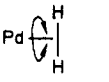
of PdH_x hydrides[13] establish that the dihydrogen moiety maintains its integrity in these matrix reactions.[14]

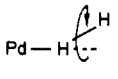
Product distributions as viewed through the IR absorbances of $Pd(H_2)$ and $Pd(D_2)$ in $H_2/D_2/Kr$ and $H_2/D_2/Xe$ mixtures following deposition implies that the reaction of Pd atoms with H_2 is downhill without an appreciable barrier, as predicted by theory.[15] Diagnostic IR signatures for $Pd(\eta^1\text{-}H_2)$ comprise ν-(Pd-(H_2)) and δ(Pd-H-H) modes at 771 and 315 cm^{-1}, respectively, and for $Pd(\eta^2\text{-}H_2)$ a ν(Pd-(H_2)) mode at 894.5/885.5 cm^{-1}. (The vibrational mode involving mainly stretching of the H-H bond is expected to absorb at much higher frequencies, 4200-2500 cm^{-1}, and to exhibit a characteristically very low intensity.[2-10] Under the highest sensitivity conditions in our experiments this IR band passed undetected.) The resemblance of ν(M-(X_2)) stretching modes of $Pd(\eta^1\text{-}X_2)$, 770, 648/585, 546 cm^{-1}, and $Pd(\eta^2\text{-}X_2)$, 960, 804, 714 cm^{-1}, in Kr and $W(CO)_3(PR_3)_2(\eta^2\text{-}H_2)$, 953, 791, 703 cm^{-1}, for $X_2 = H_2$, HD, and D_2, respectively, suggest comparable binding energies for end-on- and side-on-bonded dihydrogen in the Pd and W complexes.

Higher resolution IR scans reveal certain fine structure details for $Pd(\eta^1\text{-}H_2)$ and $Pd(\eta^2\text{-}H_2)$ which are indicative of matrix-dependent dynamical effects of the coordinated dihydrogen moiety. For example, the striking 9 cm^{-1} doublet splitting *unique* to the ν(Pd-(H_2)) mode of $Pd(\eta^2\text{-}H_2)$ in Xe but noticeably absent for $Pd(\eta^2\text{-}HD)$ and $Pd(\eta^2\text{-}D_2)$ can be interpreted in terms of a librational mode of dihydrogen in a symmetrical double-well potential created by the matrix cage and illusted by



Using the Pauling model potential,[16] $V_0(1 - \cos 2\theta)$, and the observed 9 cm^{-1}, librational splitting for $Pd(\eta^2\text{-}H_2)$, we calculate the barrier height $2V_0 \cong 1400$ cm^{-1}. This can then be used to determine the librational splittings for $Pd(\eta^2\text{-HD})$ and $Pd(\eta^2\text{-}D_2)$ which are calculated to be within the widths of the respective IR lines, namely, less than 3 cm^{-1} (Figure 2). Support for this model stems from the fact that in the more constrained sites of solid Kr, one expects a higher barrier for the librational motion and a concomitant reduction of the splitting,[16] consistent with the nonobservation of this dynamical effect in this matrix.

Another kind of dynamical effect unique to the $Pd(\eta^1\text{-}H_2)$ species in Kr is apparent from the observation of what seems to be a rotational progression of about 12 cm^{-1} spacing superimposed on the ν(Pd-(H_2)) IR band around 771 cm^{-1}. This structure, which is reproducible from run to run, may be characteristic of hindered rotor dynamics of an end-on-bonded dihydrogen moiety on a heavy Pd atom anchor, represented as



We cannot yet exclude the contribution of ortho/para dihydrogen effects on these dynamical processes.[17,18] Work is continuing on this problem.

Finally, it is noteworthy that one of the low-lying excited states of $Pd(\eta^2\text{-}H_2)$ is calculated by SCF-Xα-SW MO methods[19] to be unbound with an energy around 300-400 nm. The optical spectrum of $Pd(\eta^2\text{-}H_2)$ in Kr and Xe shows very weak absorption in this wavelength range. Broad-band photoexcitation into this region results in photodissociation of $Pd(\eta^2\text{-}H_2)$, with no sign of insertion to PdH_2, fragmentation to PdH + H, or isomerization to $Pd(\eta^1\text{-}H_2)$.

Acknowledgment. The generous financial assistance of the Natural Sciences and Engineering Research Council of Canada's Operating and Strategic Grants programs and an award from the Connaught Foundation of the University of Toronto is gratefully appreciated. G.A.O. is indebted to the 3M Corp., St. Paul, MN, for a 3M research award. We also acknowledge invaluable technical discussions with Dr. Martin Moskovits on $Pd(H_2)$ dynamics, as well as Dr. Douglas McIntosh, Mark Parnis, and John McCaffrey.

(13) Note that the fundamentals of gaseous PdH and PdD occur at 2083 and 1446 cm^{-1}, respectively. (Basch, H.; Cohen D.; Topiol, S. *Isr. J. Chem.* **1980**, *19*, 233.)

(14) Two additional weak bands were observed at 583 and 351 cm^{-1} in $Pd/H_2/Xe$ samples. These correspond to *pure rotational transitions* $S_0(1)$ and $S_0(0)$ of H_2 isolated in a Xe matrix (Warren, J. A.; Smith, G. R.; Guillory, A. *J. Chem. Phys.* **1980**, *72*, 4901. Prochaska, F. T.; Andrews, L. *J. Chem. Phys.* **1977**, *67*, 1139).

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(17) Glasel, J. A. *J. Chem. Phys.* **1960**, *33*, 252.

(18) The existence of a doublet on the low-frequency side of the ν-(Pd-(H_2)) mode of $Pd(\eta^1\text{-}H_2)$, Figure 1, could be either an ortho-/para-rotational effect, of a multiple trapping site effect.

(19) Ozin, G. A.; McIntosh, D. F.; Garcia-Prieto, J. work in progress.

Extremely Stereoselective and Stereospecific Reductive Cleavage of β-Lactams: A Highly Efficient Route to Labeled Homochiral Peptides

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Besides its importance as a fundamental structure of β-lactam antibiotics, the β-lactam skeleton has been shown to be useful as a synthetic building block in organic synthesis.[1,2] In fact, we have developed a novel route to peptides through the hydrogenolysis of homochiral 4-aryl-β-lactam intermediates on Pd catalyst, i.e., the "β-lactam synthon method",[3] and successfully applied it to the synthesis of potent enkephalin analogues.[4]

Although it was found that no racemization took place at the original C_3 position of homochiral 4-aryl-β-lactams during the hydrogenolysis on Pd catalyst,[3,4] the stereochemistry of the cleavage of the C_4-N bond had not yet been studied. Conceptually, there are three possibilities (Scheme I): (i) retention of configuration via a palladometallacycle (**1**), (ii) inversion of configuration via an S_N2-type mechanism (**2**), and (iii) racemization via a free radical mechanism (**3**). In order to look at the stereochemistry, D_2 was employed so that the products would have a chiral benzyl group.

First, a pair of homochiral diastereomeric β-lactams, **4a** and **4b**, were used as typical substrates. Compound **4** (36.7 mmg, 0.100

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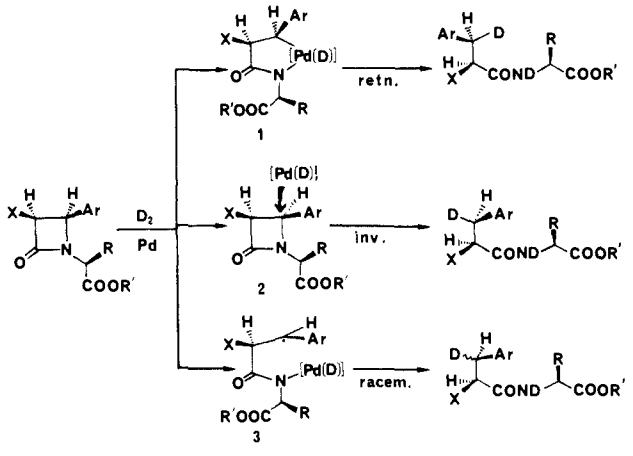
Table I. ^{1}H NMR Data for Deuterated Dipeptide Derivatives[a]

H-Position	dipeptide									
	5a	**5b**	**5a-D**	**5b-D**	**7a-D**	**7b-D**	**7a-d-H**	**7b-d-H**	**9**	**10**
C_2 H	4.795 (dd, J = 3.5, 6.6)	4.728 (dd, J = 3.5, 8.2)	4.789 (d, J = 6.7)	4.721 (d, J = 8.3)	4.654 (d, J = 6.4)	4.686 (d, J = 6.2)	4.647 (d, J = 7.2)	4.648 (d, J = 8.8)	4.647 (d, J = 8.8)	4.648 (d, J = 7.2)
C_3 H	3.186 (dd, J = 6.6, 14.1) 3.296 (dd, J = 3.8, 14.1)	3.158 (dd, J = 8.2, 14.2) 3.300 (dd, J = 3.5, 14.2)	3.172 (d, J = 6.7)	3.139 (d, J = 8.3)	3.069 (d, J = 6.4)	3.091 (d, J = 6.2)	3.014 (d, J = 7.2)	2.965 (d, J = 8.8)	2.965 (d, J = 8.8)	3.014 (d, J = 7.2)

[a] Chemical shift, ppm; J value, Hz.

Scheme I



mmol) in 5 mL of methanol-d_1 was added to a reaction flask containing 5% Pd on carbon (30 mg, 0.15 equiv of **4** as Pd metal), which was equipped with a standard hydrogenation/hydrogenolysis apparatus filled with an atmospheric pressure of D_2. The reaction mixture was stirred for 24 h at room temperature. The disappearance of **4** and the formation of a dipeptide derivative (**5**) were monitored by TLC. A simple filtration of Pd catalyst and evaporation of the solvent gave **5** in quantitative yield. In a similar manner, usual hydrogenolysis of **4a,b** was carried out for the purpose of comparison.

As shown in Table I, the reaction proceeds with virtually complete stereoselectivity (by ^{1}H NMR) and one of the two benzylic hydrogens which appears in a lower field and has a smaller coupling constant (**5a**, δ 3.296, J = 3.8 Hz; **5b**, δ 3.300, J = 3.5 Hz) disappears through the hydrogenolysis with D_2 in both cases.

We also employed two sets of homochiral diastereomeric β-lactams, **6a**, **6a-d**, **6b**, and **6b-d**, which are the precursors of monodeuterated *N*-acetylphenylalanylalanine *tert*-butyl esters: **6a** and **6b** are a pair of homochiral diastereomers and were reductively cleaved with D_2 to give **7a**-D and **7b**-D, respectively, while the monodeuterated pair, **6a-d** and **6b-d**, was cleaved with H_2 under the same reaction conditions to give **7a-d**-H and **7b-d**-H, respectively. All reactions gave the corresponding dipeptides with virtually complete stereoselectivity.[5]

The elucidation of the absolute configurations of the monodeuterated dipeptides obtained was not a straightforward task; neutron diffraction might be the only method based on physical analysis since conventional X-ray diffraction could hardly distinguish deuterium from hydrogen. However, we were fortunate to find a convenient and solid way to elucidate the stereochemistry based on ^{1}H NMR spectroscopy using authentic samples which were prepared by asymmetric hydrogenation of (*Z*)-*N*-acetyldehydrophenylalanyl-3-*d*-(*S*)-alanine *tert*-butyl ester (**8**). The stereochemical course of the asymmetric hydrogenation of dehydro-α-amino acids and dehydropeptides has been unambiguously established.[6,7] Thus, **8** was submitted to the asymmetric hydrogenation with the use of PhCAPP-Rh$^+$ and diPAMP-Rh$^+$ as catalysts at 40 °C and 10 atm of H_2 for 22 h following an well-established procedure.[7] The reactions proceeded in quantitative yields, and after recrystallization from AcOEt/*n*-hexane, **9** and **10**, *N*-acetyl-(2*R*,3*S*)-phenylalanyl-3-*d*-(*S*)-alanine *tert*-butyl ester and *N*-acetyl-(2*S*,3*R*)-phenylalanyl-3-*d*-(*S*)-alanine *tert*-butyl ester, respectively, were obtained optically pure (Scheme II).

Scheme II

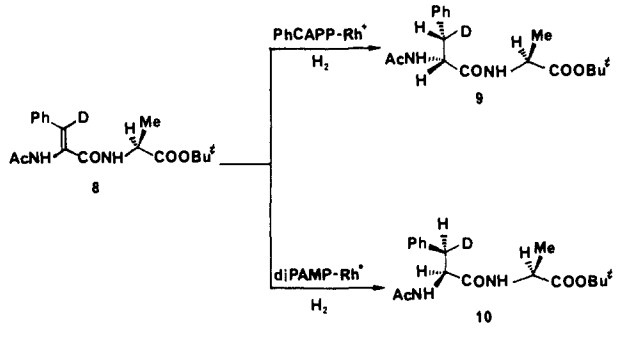
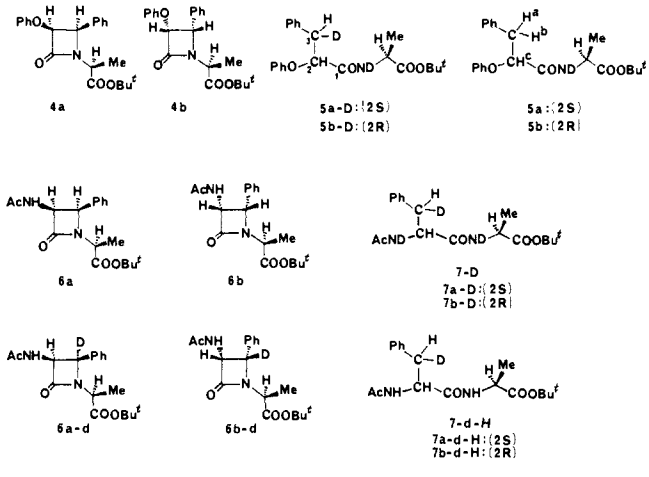


Chart I



As clearly shown in Scheme II and Table I, **9** coincides with **7b-d**-H as **10** does with **7a-d**-H unambiguously. Consequently, it is established that the stereochemical course of the reductive cleavage is *essentially complete inversion of configuration* (!). This result was surprising for us since our initial prediction was retention of configuration through a metallacycle (**1**) based on the well-known fact that low-valent metal species can insert into strained molecules to form metallacycles.[8] Although it has been

(5) When the reductive cleavage was carried out with D_2 for a substantially prolonged period of time or under heating conditions, dideuterated products which arose from C–H activation of benzylic hydrogens of the resulting dipeptides over Pd catalyst were obtained. This is another good method for regiospecific labeling, and the results will be published elsewhere.

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shown that the hydrogenolysis of chiral benzylamines over Pd catalysts tends to proceed with inversion of configuration,[9] the stereoselectivity is not necessarily high and sometimes racemization[10] and even retention of configuration[11] are observed, and the rationalization for those results is still controversial.[12] The present results provide the first clear evidence for the stereochemical course (complete inversion) of the hydrogenolysis of strained chiral benzyl–*amide* bonds over Pd catalysts.[13]

The significance of the present findings is not only the elucidation of the stereochemistry of the reaction but also its application to the synthesis of deuterium- or tritium-labeled homochiral peptides[14] since regiospecific and stereoselective labeling of C_3 positions of α-amino acid residues is extremely difficult based on conventional organic transformations.[15] The C_3-labeled homochiral peptides will play an important role (i) for the study of metabolism since C_3-labeling does not disappear through racemization (C_2-labeling will be lost by racemization), (ii) for the conformational analysis of physiologically active peptides in their binding sites by NMR spectroscopy, and (iii) for the mechanistic study of oxygenases which may produce phenylserine derivatives since such oxidation by enzymes will proceed stereoselectively distinguishing two diastereotopic benzyl protons. Although we demonstrate the usefulness of our stereoselective as well as regio- and stereospecific labeling method only with deuterium, its extention to tritium labeling is straightforward. In fact, we were successful in the stereoselective synthesis of C_3-tritiated dipeptides following the above-mentioned procedure with the use of T_2 instead of D_2 and THF instead of methanol-d_1.[16] The results will be reported elsewhere.

Further studies along this line are actively under way.

Acknowledgment. This work was supported by a grant from the Center for Biotechnology, SUNY at Stony Brook, which is sponsored by the New York State Science and Technology Foundation. The generous support from Ajinomoto Co., Inc., is also gratefully acknowledged.

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(12) The stereochemistry of the hydrogenolysis of chiral tertiary benzyl–oxygen and benzyl–nitrogen bonds was studied in 1960–1970s by several groups[9-11,17] and it was shown that benzyl–oxygen bonds were cleaved with inversion of configuration over Pd or Pt catalysts and with retention of configuration over Raney-Ni whereas the stereochemistry of benzyl–nitrogen bond cleavage was complicated and inconsistent.

(13) It is well-known that the hydrogenolysis of benzyl–nitrogen bonds is not as easy as that of benzyl–oxygen bonds and is frequently accompanied by hydrogenation of aromatic rings even in the cases of simple benzylamines.[17a] Moreover, it is also known that the hydrogenolysis of benzyl–*amide* bonds cannot be achieved under normal conditions: Addition of strong acid and high pressures are necessary to promote the reaction, which usually suffers from severe side reactions.[18] Consequently, it is apparent that the strain energy of β-lactams is indispensable for the facile and clean reductive cleavage in the present systems: See also ref 3c.

(14) At present the applicability of this method is restricted to the labeling of aromatic amino acid residues such as phenylalanine, tyrosine, tryptophan, histidine, and dopa. Nevertheless, its usefulness is obvious since there are so many physiologically important peptides which include aromatic amino acid residues.

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New Approaches to Enzyme Regulators. Synthesis and Enzymological Activity of Carbocyclic Analogues of D-Fructofuranose and D-Fructofuranose 6-Phosphate

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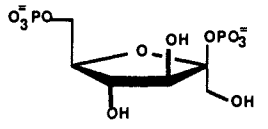
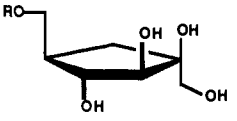
The remarkable enzyme regulatory effects of fructose 2,6-diphosphate (Fru-2,6-P_2) have been revealed only recently.[1,2] This bioregulator (**1**) is a potent positive effector for phosphofructokinase (EC 2.7.1.11) and inhibits 1,6-diphosphofructo-1-phosphatase (EC 3.1.3.11).[3] These enzymes are of major importance in controlling metabolic flux in the glycolytic pathway and the net effect of Fru-2,6-P_2 is to increase the rate of glycolysis and decrease the rate of gluconeogenesis. Analogues of fructose or fructose phosphates are therefore interesting potential agents for controlling diseases caused by errors in regulation of glycolysis.[4] This paper describes the first total syntheses of **2a** and **2b**, carbocyclic analogues of D-fructofuranose and 6-phospho-D-fructose, respectively.[5] Preliminary enzymological data for this new analogue of 6-phospho-D-fructose is also described.



1



2a R = -H
2b R = -PO3

Logical retrosynthetic considerations based on key ideas presented in our earlier work[6] suggested that the penultimate

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