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Carbocyclic sinefungin

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Abstract—(3a*S*,4*S*,6*R*,6a*R*)-Tetrahydro-2,2-dimethyl-6-vinyl-3a*H*-cyclopenta[*d*][1,3]-dioxol-4-ol, itself available from ribose, provided a convenient entry point for an 18-step preparation of carbocyclic sinefungin. This procedure is adaptable to a number of carbocyclic sinefungin analogs with diversity of heterocyclic base and in the amino acid bearing side chain.

Sinefungin (**1**)[1] is an amino acid-containing nucleoside isolated from the cultures of *Streptomyces griseolus*[2a] and *Streptomyces incarnatus*.[2b] The C-6′ primary amino center renders sinefungin structurally similar to *S*-adenosylmethionine (**2**, AdoMet). This resemblance has served as the mechanistic focal point for rationalizing sinefungin's in vivo and in vitro biological activities, including antiviral,[3–5] antifungal,[2,6] amoebicidal,[7] and antiparasitical,[8] through inhibition of, primarily,[3] AdoMet-dependent methyltransfrases.[4] However, the clinical promise of **1** is restricted by its in vivo toxicity.[9]

In our antiviral drug discovery program sinefungin represents an important target for structural modification in order to improve its therapeutic index. Among the many compounds, which have been synthesized and evaluated in the sinefungin series,[10] carbocyclic sinefungin (**3**) has been proven to be elusive.[11] This Letter discloses a practical synthesis of **3**, that is, adaptable to analog development (Fig. 1).

A retrosynthetic analysis of carbocyclic sinefungin led us to a convergent approach involving a purine base and an appropriately crafted (stereochemically and functionally) cyclopentane. Thus, protection of the secondary alcohol of **4**[12] to **5** was followed by hydroboration to provide the primary alcohol **6**. Oxidation of **6** by a modified Swern procedure gave aldehyde **7**. Calling on the

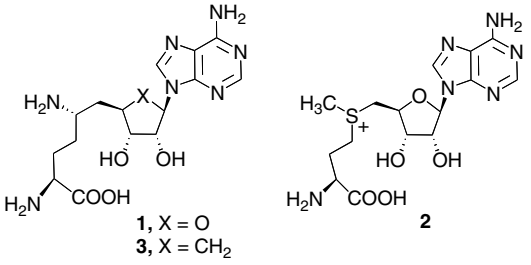

Figure 1.

Brown allylboration[13] **7** produced **8** in consistent yields (de 90% by NMR).

The side-chain stereochemistry of **8** was clarified by a modified Horeau method[14] using 2-phenylbutyryl chloride, pyridine and DMAP as reagents. The recovered optically active 2-phenylbutanoic acid was *levorotatory*. Thus,[14b] the homoallylic configuration of **8** is *S*. This result is consistent with the *si* face selectivity for the Brown allylboration conditions used.[13]

Mesylation of **8** followed by sodium azide nucleophilic substitution produced **9**. Transformation of **9** into azide–alcohol **10** was accomplished by sodium periodate glycolization/cleavage with, subsequent, Luche reduction ($NaBH_4/CeCl_3{\cdot}7H_2O$).[15] (It is to be noted that use of $NaBH_4$ alone in the last step of **9** to **10** conversion led to an intractable mixture of two products.[16])

Derivative **10** was readily converted into iodide **11** using the reagent obtained from iodine–imidazole. The lithium salt of (2*R*)-3,6-dihydro-2,5-dimethoxy-3-*iso*propylpyrazine reacted with **11** in the presence of Cu(I)[17] to

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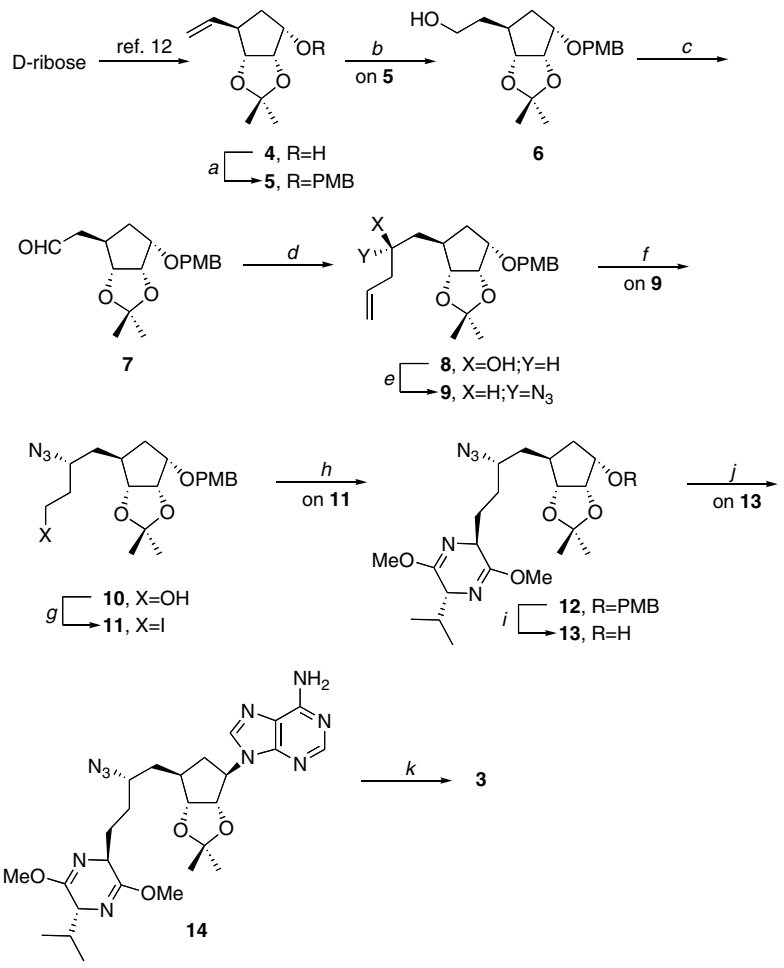

Scheme 1. Reagents and conditions: (a) PMBCl, NaH, DMF, 95%; (b) (i) 9-BBN, THF; (ii) MeOH, H_2O_2, NaOH, 98% for two steps; (c) SO_3·py, DMSO, DIPEA, CH_2Cl_2, 94%; (d) (i) (+)-B-methoxydi*iso*pinocampheylborane, $CH_2{=}CHCH_2MgBr$, Et_2O/THF; (ii) MeOH, H_2O_2, NaOH, 96% for two steps; (e) (i) MsCl, Et_3N, DMAP, CH_2Cl_2; (ii) NaN_3, DMF, 85% for two steps; (f) (i) $NaIO_4$, OsO_4, MeOH/H_2O; (ii) $NaBH_4$, $CeCl_3$·7 H_2O, MeOH, 77% for two steps; (g) TPP, imidazole, I_2, toluene/MeCN, 90%; (h) (2*R*)-3,6-dihydro-2,5-dimethoxy-3-*iso*propylpyrazine, BuLi, CuCN, THF, 87%; (i) DDQ, CH_2Cl_2/H_2O, 88%; (j) (i) Tf_2O, pyridine, CH_2Cl_2; (ii) adenine, NaH, DMF, 45% for two steps; (k) (i) 0.5 N HCl MeOH; (ii) $Pd(OH)_2$/C, cyclohexene; (iii) LiOH, MeOH/H_2O, 55% for three steps.

provide requisite **12** as one diastereomer (by NMR). Oxidative deprotection of the PMB ether group of **12** yielded **13** (Scheme 1).

Use of the Mitsunobu reaction[18] to construct the purine conjugate (that is, with **13** and 6-chloropurine) was successful but the subsequent ammonolysis at the purine C-6 center yielded mostly decomposed materials. Thus, a more traditional nucleophilic coupling process was undertaken by derivatizing **13** as its triflate that was, in turn, treated with the sodium salt of adenine to yield **14**. Hydrolytic (acidic) removal of the pyrazine and *iso*propylidene units followed by azide reduction and saponification (of the methyl ester made available by breakdown of the pyrazine ring) led to achievement of carbocyclic sinefungin (**3**).[19]

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19. Selected data for **3**: white foam; ^{1}H NMR (D_2O, 250 MHz) δ 8.23 (s, 1H), 8.18 (s, 1H), 4.80 (d, $J = 2.8$ Hz, 1H), 4.58 (m, 1H), 4.03 (m, 2H), 3.70 (m, 1H), 2.56 (m, 1H), 2.26–1.73 (m, 8H); ^{13}C NMR (D_2O, 100 MHz) δ 188.5, 158.1, 154.9, 151.8, 143.4, 121.4, 77.42, 77.38, 62.54, 62.47, 52.9, 42.4, 42.3, 34.9, 27.06, 27.00; HRMS Calcd for $C_{16}H_{24}N_6O_5$ [$M-H_2O+H^+$] 362.1945. Found: 362.1941.