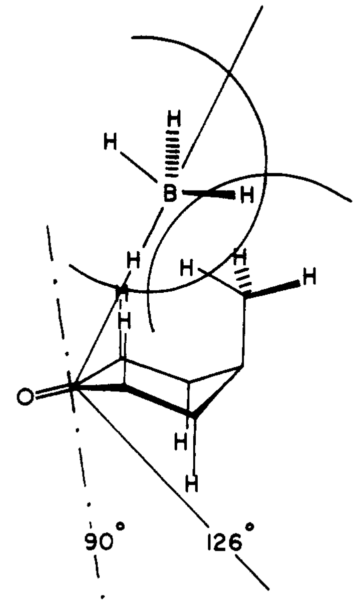

Figure 2. Attack on cyclohexanone at 126°, illustrating the effect of an axial group at C-4.

selectivity in these cyclohexanone reductions. If this attack occurs at 126° to the carbonyl group,[19] rather than at 90°, it is evident from molecular models that steric interactions with the axial hydrogen or other group at C-4 may become severe. We attempt to illustrate this point in Figure 2; what is not evident from this diagram is that the groups attached to C-4 are the only ones in the same plane as the carbonyl group. Molecular models indicate that in fact an attacking group at 126° approaches as closely to the axial group at C-4 as it does to the other axial groups, all of which are already known to markedly affect stereoselectivity. We propose that the intrinsic preference for "axial" attack may simply be the balance between the interference of two (axial 3, 5) vs. three (axial 2, 6, *and 4*) hydrogens, and that this stereoselection is modified in a predictable manner[20] by larger groups at these crucial positions. An axial methyl group at C-4 does in fact have a pronounced effect,[20] which is not accounted for by other rationalizations.

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Donald C. Wigfield,* Frederick W. Gowland[21]
Department of Chemistry, Carleton University
Ottawa, Ontario, Canada K1S 5B6

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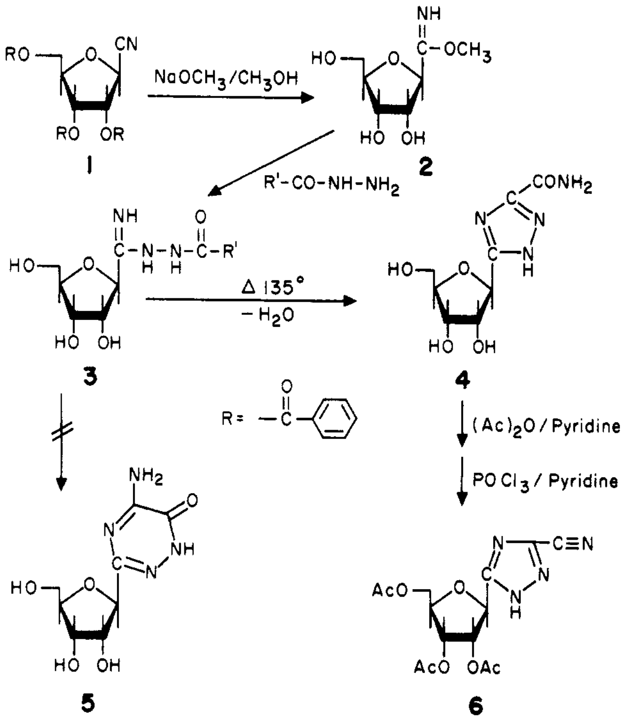
A Total Synthesis of *C*-Nucleoside Analogue of Virazole

Summary: A synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole has been developed by treating β-D-ribofuranosyl-1-carboximidic acid methyl ester with oxamido hydrazide followed by dehydrative ring closure of the open chain product by heating at 135 °C.

Sir: Several approaches[1-10] have recently been developed for synthesis of nucleosides possessing the unusual *C*-ribosyl linkage (*C*-nucleosides). In the area of *C*-triazole nucleosides, the recently reported method[9] lends itself only to the synthesis of 1,2,3-triazole *C*-nucleosides. A synthesis of DL-5-(1-β-ribofuranosyl)-3-amino-1,2,4-triazole has also been achieved[3] by a reaction of DL-2,5-anhydro-3,4-*O*-isopropylidene allonic acid lactone with aminoguanidine and subsequent removal of the isopropylidene blocking, but the approach seems to have limited application as far as the variation of C-5 substituents on the triazole nucleus is concerned. We describe here a high yield procedure for the synthesis of *C*-nucleosides of 1,2,4-triazole derivatives which has potential for wider application in the synthesis of such nucleosides. The utility of our method has been demonstrated by a total synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole (**4**) which is a *C*-nucleoside analogue of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide.[11]

Reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[12] (**1**) with catalytic amounts of $NaOCH_3$ in CH_3OH at room temperature for 1 h led to the formation of the deblocked imidic ester **2** (mp 142–143 °C) in 60–85% yield: NMR (Me_2SO-d_6) δ 3.59 (s, 3, OCH_3), 3.50–3.90 (m, 5, 2′-, 3′-, 4′-C—H and 5′-CH_2), 4.06 (d, 1, 1′-C—H, $J_{1'-2'}$ = 2 Hz), 4.93 (br s, 3, 2′-, 3′-, 5′-OH), 8.25 (s, 1, C=NH). The imidic ester **2** is susceptible to a facile nucleophilic displacement reaction with a variety of nucleophiles. For instance with ammonia or hydrazine, it formed the corresponding amidine and amidrazone ribosyl derivatives respectively. For the synthesis of open-chain precursors **3** of 1,2,4-triazole nucleosides, the imidic ester **2** was treated with the appropriate carboxylic acid hydrazides. Compound **3** (R′ = $CONH_2$) was thus synthesized in almost quantitative yield by reacting stoichiometric amounts of **2** and oxamido hydrazide in dimethyl sulfoxide at room temperature for 18 h. The structure of **3** (R′ = $CONH_2$) was established by ^{1}H NMR (Me_2SO-d_6): δ 3.6 (m, 2, 2′- and 3′-C—H), 3.8 (m, 1, 4′-C—H), 3.95 (m, 2, 5′-C—H_2),



4.15 (d, 1, 1'-C—H, $J_{1'-2'} \sim 1$ Hz), 5.2 (br m, 3, 2'-, 3'-, 5'-OH), 6.62 (br s, 2, $CONH_2$), 7.68, 8.0 (br s, 2, CONHNHC), 10.05 (br s, 1, C=NH). When precursor **3** (R' = $CONH_2$) was heated at 135 °C under vacuum (0.1 mmHg), dehydrative ring closure occurred within ~15 min to give an 80% yield of *C*-Virazole **4** (mp 193–195 °C). Compound **3** (R' = $CONH_2$) appears to have thermodynamic propensity to form compound **4** as shown by a slow conversion in aqueous solution at ambient temperature. The cyclized product gave the following proton NMR pattern (Me_2SO-d_6): δ 3.53 (m, 2, 5'-C—H_2), 3.82 (m, 1, 4'-C—H), 3.45, 4.17 (m, 1 each, 2'-, 3'-C—H), 4.73 (d, 1, 1'-C—H, $J_{1'-2'} = 5$ Hz), 7.64, 7.84 (br s, 1 each, $CONH_2$), extremely broad hydroxyl and NH protons between 5–7. Since the NMR data of the cyclized product do not allow a clear-cut distinction between structures **4** and **5**, further proof in favor of structure **4** was obtained by converting the product to its cyano derivative **6**. This was done by subjecting the tri-*O*-acetyl derivative of the product to conditions of dehydration in $POCl_3$ and pyridine. The resulting compound was shown to be 5-cyano derivative **6**: IR ($CHCl_3$) 2260 cm^{-1}; NMR (Me_2SO-d_6) δ 1.94 (s, 3, $COCH_3$), 2.07 (s, 6, 2-$COCH_3$), 3.9–4.4 (m, 3, 4'-C—H and 5'-CH_2), 5.24 (d, 1, 1'-C—H, $J_{1'-2'} = 5$ Hz), 5.31 and 5.56 (two t, 1 each, 2'- and 3'-C—H). To establish the anomeric configuration of the triazole moiety in **4**, it was converted into its 2',3'-*O*-isopropylidene derivative which gave the following NMR pattern (Me_2SO-d_6): δ 1.32 and 1.50 [two s, 3 each, *C*-$(CH_3)_2$], 3.40 (d, 2, 5'-CH_2), 3.45 (br, 1, 5'-OH), 4.05 (m, 1, 4'-C—H), 4.73 (m, 1, 3'-C—H), 4.94 (d, 1, 1'-C—H, $J_{1'-2'} = 4$ Hz), 5.05 (m, 1, 2'-C—H), 7.69 and 7.91 (two br s, 1 each, $CONH_2$), 1 NH proton burried under $CONH_2$ signals. The NMR chemical shifts of the methyl protons in the isopropylidene derivative (δ 1.32 and 1.50, $\delta\Delta = 0.18$) supported the β stereochemistry[13] of compound **4**.

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M. S. Poonian,* E. F. Nowoswiat

Chemical Research Department, Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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