(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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(15) NMR data are reported for ~1–2% solutions in Me_2SO-d_6 (tetramethylsilane internal standard) run on a Bruker WH-90 instrument. All compounds described as "isolated" in the text gave acceptable elemental analyses.
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(17) (a) Disappears upon addition of deuterium oxide. (b) Compound **7** was frequently encountered as **7**·HCl·Me_2SO, mp 156–157 °C dec.
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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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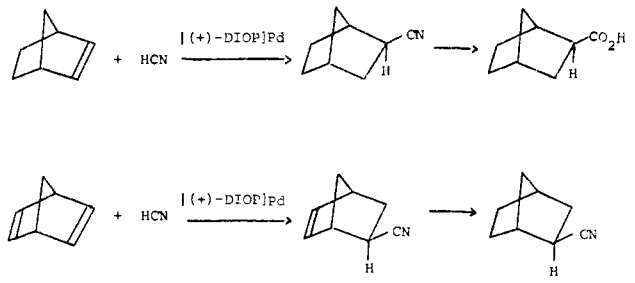
Scheme I



2-*exo*-cyanonorborn-5-ene (1.5 g, 40% based on HCN), $[\alpha]_D$ −3.0°, which on hydrogenation gave 2-*exo*-cyanonorbornane, $[\alpha]_D$ −2.1°. Thus the (1*R*,2*R*,4*S*) enantiomer predominated in the reaction mixture and was in ~17% enantiomeric excess. Reaction of benznorbornadiene gave the exo nitrile, $[\alpha]_D$ −11.3°, which was reduced to the corresponding amine, $[\alpha]_D$ −6.5°. The amine was shown to be a 2:1 mixture of enantiomers by the use of NMR chiral shift reagents. Attempted reaction of 7,7-dimethylnorbornene with hydrogen cyanide under these conditions led to the recovery of alkene, suggesting that the reaction is very susceptible to steric hindrance.

When the [(+)-DIOP]Pd was used to catalyze the addition of hydrogen cyanide to terminal alkenes, e.g., dec-1-ene and pent-1-ene, the anti-Markownikoff, terminal nitriles predominated in the product mixture by ratios of ~7:1:

$$RCH{=}CH_2 + HCN \xrightarrow{\text{(DIOP)Pd}} \underset{7}{RCH_2CH_2CN} + \underset{1}{RCH(CN)CH_3}$$

This regioselectivity compares very favorably with those quoted in many patents concerning hydrogen cyanide addition to terminal alkenes.[6,7]

The [(+)-DIOP]Pd was prepared by two independent routes. Reduction of palladium(II) chloride with hydrazine hydrate in dimethyl sulfoxide solution in the presence of (+)-DIOP or reduction of [(+)-DIOP]$PdCl_2$ with sodium borohydride in acetone solution in the presence of DIOP gave in each case an air-sensitive yellow solid, $[\alpha]_D$ −55°. This yellow solid material had previously been prepared by Trost but not fully characterized.[3] The compound showed ^1H NMR absorptions at δ 7.4 and 7.1 (m, Ph, 20 H), 3.26 (br s, H-2, -3, 2 H), 2.64 (d, H-1′, -4′, 2 H), 1.71 (dd, H-1, -4, 2 H), and 1.12 ppm (s, Me, 6 H) with $J_{1,1'} = 12.9$, $J_{1,2} = 8.0$, and $J_{1',2} < 3$ Hz. However, in addition to the above absorptions samples prepared in Me_2SO showed an absorption at δ 2.59 ppm and samples prepared in acetone showed an absorption at δ 2.16 ppm suggestive of involvement of solvent molecules as ligands. Most of the solvent could be removed by allowing the material to stand for extended periods under high vacuum. Two separate samples analyzed correctly for [(+)-DIOP]Pd. Mass spectral data suggested that the compound was not monomeric.

The ^{31}P spectrum of the compound was temperature variable showing a single resonance at 0.7 ppm (from external H_3PO_4) which broadened and separated into two singlets below −69 °C corresponding to a dynamic process with $\Delta G^{\ddagger} \approx 37$ kJ mol^{-1} at the coalescence temperature. A dynamic process with $\Delta G^{\ddagger} = 48$ kJ mol^{-1} has been reported for the ^{31}P NMR spectrum of the platinum compound, [(+)-DIOP]$_2$Pt.[8] The origins of the dynamic behavior in the platinum compound were attributed to conformational exchange between the two different seven-membered rings. In view of the different formulations for the palladium and platinum compounds, further investigation is clearly necessary.

The diphosphinoethanes, "diphos" ($Ph_2P(CH_2)_2PPh_2$) and "chiraphos" ($Ph_2PCH(CH_3)CH(CH_3)PPh_2$),[9] gave palladium compounds which analyzed for (diphosphine)$_2$Pd. These compounds showed no catalytic activity for HCN addition, and the compound $(Ph_2P(CH_2)_3PPh_2)_2Pd$ showed very reduced catalytic activity relative to the DIOP compound.

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Peptides and Their Retro Enantiomers Are Topologically Nonidentical

Sir:

One approach to the design of biologically active peptide analogues relies on topochemical analysis. A hypothesis which arose from such considerations was that of Shemyakin concerning retro-enantiomeric peptides in which the sequence is reversed and the chirality at each residue is inverted relative to parent peptides.[1] This theory was first advanced for cyclic peptides and stated that a peptide and its retro enantiomer "are very similar topologically, differing only by reversed arrangement of the atoms in the amide groups". This analysis may be extended to linear peptides if the end-group problem (reversal of amino and carboxyl termini) is solved, but it must fail for proline-containing peptides. These problems have been considered in detail by Shemyakin[1] and later by Morley[2] and Goodman.[3]

Retro-enantiomeric peptides are especially attractive synthetic targets since, if it should prove that only the side chains are important in the interaction with a biological receptor, these analogues should elicit a response similar to the parent compound. Increased resistance to enzymatic degradation would result because most peptidases are specific for L-amino acids.

Although some small degree of dissimilarity of topology between the isomers has been recognized,[4] these small differences appear to have been generally thought to be insignificant. Thus, the retro-enantiomer approach has received a great deal of attention and has been applied in a number of instances. Interestingly, however, it apparently has been successful in only a limited number of cases.[5,6]

The difficulties in attaining successful applications of the retro-enantiomer rationale led us to examine further the basic concept. One explanation of these results, of course, is that the peptide backbone does interact with the biological receptor and, therefore, cannot be neglected. A second answer might be found in a change in conformation due to a new set of intramolecular interactions from reversal of the peptide sequence. Reversal of the direction of the peptide bonds assigns values for the C′N-C$^{\alpha}$C′ torsional angle (ϕ) to the NC$^{\alpha}$-C′N

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