Total Synthesis of Griseolic Acid

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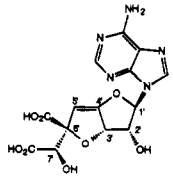
Griseolic acid A (**1**) is a member of a family of related structures isolated from the culture broth of *Streptomyces griseoaurantiacus*.[1] They have been shown to be potent, but nonselective, inhibitors of cyclic nucleotide phosphodiesterases from various tissues. The griseolic acids were of particular interest since they contain the highly unusual and strained 1,5-dioxabicyclo[3.3.0]oct-3-ene. Indeed this bicylic diacid is believed to act as a mimetic of the ribose phosphate in cyclic nucleotides. We have used the griseolic acids as a template to discover more selective and therefore therapeutically useful antihypertensive agents.[2,3] The total synthesis of griseolic acid A, described in this Communication, presents stereochemical and structural challenges absent in our previous work. Thus the key steps of this synthesis are (a) the introduction of the two-carbon acid at 6′ on the hindered α face of the bicyclic system; (b) the formation of the β adenine nucleoside; (c) the stereoselective introduction of the 7′-hydroxyl; and (d) the efficient formation of the key bicyclic enol ether of the griseolic acids.



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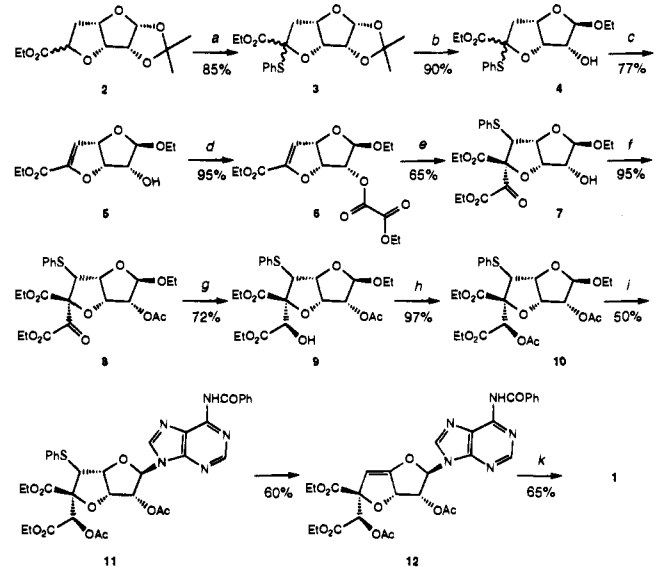
We considered griseolic acid **1** as a highly functionalized 3,6-anhydro sugar derivative. Thus we planned to use an anhydro sugar derivative **2** (Scheme 1), which is readily available from diacetone glucose,[3] for the synthesis of **1**. Accordingly, our first goal was to prepare a precursor **6** which on nucleophilic addition would generate a carbon anion at C-6 and trap the keto ester, thus installing a two-carbon unit at C-6 in a stereospecific manner. Synthesis of **6** began with sulfenylation of acetonide **2** with $PhSO_2SPh$ (prepared from the reaction of benzene sulfonyl chloride and thiophenol) to produce **3** as an epimeric mixture in 85% yield. Removal of the acetonide **3** was achieved by mild acid ethanolysis to give the two ethyl acetals **4a** and **4b**, in which the OEt group was assigned as the β-configuration based on ^1H NMR ($J_{1,2} = 0$ Hz for both compounds). Oxidation with *m*-chloroperbenzoic acid followed by a thermal elimination of each sulfoxide gave the same bicyclic vinyl ether **5**. Treatment of **5** with ethyl oxalyl chloride in the presence of pyridine at room temperature led to **6** in near quantitative yield.

Scheme 1



[a]LDA, $PhSO_2SPh$, −78 to 0 °C. [b]H_2SO_4, EtOH. [c]mCPBA, then reflux $PhCH_3$. [d]EtO_2CCOCl, pyridine, room temperature. [e]PhS^-Na^+, 0 °C to room temperature. [f]Ac_2O, pyridine. [g]$NaBH_4$. [h]Ac_2O, pyridine, 0 °C to room temperature. [i]Bis(trimethylsilyl)-*N*-benzoyladenine, TMSOTf. [j]mCPBA, then reflux $PhCH_3$. [k]1 N NaOH, room temperature.

Since the stability of enol ether **1** in acidic medium was questionable, we decided to install this bond at the last stage of the synthesis. Addition of sodium benzenethiolate to **6** produced **7** as an epimeric mixture (10:1 ratio) in 65% isolated yield. The major isomer is formed by addition from the top face of the concave-shaped **6**. The relative configuration at C-5 of **7** was established by ^1H NMR studies which revealed an NOE between H-5 and the ring protons H-3 and H-4 in the case of the minor isomer. No such NOE was observed for the major isomer.[4] The acylation of **7** with acetic anhydride/pyridine produced **8** in 95% yield. The reduction of the α-keto ester with sodium borohydride gave compound **9** and a minor isomeric alcohol in a 5:1 ratio.[5] These diastereoisomers were easily and completely separated by flash chromatography. Each isomer was then converted to the corresponding Mosher ester to establish the absolute stereochemistry of this chiral center by application of the modification to Mosher's method described by Ohtani et al.[6] The major isomer was determined to have the desired stereochemistry at C-7, and this was confirmed by converting it into griseolic acid A.

Compound **9** was acylated with pyridine/acetic anhydride in almost quantitative yield. The Vorbruggen reaction[7] of **10** with 6*N*,*N*,[9]-bis(trimethylsilyl)-*N*-benzoyladenine in the presence of (trimethylsilyl)methyl trifluoromethanesulfonate gave rise to nucleoside **11** ($J_{1',2'} = 5.6$ Hz) in 50% yield. In this reaction, a small amount (<10%) of unwanted anomeric α nucleoside as well as N-7 alkylation product were also formed. These side

(1) (a) Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. *J. Antibiot.* **1985**, *38*, 823. (b) Takahaski, S.; Nakagawa, F.; Sato S. *J. Antibiot.* **1988**, *41*, 705. (c) Iijima, Y.; Nakagawa, F.; Handa, S.; Oda, T.; Naito, A.; Yamezaki M. *FEBS Lett.* **1985**, *192*, 179. (d) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneko M. *Chem. Pharm. Bull.* **1987**, *35*, 1036. (e) Murofushi, Y.; Kimura, M.; Kuwano, H.; Iijima; Y.; Mitsuo, Y.; Kaneka, M. *Nucleic Acid Res. Symp. Ser.* **1986**, *17*, 45. (f) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneka, M. *Chem. Pharm. Bull.* **1987**, *35*, 4442. (g) Murofushi, Y.; Kimura, M.; Iijima, Y.; Yamazaki, M.; Kaneka, M. *Ibid.* **1988**, *36*, 1309.

(2) Tulshian, D.; Czarniecki, M.; Doll, R. J.; Ahn, H. S. *J. Med. Chem.* **1993**, *36*, 1210.

(3) Tulshian, D.; Doll, R. J.; Stansberry, M. F.; McPhail, A. T. *J. Org. Chem.* **1992**, *56*, 6819.

(4) Oxidation and thermal elimination of the major product gave a single product by ^1H NMR, thus establishing the configuration at C-6. This reaction also validated the method which would be used in the formation of the 1,5-dioxabicyclo[3.3.0]oct-3-ene ring system in the penultimate step of the synthesis.

(5) Compound **8** was subjected to conformational analysis (MacroModel V 4.5, 1000 Monte Carlo steps followed by MM2 minimization). An examination of all the low-energy conformers (<3 kcal above the lowest energy structure) suggests that one face of the ketone is always shielded by other structural elements of **8**. Reduction from the open face would give the observed major isomer of **9**.

(6) Ohtani, I.; Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(7) Vorbruggen, H.; Krolikiewicz, K.; Bennue B. *Chem. Ber.* **1981**, *114*, 1234.

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products have been observed previously in the nucleosidation of these bicyclic system by us[2] as well others.[8] The side products were removed by flash column chromatography. Oxidation and thermal elimination produced **12**. Deprotection of **12** with 1 N sodium hydroxide gave synthetic griseolic acid A (**1**) (65%). Spectral comparison proved this compound identical with an authentic sample obtained by fermentation of *S. griseoaurantiacus*. The optical rotation of our synthetic **1** ($[\alpha]_D^{20}$ +6.5° (*c* 0.1, DMSO)) agreed very closely to that reported by Nakagawa et al. ($[\alpha]_D^{20}$ + 6.9° (*c* 0.1, DMSO)).[1a] The total synthesis of griseolic acid A was thus accomplished.

(8) Murofushi, Y.; Kimura, M.; Kuwano, H.; Iijima, Y.;Yamazaji, M.; Kaneko, M. *Chem. Pharm. Bull.* **1988**, *36*, 3760.

Acknowledgment. We thank Dr. J. Kaminski for invaluable information and discussion and Drs. T. M. Chan and M. Puar for performing the NMR experiments. We wish to thank Dr. V. Gullo and his group for isolating a sample of natural griseolic acid A.

Supporting Information Available: Experimental procedures with spectral and physical characterization of key intermediates (**3**, **7**, **10**, **12**) and griseolic acid A (**1**) (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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