this represents the *terminal* vinyl carbon comes from the undecoupled spectrum in which this peak appears as a triplet. Thus **4** is not involved in the formation of the vinyl compound.

The detailed mechanism of rearrangement remains to be worked out as do the structures of any possible intermediates analogous to those postulated in the phenylcarbene rearrangement. Although even gross questions remain (can the carbene rearrangement traverse borons on its way to stability?), it is clear that one of our initial questions has been answered—the *o*-carborane polyhedral frame can act as a transport system for a carbene. To this extent the analogy between benzene and its three-dimensional cousin holds.

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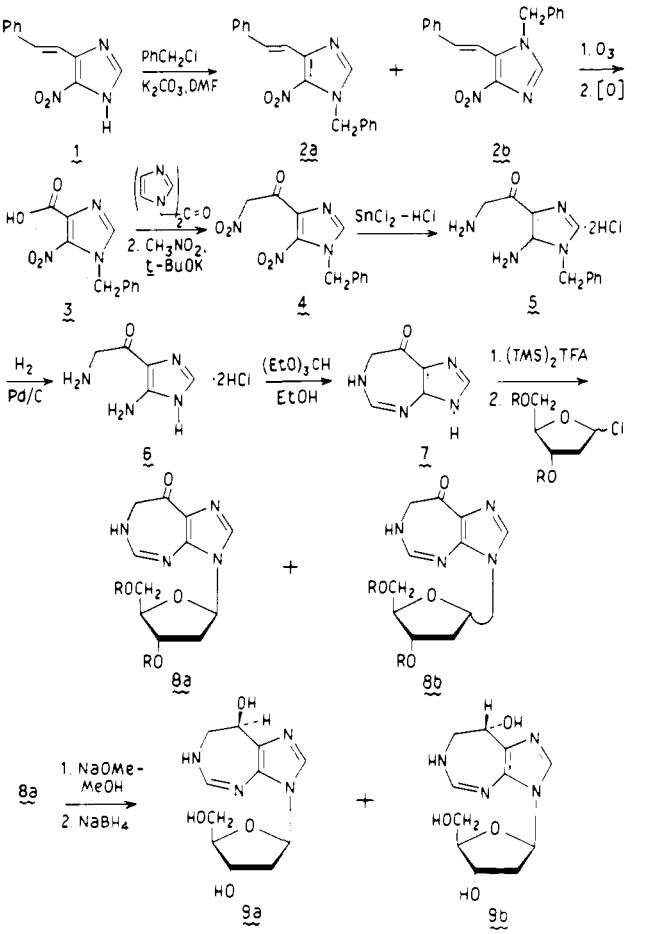
A Total Synthesis of Pentostatin,[1] the Potent Inhibitor of Adenosine Deaminase

Sir:

Pentostatin[1-3] (**9a**) has been shown to be the most potent inhibitor known[4] for adenosine deaminase (adenosine aminohydrolase, E.C. 3.5.4.4), the enzyme responsible for the N^6-deamination of adenine nucleosides. This compound has generated considerable interest as a potentially useful drug for use in combination with certain adenine nucleosides, especially ara-A,[5] whose antiviral and antitumor properties[6-9] are greatly enhanced, both in vitro and in vivo, in the presence of miniscule amounts of pentostatin. Moreover, pentostatin has alone demonstrated a most unique activity as an immunosuppressant,[10,11] acting to prevent the maturation of lymphocytes to limit their role in the immune response.

Herein is described a total, practical synthesis of pentostatin from an available imidazole precursor. In attacking the problem of a total synthesis, it was early recognized that the problem was essentially twofold: (1) developing a synthesis of the unique, chiral, five- and seven-membered fused-ring heterocyclic aglycone, and (2) devising a scheme whereby the fragile 2-deoxy sugar could be efficiently incorporated in the synthetic sequence.[12]



Toward developing a synthesis of the heterocyclic moiety, a diamine **6** was envisioned as a reasonable precursor for the 1,3-diazepinone **7,** the latter being formed via insertion of a one-carbon fragment into **6.** To this end, the chemistry evolved in the following manner. 5-Nitro-4-styrylimidazole (**1**), prepared by an improvement in the published procedure[13] from the condensation of 4-methyl-5-nitroimidazole and benzaldehyde in base (>80%), afforded, upon benzylation with benzyl chloride in *N,N*-dimethylformamide-potassium carbonate, an ~75:25 mixture (>95%) of the benzyl isomers **2a** and **2b,** respectively.[14] Ozonolysis of the mixture of **2a** and **2b,** followed by oxidation of the ozonide with performic acid, gave the crystalline carboxylic acid **3,** isolated directly from the reaction mixture: 75%; mp 155-156 °C dec; λ_{max}^{MeOH} 290 nm (ϵ 4350); ν(C=O) 1736 cm^{-1}; NMR δ 5.50 (s, 2, $-CH_2Ph$), 7.37 (m, 5, aryl), 8.17 (s, 1, 2H).[15] Elaboration of the $-CH_2N<$ portion of the molecule, usually a most difficult process, was achieved in a straightforward manner by C-acylation of potassium methanenitronate, using the imidazoyl derivative of the acid **3,** a new process[16] found to be exceedingly useful for a general synthesis of α-nitro ketones. Data for **4:** 75% yield; mp 107-108.5 °C; λ_{max}^{MeOH} 298 nm (ϵ 4900); ν(C=O) 1642 (NO_2), 1561 cm^{-1}; NMR δ 5.61 (s, 2, $-CH_2Ph$), 6.27[17a] (s, 2, $-CH_2NO_2$), 7.22-7.46 (m, 5, aryl), 8.42 (s, 1, 2*H*). Reduction of the nitro groups on **4** was cleanly effected using 6 equiv of tin(II) chloride in concentrated hydrochloric acid to give the *N*-benzyl diamine dihydrochloride **5** (74%; mp 155 °C dec; $\lambda_{max}^{H_2O}$ 303 nm (ϵ 13 200); ν(C=O) 1620 cm^{-1}; NMR δ 4.14 (d, 2, J = 6.0 Hz, $-CH_2NH_2$), 5.33 (s, 2, $-CH_2Ph$), 7.36

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(s, 5, aryl), 8.25 (s, 1, 2H)) as a white, crystalline solid. Debenzylation was achieved by hydrogenolysis over a palladium-on-charcoal catalyst at pH <2 to furnish the free diamine dihydrochloride **6** (96%; mp >250 °C dec, chars by 310 °C; $\lambda_{max}^{H_2O}$ 304 nm (ϵ 11 700); NMR δ 4.13 (d, 2, J = 6.0 Hz, $-CH_2NH_3^+$), 8.28 (s, 1, 2H)) as a highly organic-insoluble, brittle solid. Using an ethanol-methyl sulfoxide solution of triethyl orthoformate, ring closure to **7**[17b] was effected cleanly and efficiently (88%; mp >250 °C dec; λ_{max}^{MeOH} 300, 227 nm (ϵ 3360, 17 200); ν(C=O) 1682 cm^{-1}; NMR δ 4.33 (s, 2, $-CH_2NH-$), 8.08, 8.24 (s, s, 1, 1, 2-H and 5-H)),[17] in contrast to low-yielding syntheses reported for other 1,3-diazepins.[18] Glycosylation of the per(trimethylsilyl)ated **7** with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranosyl chloride in 1,2-dichloroethane gave an anomeric mixture of the protected nucleosides **8a** and **8b,** isolated from byproducts of the reaction by a rapid chromatography over a bed of silica gel, using ethyl acetate-methanol as the eluant. The anomeric nucleosides were separated by crystallization from ethyl acetate to give the less soluble α anomer **8b** (15%; mp 220 °C dec; $[\alpha]^{23}_D$ +1.8, $[\alpha]^{23}_{436}$ +28° (*c* 1, DMF); λ_{max}^{MeOH} 350, 300, 282 and 235 nm (ϵ 3744, 2789, 3040, 51 258); NMR δ 2.23-3.11 (m, 2, H-2′,2′$_a$), 2.37, 2.47 (s, s, 3, 3, PhCH_3), 3.73 (m, 2, -NHCH_2C=O), 4.47 (m, 2, H-5′,5′$_a$), 4.93 (m, 1, H-4′), 5.60 (dd 1, H-3′), 6.42 (dd, 1, *H*-1′, $J_{1',2'}$ = 2.3, $J_{1',2'_a}$ = 6.8 Hz), 7.4, 7.9 (m, 10, aryl), 8.44, 8.48 (s, s, 1, 1, H-2,H-5)) followed by the β anomer **8a** (14%; mp 129-155 °C dec; $[\alpha]^{23}_D$ −35, $[\alpha]^{23}_{436}$ −87° (*c* 1, DMF); NMR δ 2.06-3.02 (m, 2, H-2′, 2′$_a$), 2.36, 2.47 (s, s, 3, 3, PhCH_3), 3.76 (m, 2, -NHCH_2C=O), 4.42 (m, 1, H-4′), 4.52 (m, 2, H -5′,5′$_a$), 5.64 (dd, H-3′), 6.42 (t, 1, H-1′, $J_{1',2'} \approx J_{1,2'_a}$ = 6.8 Hz)).[19] The anomeric nucleosides **8a** and **8b** are clearly distinguished on the basis of the characteristic doublet of doublets exhibited by the H -1′ signal of the α anomer **8b,** while its β counterpart **8a** gave a pseudotriplet. The H-4′ signal for the α anomer **8b** was also shifted downfield owing to the apparent deshielding effects of the heterocyclic ring. A wide divergence in optical activity, coupled with identical UV spectra under acidic, neutral, and basic conditions, further substantiated the assignments of these compounds as an anomeric pair (as opposed to possible positional isomers).

Deacylation of **8a** in sodium methoxide-methanol, followed by reduction of the crude, keto nucleoside with sodium borohydride, afforded an ~60:40 mixture of *R* and *S* alcohols **9a** and **9b,** having 60 ± 5% of the activity of natural pentostatin. Separation of the diastereomeric pair using a preparative, reverse-phase, octadecylsilyl-derivatized column of silica gel gave the pure *R* isomer that was identical with authentic pentostatin by TLC (silica gel), reverse-phase LC, optical rotation, and UV and NMR spectroscopy; **9a** showed 100 ± 5% of the adenosine deaminase inhibitory activity of natural pentostatin.

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References and Notes:

(1) (a) Pentostatin is the USAN-approved generic name for (*R*)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]-diazepin-8-ol, formerly referred to (see ref 2 and 3) as covidarabine (CoV) and occasionally as 2′-deoxycoformycin (2′-dCF). (b) For a preliminary account, see Baker, D. C.; Putt, S. R. Abstracts of Papers, the American Chemical Society Meeting of the Southern Arizona Section, C.S. Marvel Symposium, Tucson, Ariz., March 19–20, 1979; U.S. Patent 4 117 229.
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Asymmetric Addition of Hydrogen Cyanide to Alkenes Catalyzed by a Zerovalent Palladium Compound

Sir:

We report herein that addition of hydrogen cyanide to alkenes can be carried out in high yields and with significant amounts (~30%) of asymmetric induction when transition metal catalysts with chiral ligands are used. Many asymmetric hydrogenation reactions have been reported,[1] but in contrast few examples have been published in which new carbon-carbon bonds have been formed. Two examples where significant asymmetric induction has been achieved are in reactions of norbornene with other alkenes[2] and in catalytic allylic alkylations.[3]

Reaction of hydrogen cyanide with norbornene using a palladium catalyst which we formulate as [(+)-DIOP]Pd[4] gave 2-*exo*-cyanonorbornane, $[\alpha]_D$ +3.4° in which the (1*S*,2*S*,4*R*)-(+) enantiomer predominated (Scheme I). This was demonstrated by hydrolysis to the corresponding carboxylic acid which had $[\alpha]_D$ +3.0°. The pure (1*S*,2*S*,4*R*) enantiomer has $[\alpha]_D$ +10.7° [5] and thus the optical induction is 28%. When reactions were carried out with a deficiency of hydrogen cyanide (32 mmol) vs. norbornene (64 mmol) in benzene at 130 °C in the presence of [(+)-DIOP]Pd (0.09 mmol) the yield of 2-*exo*-cyanonorbornane was 40%. This yield increased to 80% when a small amount of free (+)-DIOP (0.025 mmol) was added. Reaction with this amount of (+)-DIOP, but at lower temperature (80 °C), gave a lower yield (40%) but a slight increase in optical induction (31%). Reaction with equimolar amounts (64 mmol) of norbornene and hydrogen cyanide at 130 °C in the presence of (+)-DIOP and catalyst gave 2-cyanonorbornane (53%) with similar optical induction (29%). Addition of a Lewis acid, e.g., $ZnCl_2$, for a reaction in acetonitrile solution did not lead to any improvement in yield[6] or optical yield.

Reaction of norbornadiene under similar conditions gave

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