Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel Synthesis of (+/-)-cis-4-Amino-2-cyclopentene-1-methanol, a Key Intermediate in the Preparation of Carbocyclic 2′,3′-Didehydro-2′,3′-dideoxy Nucleosides

Mark H. Norman [a] , Merrick R. Almond [a] , Barbara E. Reitter [a] & S. George Rahim [b]
[a] Division of Organic Chemistry , Burroughs Wellcome Co. , Research Triangle Park, NC, 27709
[b] Medicinal Chemistry Department , Wellcome Research Laboratories Beckenham , Kent, England , BR3 3BS
Published online: 23 Sep 2006.

SYNTHETIC COMMUNICATIONS, 22(22), 3197-3204 (1992)

NOVEL SYNTHESIS OF (+/-)-*cis*-4-AMINO-2-CYCLOPENTENE-1-METHANOL, A KEY INTERMEDIATE IN THE PREPARATION OF CARBOCYCLIC 2',3'-DIDEHYDRO-2',3'-DIDEOXY NUCLEOSIDES

Mark H. Norman,* [1] Merrick R. Almond,[1] Barbara E. Reitter[1] and S. George Rahim[2]

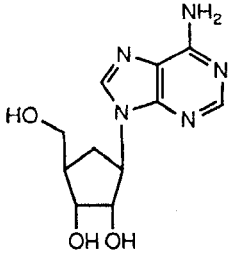
[1]Division of Organic Chemistry, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
[2]Medicinal Chemistry Department, Wellcome Research Laboratories, Beckenham, Kent, England BR3 3BS.

Abstract: Novel synthetic routes directed toward the preparation of (+/-)-*cis* -4-amino-2-cyclopentene-1-methanol are described. The routes investigated involve azide openings of chiral and non-chiral cyclopentyl epoxides.

Interest in the synthesis of carbocyclic nucleosides has grown tremendously since the discovery of their potent antiviral activities. For example, aristeromycin (**1**), active against the vaccinia virus, has been the synthetic target of a number of research groups.[1-4] The 2',3'-didehydro analogues, the carbocyclic-ene class, have also been the focus of many recent investigations, in large part owing to the in vitro activity of carbovir (**2**) against the human immunodeficiency virus.[5,6]

* To whom correspondence should be addressed.

Increased interest in these types of nucleosides makes alternative syntheses of these compounds increasingly important. In this communication, we report a novel synthesis of (+/-)-*cis*-4-amino-2-cyclopentene-1-methanol (**12**), a key intermediate used in the preparation of carbocyclic-ene purine nucleosides, from inexpensive, readily available starting materials. A number of carbocyclic 2',3'-didehydro-2',3'-dideoxy-2,6-disubstituted purine nucleosides can be prepared from this amino alcohol. For example, Vince and coworkers recently employed **12** in their synthesis of several carbocyclic-ene nucleosides related to carbovir.[5] This type of primary amine can also be converted to carbocyclic-ene pyrimidine nucleosides by the methods described by De Clercq et al.[7]



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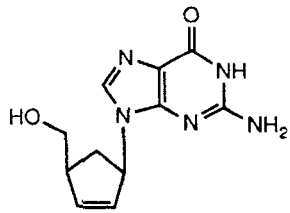

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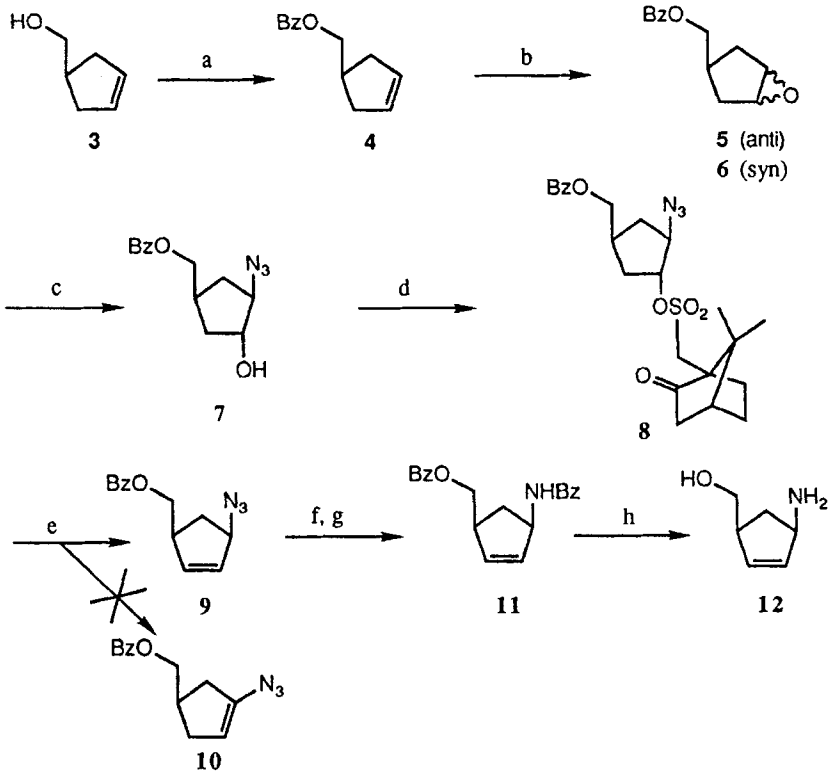
The synthesis of amino-alcohol **12** is outlined in Scheme 1. The starting material, 3-cyclopentene-1-methanol (**3**), was obtained by the method of Depres and Green from *cis* -1,4-dichlorobutene and dimethyl malonate.[8,9] Treatment of alcohol **3** with benzoyl chloride in pyridine gave the benzoyl protected cyclopentene alcohol **4** in an 82% yield. All of the reactions leading to the preparation of compound **4** proceeded cleanly and provided products requiring little if any purification. Analytically pure samples of each of the compounds were obtained either by recrystallizations or simple distillations. These intermediates would be amenable to large-scale preparations.

Scheme 1.



a. BzCl, pyridine, 0 °C-RT; b. m-CPBA, CH_2Cl_2, -78-0 °C; c. LiN_3, $(NH_4)SO_4$, $EtOH/H_2O$, reflux; d. (+)-10-camphorsulfonyl chloride, Et_3N,CH_2Cl_2; e. DBU, THF, reflux; f. 1,3-propanedithiol, Et_3N ; g. BzCl, pyridine; h. $Ba(OH)_2$, H_2O, reflux.

Epoxidation of (3-cyclopenten-1-yl)methyl benzoate (**4**) with m-chloroperoxybenzoic acid proceeded smoothly to give the corresponding epoxides **5** and **6**. The epoxides were obtained as a 3:1 mixture of anti and syn isomers, which were separated by employing preparative LC (Waters prepLC/system 500A) using two columns in succession and 9:1 hexanes/ethyl acetate as eluent (73% total yield). Attempts to assign the relative stereochemistry of these epoxides by n.O.e.

techniques were unsuccessful. As the synthesis progressed, verification of the tentative assignments (major-anti and minor-syn) were made via correlation with the azide-cyclopentene product, **9** (vide infra).

Treatment of the anti epoxide **5** with lithium azide and ammonium sulfate in either 90% ethanol/water or 85% 2-methoxy ethanol/water at reflux provided azide-alcohol **7** in good yield (83-98%). Formation of the chiral sulfonate **8** by the reaction of azide alcohol with (+)-10-camphorsulfonyl chloride and triethylamine in methylene chloride was straightforward (76% yield). We envisaged that this chiral derivative might provide separable diastereomers and thereby a chiral resolution would result at this stage of the synthesis. Unfortunately, the diastereomers formed from the racemic alcohol were inseparable by chromatography.

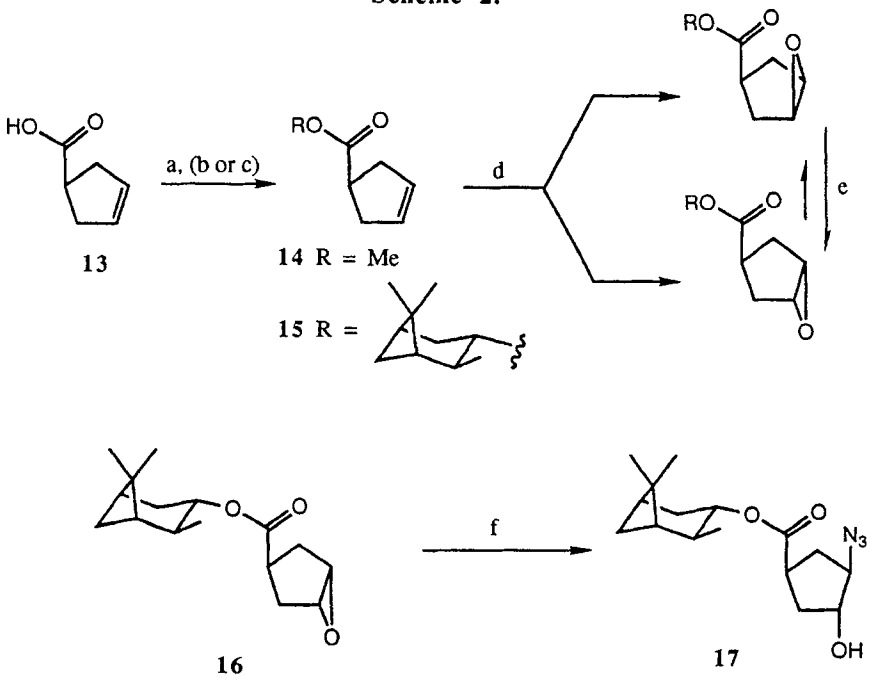
Elimination of the sulfonate with DBU in tetrahydrofuran provided *cis* -(4-azido-2-cyclopenten-1-yl)methyl benzoate (**9**).[10] The product that might be expected from syn elimination in the direction of the azide (i.e., unsaturated azide **10**) was not observed. The protected amino alcohol **11** was obtained by the reduction of azide **9** with 1,3-propanedithiol and triethylamine,[11] followed by treatment of the resulting primary amine with benzoyl chloride. This material can be deprotected in 69% yield immediately prior to use for subsequent elaboration to the purine (or pyrimidine) nucleosides.[6]

Alternative approaches to amino alcohol **12** involving cyclopentyl esters were also investigated. The initial steps in these routes are shown in Scheme 2. We postulated that epoxidation of the ester might provide an anti/syn ratio of epoxides different from that obtained with the use of the protected alcohol **4**. On the other hand, if an unfavorable kinetic mixture did result, it might be possible to epimerize the position alpha to the ester to give the more thermodynamically stable anti product. Some interesting observations resulted from this study. Reaction of cyclopentene acid **13** [8] with thionyl chloride in toluene followed by treatment of the

resulting acid chloride with either methanol or 3-pinanol provided esters **14** and **15**, respectively. Epoxidation was accomplished by treatment of these esters with m-chloroperoxybenzoic acid in dichloromethane at 0 °C. In each case, epoxidation provided approximately 3:1 mixtures of isomeric epoxides in yields ranging from 61-91%. The configuration of the major product from the pinanol ester was shown to be anti via difference n.O.e. experiments. The major isomer of the methyl ester was also assigned the anti configuration via analogy. Although a similar isomeric mixture was obtained as compared to the protected alcohol (i.e., epoxides **5** and **6**), the ester approach possesses distinct advantages. First, separation of the isomers was easily accomplished with the use of flash chromatographic techniques (prep-LC was not required). Second, the esters provided a means by which stereochemistry could be controlled. For example, epimerization of the syn methyl ester epoxide was accomplished by treatment of the pure isomer with sodium methoxide in refluxing methanol. Equilibrium mixtures of approximately 2:1 anti/syn were obtained. Recycling the unwanted isomer in this way should minimize loss of material.

We envisaged that the use of a bulky chiral ester such as **16** might serve two purposes: help direct the epoxidation reaction to give more of the anti isomer, and provide some asymmetric induction in the addition of azide ion to the epoxide. To test these hypotheses, we studied reactions of ester **16**. As mentioned previously, no significant enhancement was obtained in the epoxidation reaction. We realized that the chiral center was distant from the reacting center; however, spectral data of both cyclopentene **15** and epoxide **16** suggested that some stereodifferentiation might be possible. ^{13}C NMR spectra of these cyclopentyl ring systems showed diastereotopic chemical shifts for the vinyl carbons and the epoxide carbons, respectively. These signals indicated an effect of the distant asymmetric center on the reacting site (attributed to asymmetric anisotropic effects of the ester carbonyl on

Scheme 2.



a. $SOCl_2$, toluene, reflux; b. MeOH, CH_2Cl_2; c. (+)-isopinocamphenol, CH_2Cl_2, 0 °C-RT; d. m-CPBA, CH_2Cl_2; e. NaOMe, MeOH, reflux; f. LiN_3, $(NH_4)SO_4$, $EtOH/H_2O$, reflux.

the cyclopentyl ring system). The effect was indeed realized in the azide opening of the epoxide, however, the result was minimal. Treatment of epoxide **16** with lithium azide in ethanol provided a clean conversion to azide alcohol **17** in 96% yield; however, only a 6% d.e. was obtained (determined by integration of the diastereomeric ^{13}C chemical shifts). These results indicate that a chiral auxiliary must be closer in to the reacting center to achieve significant asymmetric induction in the epoxide ring opening. We are currently considering alternative chiral auxiliaries.

The investigations described above represent novel approaches to a valuable intermediate, amino alcohol **12**, used in the preparation of an important class of potential antiviral drugs.

Acknowledgements

The authors gratefully acknowledge Susan Daluge for her helpful discussions and Gary Martin, Ron Crouch and Aris Ragouzeos for their NMR studies leading to the stereochemical assignments of chiral epoxide **16** and azide-cyclopentene **9**.

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9. Cyclopentene-methanol **3** has been the convenient starting material for other carbocyclic- nucleoside syntheses (see refs. 2 and 12).
10. Methyl benzoate **9** and amino alcohol **11** were obtained in a 34% and 33% isolated yields, respectively. Reaction conditions were not optimized.

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(Received in USA 1 July, 1992)