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STUDIES RELATED TO THE TOTAL SYNTHESIS OF PENTOSTATIN: AN EFFICIENT, REGIOSPECIFIC GLYCOSYLATION OF 6,7-DIHYDROIMIDAZO[4,5-*d*][1,2]DIAZEPIN-8(3*H*)-ONE AND RELATED HOMOLOGS.[1]

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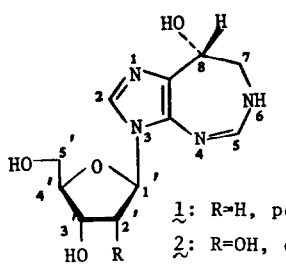
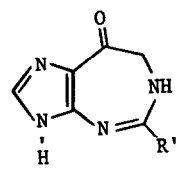
Abstract: A much improved glycosylation procedure for the synthesis of pentostatin-like nucleosides is described.

There is currently a burgeoning interest in pentostatin (1),[2] a nucleoside of unusual structure derived initially from the fermentation beers of *Streptomyces antibioticus* NRRL 3238[3] and more recently by total synthesis from these laboratories.[4] This, along with its structural relative coformycin (2),[5] represents the most potent inhibitor known of adenosine deaminase (ADA), the ubiquitous enzyme responsible for the N^6 - deamination of adenine nucleosides. This agent holds considerable promise as a co-drug in combination with other therapeutically useful adenosine-type nucleosides for the treatment of both hematologic malignancies and various solid tumors, including those of the lung and breast, based on human *in vitro* tissue culture and *in vivo* xenograph studies.[6]

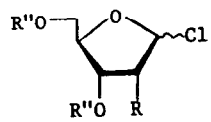
Recently Baker and Putt reported the first total synthesis of pentostatin.[4] Their strategy was to (a) construct the unique 5-7-membered



1: R=H, pentostatin
2: R=OH, coformycin



3: R'=H
4: R'=CH_3
5: R'=CH_2CH_3



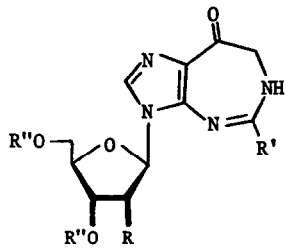
6: R"=p-toluoyl; R=H
7: R"=benzoyl; R=OR"

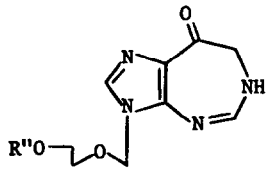
fused 1,3-diazepinone aglyconic moiety 3, then (b) attach this to requisite 2-deoxy sugar 6. Their synthesis, while achieving both objectives, failed to provide a satisfactory solution to (b) as glycosylation of persilylated 3 under thermal conditions afforded an α,β mixture of both N-1 and N-3 nucleosidic materials (ratio, ~1:3), with the desired N-3 β-anomer isolated in <10% yield.

We are pleased to report the first example of an efficient regiospecific glycosylation of a 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one moiety utilizing $SnCl_4$ Lewis acid catalysis under conditions similar to those outlined earlier by Vorbruggen.[7] Not only is complete N-3 regiospecificity observed in all cases, but for diazepinone homologs 4 and 5 a moderate stereoselectivity for β-anomers 9 and 10, respectively, is seen. Furthermore, we have extended this methodology to the synthesis of coformycin precursor 11 and acyclic nucleoside 12 which incorporates the simplified sugar moiety found in acycloguanosine, a potent antiviral agent.[8]

Treatment of a persilylated solution of 3 in CH_3CN at -35° with 1.5 equivalents of anhydrous $SnCl_4$ followed by cooling to -45°, then rapid addition of a 25° solution of sugar 6 dissolved in $ClCH_2CH_2Cl$ gave a black solution which was stirred vigorously for 45 minutes with gradual temperature elevation to -35°. Following a bicarbonate quench, extractive workup, and SiO_2 flash chromatography, there resulted a 80-95% crude yield of ~1:1 α/β anomeric mixture of N-3 isomers which were separated by fractional crystallization as previously described[4] to afford 30% of β-anomer 8 and 32% of its α-anomer counterpart. Similar reaction of the persilylated hydrochlorides of homologous diazepinones 4, mp >300°(d), and 5, mp 260°(d), afforded regioselectively 2:3 α/β mixtures of 9 in 89% crude yield and of 10 in 77% crude yield,[9] respectively. Separation of each mixture was effected by SiO_2 chromatography. 9: mp 176-177.5°; $[\alpha]_D^{23}$ -40° (c 1.02, DMF) following crystallization from EtOAc:Et_2O. 10: mp 204-206°; $[\alpha]_D^{23}$ -38° (c 1.02, DMF) by trituration from EtOAc. Attempts to crystallize the α-anomer in either case failed.

Extension of the above methodology to the synthesis of coformycin precursor 11 was carried out in CH_3CN in similar fashion on sugar 7 to afford almost exclusively β-anomer 11, white amorphous glass, mp 122-128°, $[\alpha]_D^{23}$ -69° (c 1.03, MeOH), in 51% yield[9] and on 1-*p*-toluoyoxy-2-chloromethoxyethane to afford 12, mp 188-191°, in 27% yield.[9,10]





R"=p-toluoyl

12

8: R=H; R'=H; R"=p-toluoyl
9: R=H; R'=CH_3; R"=p-toluoyl
10: R=H; R'=CH_2CH_3; R"=p-toluoyl
11: R=OR"; R'=H; R"=benzoyl

During the course of this work, we directed considerable effort toward ascertaining the optimum conditions for this glycosylation procedure. We would like to cite the following observations:

(a) Silylation conditions appear to be critically important, especially in the case of 3, and relate to reaction reproducibility. The highest yields were obtained by utilizing two equivalents each of bis-(trimethysilyl)-trifluoroacetamide (BSTFA) and pyridine in CH_3CN, and codistilling repeatidly with CH_3CN, all operations being carried out under *strictly* anhydrous conditions. The effect of pyridine probably serves to buffer the medium. Its absence was not detrimental to the reaction in some cases, especially for homologous heterocycles 4 and 5.

(b) For persilylated diazepinone 3, a 1:1 mixture of CH_3CN and $ClCH_2CH_2Cl$ provided for an optimum reaction rate and yield. The use of CH_3CN alone or in higher proportions favored predominant formation of α-anomer, especially as the reaction temperature was raised from -35° to 0°. Reaction in $ClCH_2CH_2Cl$ at -35° afforded 60% β-anomer, albeit at a much slower rate and with poor conversion. The substitution of CH_2Cl_2 for $ClCH_2CH_2Cl$ in a solvent mixture resulted in slower reaction rates, poorer yields, and erratic ratios of anomeric products, although the α-anomer normally predominated. Similar results were observed for homologous diazepinone 4, in which case a 1:4 solvent mixture of CH_3CN:$ClCH_2CH_2Cl$ was found to be optimum. Monitoring the reaction kinetics of 4 by hplc indicated a constant α/β ratio of ~45:55 as the reaction progressed from -25° to 0°. When the reaction was monitored in CH_3CN, the initial 1:1 ratio of anomers at -25° adjusted to >90% α-anomer as the reaction slowly warmed to 0°.

(c) The catalyst concentration is not critical. $SnCl_4$/Heterocycle = 1.5-2.0 resulted in optimum reproducibility. Generally, heterocycle/sugar = 1.2-1.5 was employed.

(d) The highest reaction rate and yield of desired β-anomer results when one stannylates the persilylated heterocycle in CH_3CN at -25° to -35° followed by addition of the sugar dissolved in $ClCH_2CH_2Cl$. In all cases of high-yielding reactions, tlc indicated completion of reaction after ~15 minutes. The order of addition of reagents can be varied although erratic results were observed in some cases, probably relating to nonhomogeneity of the reaction medium.

Studies directed toward a proposed reaction mechanism along with experimental details for some transformations reported herein will be forthcoming in the full paper. Conversion of intermediates 9, 10, and 12 to pentostatin analogs, along with accompanying biological data, will be delineated in due course.

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