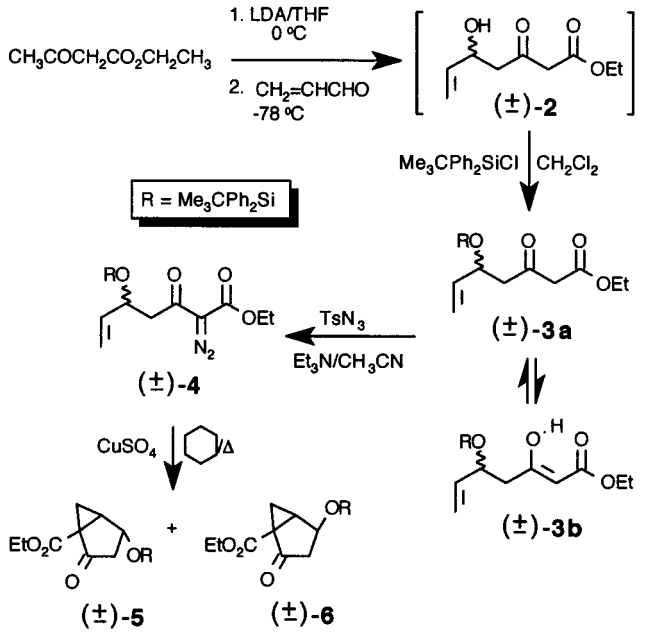
Scheme 3

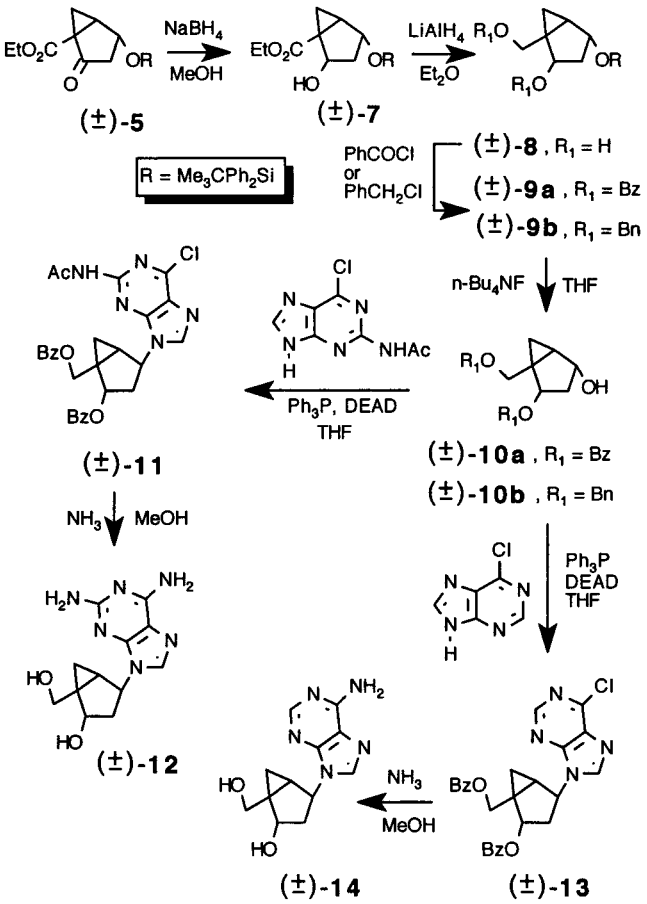


produced compound (±)-**10b**, which, except for its lack of optical rotation, was identical to authentic chiral material made previously from (+)-**1**.[1g] The stepwise reduction of (±)-**5**, first with sodium borohydride to reduce the keto group, produced compound (±)-**7** exclusively as hydride attack occurred stereoselectively from the less encumbered convex face of the bicyclo[3.1.0]hexane system. In this manner, the generated hydroxyl group and the fused cyclopropane ring appear to be located on the same face of the cyclopentane ring. Surprisingly, the simultaneous reduction of both ester and keto functions of (±)-**5** with diisobutylaluminum hydride resulted in a mixture of epimeric alcohols. Presumably, the ester group plays an important role in the initial borohydride reduction by directing hydride attack through chelation.

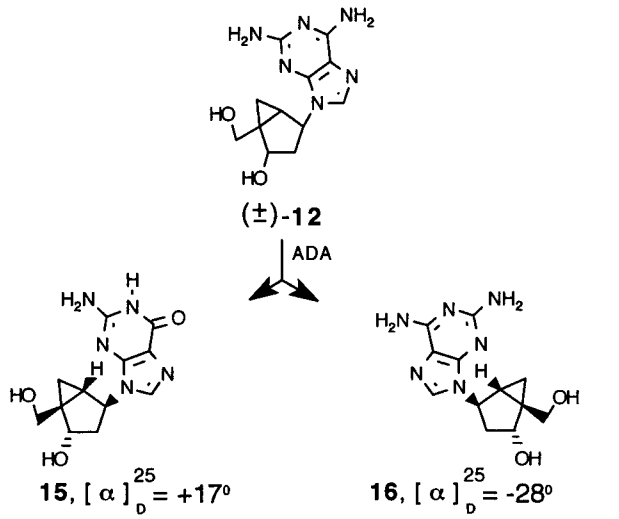
Diol (±)-**8** was easily converted to the dibenzoate ester (±)-**9a** in 98% yield. The selection of the benzoyl group (Bz) for the requisite synthon [(±)-**9a**] was based on its ease of removal during the final ammonolysis (vide infra). Removal of the silyl ether protection from (±)-**9a** gave (±)-**10a** in 95% yield, which was used for direct coupling with 2-acetamido-6-chloropurine or 6-chloropurine, under Mitsunobu conditions, to give ca. an 80% yield of (±)-**11** and (±)-**13**, respectively. The final 2,6-diaminopurine [(±)-**12**] and adenine [(±)-**14**] analogues were finally obtained after simple ammonolysis.

The overall yields of (±)-**12** and (±)-**14** obtained from two extremely simple and cheap starting materials, such as ethyl acetoacetate and acrolein, were 19% and 15%, respectively. This is remarkable considering the complexity of the resulting structures with four asymmetric carbons. The ease of the synthesis makes the scale-up preparation of (±)-**10a** quite simple and convenient to perform and stands in sharp contrast to the more difficult synthesis of (+)-**1** which is still several steps away from the required bicyclo[3.1.0]-hexane synthon.[5a]

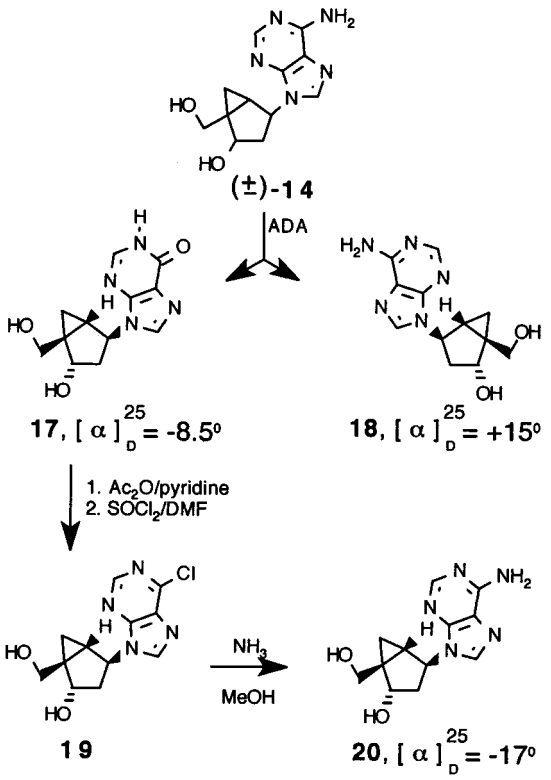
Scheme 4



Scheme 5



Scheme 6



The enzymatic resolution of an aqueous solution of (±)-**12** with adenosine deaminase (ADA) was very effective (Scheme 5), and after reverse phase HPLC chromatography, the desired chiral β-D-analogue (+)-**15** was obtained in 46% yield. This compound matched all spectral and optical properties of the authentic compound prepared from chiral (+)-**1**.[1b] The undeaminated β-L-nucleoside (−)-**16** was obtained in 39% yield.

Resolution of the adenine analogue (±)-**14** was not as straightforward because the deaminated hypoxanthine β-D-nucleoside (−)-**17**, isolated in 50% yield, had to be converted back to the β-D-nucleoside (−)-**20**. However, this transformation was performed effectively without any isolation of intermediates (Scheme 6). Following purification by reverse phase HPLC, the desired adenine carbocycle (−)-**20** was obtained in 79% yield from (−)-**17**. Again, this compound matched all spectral and optical properties of the authentic compound prepared from chiral (+)-**1**.[1b]

We have shown that the synthesis of two racemic ADA−substrate purine analogues built on the complex bicyclo-[3.1.0]hexane platform can be efficiently executed from the carbobicyclic synthon (±)-**10a** and resolved via a chemicoenzymatic approach that relies on the remarkable enantioselectivity of ADA. Current approaches to resolve (±)-**10a** or any of its precursors prior to coupling with the nucleoside bases are underway.

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