A Short and Stereoselective Synthesis of (±)-Aristeromycin

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Received September 30, 1988

A new stereoselective three-step total synthesis of (±)-aristeromycin starting from readily available 1-hydroxymethyl-3-cyclopentene is described.

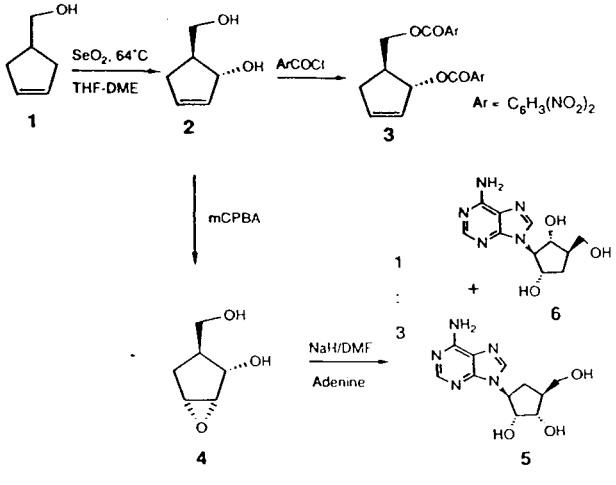
J. Heterocyclic Chem., **26**, 451 (1989).

Aristeromycin is a carbocyclic analog of adenosine which was first synthesized in racemic form by Shealy and Clayton in 1966 [1] and later isolated as a natural product as the (−)-enantiomer, from the culture filtrate of *S. citricolor* [2]. The cytostatic and antiviral activity [3] of aristeromycin has attracted a great deal of synthetic and biological study. However, early routes [4] to carbocyclic nucleosides have been lengthy and tedious. More recently, Madhavan and Martin [5] described a new synthetic route to aristeromycin using singlet oxygen cycloaddition as its key feature to construct the carbocyclic ribofuranosylamine. Trost and his coworkers [6] also reported a transition-metal-controlled synthesis of (±)-aristeromycin in nine steps with an overall yield of 8%.

The above work and growing importance of carbocyclic nucleosides prompted us to develop a synthetic approach which is versatile enough to present the elaboration of other purine and pyrimidine congeners. We now report our studies on this class of compounds with a conceptually different strategy which leads to the synthesis of (±)-aristeromycin and potential accessibility to its (−)-enantiomer.

The synthesis of aristeromycin is outlined in Scheme 1. Reaction of hydroxymethyl cyclopentene **1** [7a] with selenium dioxide (THF-DME, 64°, 18 hours) led to diol **2** (32%). The regio and stereoselectivity of the selenium dioxide oxidation was very good. We observed less than 5% of the *cis* isomer. The structure and stereochemistry of the *trans* diol was confirmed by comparing the melting point and 400 MHz nmr spectra of its bisdinitrobenzoyl derivative **3** with the known compound in the literature [7b].

Scheme 1



Epoxidation of diol **2** using *m*-chloroperbenzoic acid at room temperature yielded the *cis* epoxide **4** as the major product and only trace amounts of the *trans* epoxide were observed. The epoxide **4** was then treated with the sodium salt of adenine in DMF at 105° for 15 hours to afford a 3.5:1 mixture of aristereomycin **5** (52%) and its isomer **6** (15%) after reverse phase flash column chromatography. Our synthetic aristeromycin has a melting point and spectral data that are identical with that reported [8].

In conclusion, aristeromycin was synthesized in three steps with an overall yield of 17% which represents the most efficient and convergent synthesis known. We are also applying this methodology to synthesize other carbocyclic nucleosides. These results will be published in due course.

EXPERIMENTAL

Commercially available chemicals and solvents were reagent grade and used as received. The C18 reverse phase gel was purchased from J. T. Baker Chemical Co. Selenium dioxide was purchased from Aldrich Chemical Co. Proton nmr spectra were recorded on a Varian EM-390 or XL-400 spectrometer, using tetramethylsilane as the internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

1-Hydroxymethyl-3-cyclopentene (**1**).

A solution of dimethyl-3-cyclopentene-1,1-dicarboxylate [7a] (20 g, 110 mmoles), 45% potassium hydroxide (28.68 g, 233 mmoles), 15 ml of water, and 75 ml of ethanol was heated at reflux for 15 hours. The solvent was removed under vacuum and the residue diluted with water and washed with diethyl ether. The aqueous layer was cooled to 0° and acidified with concentrated hydrochloric acid to *p*H 1. The acidic solution was saturated with sodium chloride and extracted three times with ethyl acetate. The combined ethyl acetate layers were dried over magnesium sulfate, concentrated under reduced pressure to yield 16.0 g (95%) of crude 3-cyclopentene-1,1-dicarboxylic acid as a white crystalline solid; ^{1}H nmr (deuteriochloroform): δ 5.5 (s, 2 H), 3.0 (s, 4 H). Crude 3-cyclopentene-1,1-dicarboxylic acid (15 g, 0.095 mole) was heated neat at 185-195° for one hour until gas evolu-

tion ceased. The residual oil was purified by Kugelrohr distillation (bp 85°, 1.0 mm Hg) to yield 10.6 g of 3-cyclopentene-1-carboxylic acid as colorless oil (100%); ^{1}H nmr (deuteriochloroform): δ 5.80 (s, 2 H) 3.20 (m, 1 H) 2.70 (d, 4 H). A solution of 3-cyclopentene-1-carboxylic acid, (10.6 g 0.095 mole) in 30 ml diethyl ether was added dropwise to a stirred suspension of lithium aluminum hydride (5.5 g, 0.145 mole) in 100 ml of diethyl ether at 0°. After the addition was completed (*ca* 1 hour) the reaction mixture was stirred at 0-5° for 30 minutes then at room temperature for 2.5 hours. The reaction mixture was cooled to 5° and quenched using Fieser's procedure. The solids were filtered and washed with diethyl ether. The filtrate was washed with 0.1*N* sodium hydroxide, brine, dried over magnesium sulfate and concentrated under reduced pressure to give 8.2 g (88%) of 1-hydroxymethyl-3-cyclopentene as a colorless oil; ^{1}H nmr (deuteriochloroform): δ 5.69, (s, 2 H), 3.50 (m, 3 H), 2.30 (m, 4 H).

trans-1-Hydroxymethyl-2-hydroxy-3-cyclopentene (**2**).

A solution of 1-hydroxymethyl-3-cyclopetene (7.5 g, 76 mmoles) in 500 ml of dry tetrahydrofuran and 250 ml of dimethoxyethane was treated with selenium dioxide (7.5 g, 68 mmoles) at room temperature. The resulting mixture was heated at 64° for 18 hours, then cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum and the residue was chromatographed on 100 g of silica gel (eluent, 4% methanol in ethyl acetate) to give first the recovered starting material 1.1 g and the desired product **2** (2.4 g, 32%) as an oil; ^{1}H nmr (deuteriochloroform): δ 5.8 (m, 1 H), 5.65 (m, 1 H), 4.6 (m, 1 H), 3.6 (m, 2 H), 2.5 (m, 1 H), 2.15 (m, 1 H), 1.9 (m, 1 H). The bisdinitrobenzoyl derivative **3** was made as described. Its melting point and spectral data are identical to the known compound [7].

1β-Hydroxymethyl-2α-hydroxy-3α,4α-epoxycyclopentane (**4**).

A solution of **2** (818 mg, 7.2 mmoles), 2.2 g of *m*-chloroperbenzoic acid (12.7 mmoles) and 40 ml of dichloromethane was stirred at room temperature for 80 minutes. The solvent was removed under reduced pressure and the residue was partitioned between ether and water. The aqueous layer was then concentrated *in vacuo* to obtain the epoxide **4** quantitatively. This compound was used without purification; ^{1}H nmr (deuteriochloroform): δ 4.1 (d, 1 H), 3.8-3.45 (m, 4 H), 3.0 (br s, 2 OH), 2.4-1.3 (m, 3 H).

Aristeromycin **5** and its Isomer **6**.

To a suspension of sodium hydride (44 mg, 1.1 mmoles, 60%, washed with dry ether) in 2 ml of dry DMF was added adenine (100 mg, 0.74 mmole). After 10 minutes stirring at room temperature, the resulting mixture was treated with epoxide **4** (275 mg, 2.1 mmoles) in 5 ml of dry DMF and heated at 105° for 18 hours, then cooled. The reaction mixture was quenched with water and concentrated to dryness. The crude product was chromatographed on silica gel with 15% methanol in dichloromethane as the eluent to recover 59 mg of adenine and 86 mg of the mixture. This mixture was then chromatographed on 20 g of reverse phase octadecylsilane (C18) bonded gel (eluent, 5% methanol in water) to give 2α,4α-dihydroxy-1β-hydroxymethyl-3β-(9-adenyl)cyclopentane (**6**, 20 mg, 15%) mp 252-254° and aristeromycin. (42 mg, 52%) mp 236-238° (lit [1] 237-240°).

Acknowledgment.

We thank Professor B. Ganem and Dr. H. W. Gschwend for many stimulating discussions. We appreciate the assistance of R. Behnke and M. Brzechffa for providing nmr and mass spectra.

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