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Synthesis of Griseolic Acid B by π-Face-Dependent Radical Cyclization

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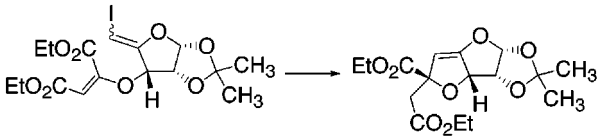
ABSTRACT

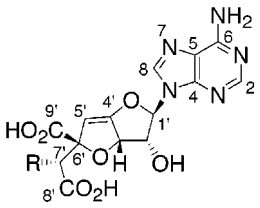


6 **9**

Radical cyclization of 6 affords the bicyclic vinyl ether 9 with the appropriate stereochemistry for elaboration (seven steps) to griseolic acid B (1).

Radical reactions have been heralded for application to the synthesis of densely functionalized targets because polar functional groups are often less conflictive in uncharged radical intermediates than they might be in anionic or cationic species, particularly during C−C bond formation. Furthermore, predicting and exploiting stereoselectivity in radical reactions grows easier with each new application.[1] We report the synthesis of griseolic acid B (**1**) based upon a novel vinyl radical cyclization reaction in which the acceptor alkene face selectivity dictates both stereochemistry and ring size.

Griseolic acids are a family of complex nucleosides isolated at Sankyo Co. from a cultured broth of *Streptomycetes griseoaurantiacus*.[2] Three representatives, griseolic acids A, B, and C, exhibited comparable nanomolar inhibition of cyclic adenosine 3′,5′-monophosphate phosphodiesterases.[3] Spectroscopic and crystallographic analysis revealed nucleoside skeletons that broadly resemble cyclic AMP: A (**2**) and B (**1**) feature unsaturated bicyclic sugar dicarboxylate gly-



1: R = H
2: R = OH

cones, whereas C is a 4′(*R*),5′-dihydro version of B. Extensive studies of griseolic analogues were carried out at Sankyo[4] and at Schering-Plough,[5] and a synthesis of **2** has been published by Tulshian and Czarniecki.[6]

Sporting almost as many functional groups as carbon atoms, griseolic acid B (**1**) carries additional synthetic challenges: a [3.3.0] ring system without obvious convex facial bias, a quaternary stereogenic center at C-6′, a reactive

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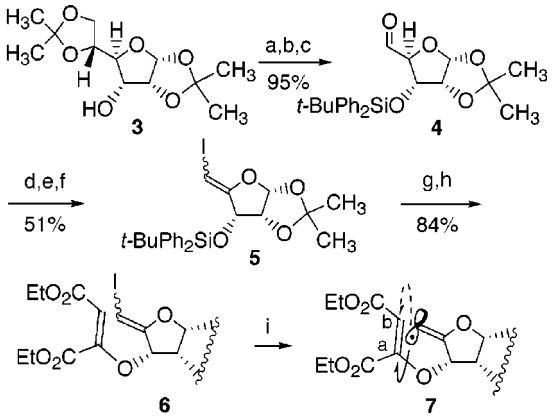
C-4′ vinyl ether with a greater tendency to form a cation than the C-1′ acetal, and a purine with multiple Lewis basic sites. Radical cyclization to form the C-5′,6′ bond is an interesting possibility. On the basis of our familiarity with the synthesis of complex nucleoside antibiotics,[7] we considered both early and late introduction of the purine but found more success with late purine attachment even though this necessitated installation of the reactive vinyl ether later still.

A C-5′ (griseolic acid numbering) vinyl radical precursor was assembled from the commercial D-*allo*-furanose **3** as shown in Scheme 1. Aldehyde **4** was converted to vinyl

Scheme 1. Synthesis of the Radical Cyclization Substrate[a]

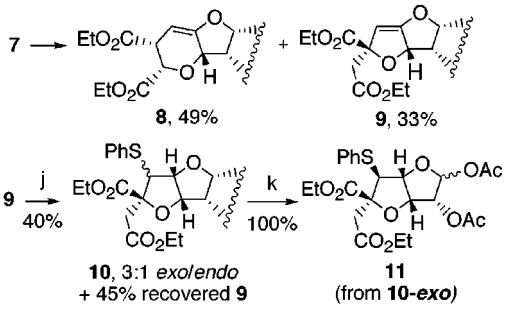


[a] Conditions: (a) *t*-BuPh$_2$SiCl, imidazole, DMF; (b) aqueous HOAc; (c) NaIO$_4$, aqueous THF; (d) NH$_2$NH$_2$, EtOH; (e) I$_2$, Et$_2$O, tetramethylguanidine; (f) DBU, toluene, 60 °C; (g) *n*-Bu$_4$NF, THF; (h) LiN(SiMe$_3$)$_2$ (0.2 equiv), Et$_2$O, diethyl acetylenedicarboxylate; (i) *n*-Bu$_3$SnH, AIBN, benzene, 80 °C.

iodide **5** (95:5 mixture of isomers) by iodination of the derived hydrazone,[8] and then deprotection at O-3′ and addition of this hydroxyl to diethyl acetylenedicarboxylate under basic conditions afforded maleate derivative **6**. The *E* geometry is assigned on the basis of the vinyl-H chemical shift (5.36 ppm).[9] Iodine atom abstraction from **6** should give vinyl radical **7**.

A variety of reducing reagents, initiators, solvents, concentrations, and temperatures were tried in order to generate **7**, but the most success was realized with 0.05 M *n*-Bu$_3$SnH in refluxing benzene. Under these conditions, two products, **8** and **9** (Scheme 2), were formed in a 3:2 ratio and 82%

Scheme 2. Radical Cyclization and C=C Protection[a]



[a] Conditions: (j) PhSH, AIBN, CHCl$_3$, NaHCO$_3$, reflux; (k) H$_2$SO$_4$, HOAc, Ac$_2$O, CH$_2$Cl$_2$, 0 °C.

combined yield. The ratio was essentially unchanged at *n*-Bu$_3$SnH concentrations from 0.02 to 0.33 M. No other product was discernible by TLC or NMR analysis. Characterization of **8** and **9** as 6-*endo*-trig and 5-*exo*-trig cyclization products, respectively, followed from ^{1}H NMR analysis, and the stereochemistry of each was established unambiguously by X-ray crystallography. Thus, **9** matches the required griseolic acid stereochemistry at C-6′.

The stereoselectivity of the cyclization of **6** is remarkable. The presumed intermediate vinyl radical in **7** (Scheme 1) must add, in the *endo* mode, to the *re* face of C-b in the maleate alkene to set the stereochemistry at C-6′ of **8** (dashed arrow), and in the *exo* mode to the *opposite* maleate face of C-a (also *re*) to set the stereochemistry at C-6′ of **9** (solid arrow). Subsequent hydrogen atom abstraction from the less hindered β-face sets the stereochemistry at C-7′ of **8**. In other words, the maleate face that is exposed to the vinyl radical determines both the stereochemistry and ring size of the products. Possible interconversion of homoallylic radical intermediates is ruled out by the concentration studies and by stereoelectronic considerations.[10]

For the synthesis to proceed from **9**, temporary protection of the C=C is required. This was accomplished by radical addition of thiophenol to C-5′ (Scheme 2). Chloroform proved to be a superior solvent for this addition, and NaHCO$_3$ was added to neutralize any trace of acid that might promote competing Markovnikov addition. In the best case the reaction was run to half-completion, and unreacted **9** was recycled. An easily separable mixture of thiophenol adducts **10** was obtained: the structure of **10-*endo*** was proven crystallographically, while **10-*exo*** was taken on by acetolysis to the anomeric acetate **11**.

Vorbrüggen glycosylation[11] of **11** (Scheme 3) with bis-(trimethylsilyl)-*N*^{6}-benzoyladenine in refluxing acetonitrile

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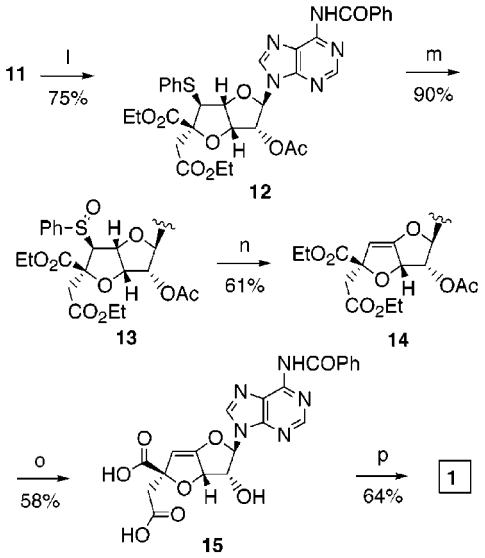
Scheme 3. N-Glycosylation and Deprotection[a]



[a] Conditions: (l) bis(trimethylsilyl)-N^6-benzoyladenine, Me_3SiOTf, CH_3CN, 80 °C; (m) *m*-CPBA, CH_2Cl_2, $NaHCO_3$, 0 °C; (n) Ph_2O, *N*-benzoyladenine, 270 °C bath, 2.0 min; (o) 0.5 M LiOH, EtOH, 1.5 h; (p) concentrated NH_4OH, 18 h.

gave the nucleoside **12** apparently uncontaminated with other stereo- or regioisomers (NMR, TLC analysis). Only regeneration of the alkene and final deprotection remained for conversion to **1**.

Oxidation of **12** to the sulfoxides **13** with exactly 1.0 equiv of *m*-CPBA was accomplished without incident. However, the thermal elimination proved to be particularly troublesome. No elimination of PhSOH occurred in refluxing toluene or refluxing xylenes (137 °C). At the latter temperature, significant depurinylation occurred, and **13** was destroyed over several hours. Control experiments on the sulfoxides derived from **10-*exo*** (which cannot depurinylate) supported these results; the small amount of **9** that formed after 5 h at 137 °C was also destroyed after 12 h, possibly by action of PhSOH. Separate thermolysis of N^6-benzyl-2′,3′,5′-tri-*O*-acetyladenosine (which cannot eliminate PhSOH) in refluxing toluene gave some depurinylation after 2 h. The inescapable conclusion is that depurinylation of these adenosines is at least as fast as sulfoxide elimination.

The depurinylation problem was solved by conducting the thermolysis in refluxing Ph_2O (259 °C) for 2.0 min in the presence of 5 equiv of N^6-benzoyladenine. Presumably the added purine scavenged PhSOH and allowed the elimination to compete successfully at the higher temperature.

Attempted deprotection of **14** with 1 M NaOH destroyed the nucleoside; however, brief treatment with 0.5 M LiOH cleaved the esters (the N^6 is deprotonated[12]), and subsequent ammonolysis[13] removed the *N*-benzoyl to afford **1**. Its identity was secured by ^1H NMR comparison (D_2O, 600 MHz) with the authentic natural product and with a 1:1 admixture.

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Supporting Information Available: Experimental details and spectral characterization for all new compounds, ^1H NMR comparison for **1**, and details of crystallographic analyses of **8**, **9**, and **10-*endo***. This material is available free of charge via the Internet at http://pubs.acs.org.

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