94-1; 2,3:5,6-*O*-dicyclohexylidene-D-mannose, 111025-78-6.

Supplementary Material Available: Procedures for the preparation of benzyl 2,3-*O*-cyclohexylidene-D-ribofuranoside, benzyl 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribofuranoside, 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribofuranose, 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribose oxime, 2,3:5,6-*O*-dicyclohexylidene-D-mannofuranose, and 2,3:5,6-*O*-dicyclohexylidene-D-mannose oxime (4 pages). Ordering information is given on any current masthead page.

Notes

Highly Chemoselective and Stereocontrolled Catalytic Hydrogenolysis of the Carbon-6–Halogen Bond of (Pivaloyloxy)methyl 6,6-Dihalopenicillanate by Chlorotris(triphenylphosphine)rhodium(I) in Homogeneous Phase

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Catalytic hydrogenolysis of the carbon–halogen bond is an important and frequently encountered synthetic transformation in organic synthesis. A number of catalytic hydrogenolysis procedures using heterogeneous catalysts have been developed.[2] Homogeneous transition metal catalyst for this process are less common, although examples involving both molecular hydrogen[3] and hydrogen transfer from organic compounds[4,5] are known.

The transition metal complex chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$, known as Wilkimson's catalyst,[6,7] as well as a variant of it with chiral ligands,[8] has been thoroughly studied in the hydrogenation of alkenes by molecular hydrogen. This complex has also shown high catalytic activity in hydrogen transfer reactions from alcohols,[9] dioxane,[10] amines,[11] and various other organic compounds[11,12] to alkenes and other substrates. The mechanism of hydrogenation[6–8,13] and hydrogen transfer[9,10,14] has been extensively studied.

This paper describes in details the catalytic hydrogenolysis of the carbon-6–halogen bond in (pivaloyloxy)methyl (Pom) 6,6-dihalopenicillanates (**1**, **3**, **5**) by $RhCl(PPh_3)_3$ in the presence of molecular hydrogen and by a stoichiometric amount of $RhCl(PPh_3)_3$ in the absence of molecular hydrogen, in solutions containing methanol as cosolvent, in the presence of $CaCO_3$.

Results and Discussion

Pom 6β-iodo-6α-bromopenicillanate (**1**),[15a] and Pom 6,6-diiodopenicillanate (**3**)[15b] were effectively and stereoselectively hydrogenolyzed by $RhCl(PPh_3)_3$ in the presence of molecular hydrogen and $CaCO_3$ in 24 h by using a mixture of ethyl acetate and methanol (5:8, v/v) as solvent. The former (**1**) gave a mixture of Pom 6α-bromo- (**2a**) and 6β-bromo- (**2b**)[16] penicillanates, and the latter (**3**) a mixture of Pom 6α-iodo- (**4a**) and 6β-iodo- (**4b**) penicillanates, in a ratio 10:1, in 90% yield. Conversely, hydrogenolysis of Pom 6,6-dibromopenicillanate (**5**),[15b] gave only 10% yield of a mixture of **2a** and **2b** in a ratio of 10:1 along side 87% recovery of remaining starting material. Unequivocal proof of the configuration at carbon-6 was secured by ^1H NMR spectroscopy on the basis of the H(5)–H(6) coupling constant.[17]

Complete hydrogenolysis of compounds **1** and **3** in ethyl acetate under the same conditions required 72 h and gave mixtures of **2a** and **2b** from **1** and **4a** and **4b** from **3** in a ratio of 1:1. In contrast, compound **5**, under these conditions, did not react (see Table I, entries 1–6). These

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(1) Research fellow of the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina.

(2) For a review, see: Pinder, A. R. *Synthesis* **1980**, 425.

(3) Kvintovic, P.; Heil, B.; Palagyi, J.; Marko, L. *J. Organomet. Chem.* **1978**, *148*, 311.

(4) (a) For a review, see: Briegger, G.; Nestrick, T. *Chem. Rev.* **1974**, 567. See also (b) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1620. (c) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S. *Tetrahedron Lett.* **1979**, 1607. (d) Urata, H.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *J. Organomet. Chem.* **1982**, *234*, 367.

(5) Yashui, S.; Nakamura, K.; Fujii, M.; Ohno, A. *J. Org. Chem.* **1985**, *50*, 3283 and references therein.

(6) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.

(7) Reviews: (a) Birch, A. J.; Wiliams, D. H. *Org. React.* (*N.Y.*) **1976**, *24*, 1. (b) James, B. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1982; Vol. 8, p 285. (c) Tolman, C. A.; Faller, J. W. In *Homogeneous Catalysis with Metal-Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983; Chapter 2, p 13. (d) Halpern, J. *Inorg. Chim. Acta* **1981**, *50*, 11. (e) Jardine, F. H. In *Progress in Inorganic Chemistry*; Lippard, S. J., Ed.; Wiley: New York, 1981; Vol. 28, p 63. (f) For ^{31}P, ^{13}C, and ^1H NMR studies, see: Tolman, C. A.; Meakin, P. Z.; Lindner, D. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1974**, *96*, 2762.

(8) Reviews: (a) Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85. (b) Halpern, J. *Science* (*Washington, D.C.*) **1982**, *217*, 401. (c) Apsimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5254. (d) For recent papers on kinetic and mechanism, see: Brown, J. M.; Parker, D. *Organometallics* **1982**, *1*, 950. Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746 and 6217.

(9) Imai, H.; Nishiguchi, T.; Fukuzumi, K. *J. Org. Chem.* **1974**, *39*, 1622.

(10) Nishiguchi, T.; Fukuzumi, K. *J. Am. Chem. Soc.* **1974**, *96*, 1893.

(11) Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Org. Chem.* **1975**, *40*, 237.

(12) Hudlicky, M. *Reduction in Organic Chemistry*; Wiley: New York, 1984; p 13.

(13) (a) For theorethical studies of the catalytic cycle of olefin hydrogenation by Wilkinson catalyst, see: Koga, N.; Daniel, C.; Han, J.; Fu, X. Y.; Morokuma, K. *J. Am. Chem. Soc.* **1987**, *109*, 3455. (b) For information about the stereochemistry of intermediate in the catalytic cycle of hydrogenation by Wilkinson's catalyst, see: Brown, J. M.; Evans, P. L.; Lucy, A. R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1589.

(14) Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Org. Chem.* **1975**, *40*, 240.

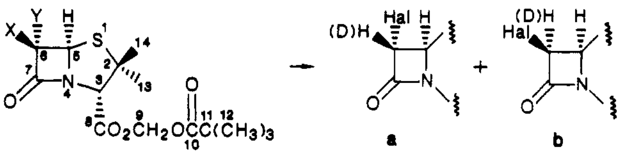
(15) (a) Belinzoni, D. U.; Mascaretti, O. A.; Alzari, P. M.; Punte, G.; Faerman, C. H.; Podjarny, A. D. *Can. J. Chem.* **1985**, *63*, 3177. (b) Belinzoni, D. U.; Setti, E. L.; Mascaretti, O. A. *J. Chem. Res., Synop.* **1988**, 176.

(16) Identification of products was done by comparison of IR, NMR, and MS spectra of isolated product with those of the corresponding authentic samples.

(17) (a) Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, 3325. (b) Green, G. H. F.; Page, J. E.; Stanforth, S. E. *J. Chem. Soc. C* **1965**, 1595. (c) Demarco, P. V.; Nagarajan, R. In *Cephalosporin and Penicillins*; Flynn, E. H., Ed.; Academic: New York, 1972; p 330.

0022-3263/89/1954-2233$01.50/0

Table I. Hydrogenolysis of Pom 6-Halo- and 6,6-Dihalopenicillanates by Chlorotris(triphenylphosphine)rhodium(I)[a]



1: X = I; Y = Br
3: X = Y = I
5: X = Y = Br
7: X = D; Y = I

2: Hal = Br, H
4: Hal = I, H
6: Hal = Br, D
8: Hal = D, H

entry	substrate	solvent[b]	atmosphere	time, days	products	ratio	yield **a** + **b**
1	1	A	H_2	1	**2a** + **2b**	10:1	90
2	3	A	H_2	1	**4a** + **4b**	10:1	91
3	5	A	H_2	1	**2a** + **2b**	10:1	10
4	1	B	H_2	3	**2a** + **2b**	1:1	90
5	3	B	H_2	3	**4a** + **4b**	1:1	90
6	5	B	H_2	3	no reaction		
7	1	C	H_2	1	**6a** + **6b** + **2a**	10:1:1	90
8	1	A	D_2	1	**2a** + **2b**	10:1	93
9	1	A	N_2	1	**2a** + **2b**	10:1	10
10[c]	1	A	N_2	1	**2a** + **2b**	10:1	90
11[c]	3	A	N_2	2	**4a** + **4b**	10:1	90
12	4a	C	H_2	2	**8**		50[d]
13	4b	C	H_2	2	dec		

[a] The ratio of $RhCl(PPh_3)_3$/substrate was 1/10, unless otherwise indicated. [b] A = ethyl acetate–methanol, 5:8 (v/v); B = ethyl acetate; C = ethyl acetate–methanol-d_1, 5:8 (v/v). [c] Stoichiometric amount of $RhCl(PPh_3)_3$ was used. [d] 50% of starting material was recovered. *Note*: The reactions were carried out at 25 °C and 1 atm of pressure, in the presence of $CaCO_3$.

results indicate that the addition of methanol accelerated the rate of hydrogenolysis, a fact that is known in the hydrogenation of some olefins with the Wilkinson's catalyst,[6,18] and affords a high degree of site selectivity.

To test the origin of the hydrogen transferred to C-6, the hydrogenolysis of compound **1** was carried out in ethyl acetate–methanol-d_1/H_2 and in ethyl acetate–methanol/D_2 under the same conditions as described above. The hydrogenolysis of **1** in methanol-d_1/H_2 gave a mixture of Pom 6β-deuterio-6α-bromo- (**6a**), 6α-deuterio-6β-bromo- (**6b**) penicillanates and **2a** in a ratio of 10:1:1, respectively. The crude product, analyzed by ^1H NMR, showed 90% of deuterium incorporation into carbon-6, while with methanol/D_2 the deuterium incorporation was only 2%, determined by mass spectrometry. To establish that the formation of the α-epimer is not due to a secondary product equilibration, compound **2b** was dissolved in a mixture of ethyl acetate–methanol and stirred with $RhCl(PPh_3)_3$ and $CaCO_3$ for 24 h. The recovery of unchanged **2b** confirms that the epimerization does not occur under these reaction conditions. These results show clearly that the hydrogen is transferred selectively from the hydroxylic hydrogen of methanol to carbon-6 of the penicillanate.

In order to determine whether or not the $RhCl(PPh_3)_3$ has catalytic activity in hydrogen transfer from methanol in the absence of molecular hydrogen, we carried out the reaction of **1** with 0.1 equiv of $RhCl(PPh_3)_3$ in a solution of the mixture of ethyl acetate–methanol, at 25 °C, for 24 h, under a nitrogen atmosphere. This reaction showed only 10% of hydrogenolysis. Conversely, when **1** or **3** was reacted in a nitrogen atmosphere in the presence of stoichiometric amount of $RhCl(PPh_3)_3$, the hydrogenolysis took place, affording a product mixture of **2a** and **2b**, or **4a** and **4b**, which showed the same diastereoisomeric ratio as that obtained in the reactions under the conditions of entries 1 and 2 of Table I. These results clearly indicate that the presence of molecular hydrogen is necessary for the $RhCl(PPh_3)_3$ to act as a catalyst.

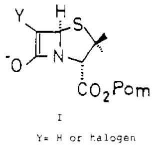


Figure 1.

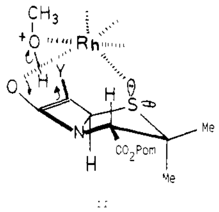


Figure 2.

In every reaction, an excess of $CaCO_3$ was used to neutralize the halogen acid released from the hydrogenolysis of the 6-halopenicillanate. When compound **1** was hydrogenolyzed in the absence of $CaCO_3$, decomposition of penicillanate was observed.

Since the hydrogenolysis of Pom 6α-iodopenicillanate **4a** (Table I, entry 12) gave Pom 6β-deuterio-6α-hydropenicillanate (**8**) as the only dehalogenated product, we conclude that the hydrogen (or deuterium when methanol–d_1 is used) is always transferred at the β-face of the penam system, independently of the position of the halogen, which is in contrast to the results obtained with alkyltin hydride reductions of Pom 6,6-dihalopenicillanates.[19] These finding could be explained by assuming the existence of a common planar intermediate I[20] (See Figure 1). Furthermore, the high stereoselectivity showed by hydrogenolytic reactions (entries 1–3, 7–11, Table I) carried out in methanol as cosolvent suggests that the rhodium atom might coordinate with the β lone electron pair of the sulfur atom of the thiazolidine ring,[21] thus directing the

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(18) Hussey, A. S.; Takeuchi, Y. *J. Org. Chem.* **1970**, *35*, 643.

(19) Belinzoni, D. U.; Mata, E. G.; Mascaretti, O. A. *J. Chem. Res.; Synop.* **1988**, 178.

(20) Denton, D. A.; McQuillin, F. J.; Simpson, P. L. *J. Chem. Soc.* **1964**, 5535.

hydrogen delivery to the more encumbered β-face of the penicillin molecule.[22] The coordination of a molecule of methanol with the metal could increase the acidity of the hydroxylic hydrogen, giving rise to the idea that the hydrogen might be transferred as proton, rather than as a hydride transfer from the metal complex. Here, we suppose that hydrogen could be transferred intramolecularly from the methanol coordinated to the metal in a suprafacial-type fashion. (See Figure 2).

The lack of stereoselectivity when the hydrogenolytic reactions were performed by using ethyl acetate as the unique solvent suggests that in these cases the mechanism of the hydrogen transfer may be different to those reactions carried out in methanol as cosolvent.

At the present stage of our work, the experimental results do not permit an exact knowledge of the nature of the interaction between the substrate, the catalyst, and the hydrogen donor.

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 penam derivatives, since regiospecific and stereoselective labeling of C6β is now possible. This result is complementary to dehalogenation with tributyltin deuteride or tritide $Bu_3SnD(T)$ at C6α.[19] Labeling the carbon-6 of penam derivatives, inter alia, of 6β-bromo-, 6β-iodopenicillanic acid,[23] 6α-chloro- and penicillanic acid sulfone,[24] should be useful in mechanistic studies of these β-lactamase inactivators for various β-lactamases.[25]

Experimental Section

^{1}H NMR spectra were taken on a Bruker WP 80 SY spectrometer at 80.13 MHz, and chemical shift are expressed in parts per million downfield from internal tetramethylsilane. Low-resolution mass spectra (electron impact, 70 eV) was obtained with a Varian MAT CH-7A spectrometer interfaced to a Varian-MAT Data System 166 computer. The Wilkinson's catalyst, monodeuteriomethanol, and deuterium were obtained from Fluka. The ethyl acetate and methanol were purified by distillation. Pom 6β-iodo-6α-bromo- (**1**),[15a] 6,6-diiodo- (**3**),[15b] 6,6-dibromo- (**5**),[15b] 6α-bromo- (**2a**),[15b] 6β-bromo- (**2b**),[26] 6β-iodo- (**4b**),[26] and 6α-iodo- (**4a**)[27] penicillanates were synthesized and described as previously reported.

General Procedure for Catalytic Dehalogenation. The hydrogenolytic reactions were performed at room temperature in a two-necked, round-bottomed flask connected to a hydrogen reservoir maintaned at ambient pressure. The catalyst was placed in the flask and flushed with H_2 several times to remove any air.

A typical experiment for catalytic dehalogenation is as follow: In a 5-mL round-bottom flask, fitted with a magnetic stirring bar, 4 mg (0.005 mmol) of $RhCl(PPh_3)_3$ and 40 mg (0.4 mmol) of calcium carbonate were suspended in methanol (1 mL). After a period of 20 min of stirring under H_2 at 25 °C (prehydrogenation), Pom 6,6-dihalo- or Pom 6-halopenicillanate (0.05 mol) dissolved in ethyl acetate (0.6 mL) was added. After the period of time indicated in Table I, the solution was filtered through silica gel, and the products were identified by TLC and spectroscopic comparison with authentic materials.

Catalytic Deuteriation of Pom 6β-Iodo-6α-bromopenicillanate (1). The procedure followed was as described above. **Entry 7**: Methanol-d_1 (99.5% D) was used. The analysis of the product by ^{1}H NMR, indicated ca. 90% of deuterium incorporation in **6a** and **6b** in a ratio of 10:1. **Entry 8**: Analysis of the products by mass spectrometry indicated 2% of deuterium incorporation.[28] **Entries 10 and 11**: The procedure described above was repeated by using 0.05 mmol of $RhCl(PPh_3)_3$, under an atmosphere of nitrogen.

2a: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.49 (s, 3 H), 1.60 (s, 3 H), 4.56 (s, 1 H), 4.80 (d, 1 H, J = 1.6 Hz), 5.40 (d, 1 H, J = 1.6 Hz), 5.81 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.84 (d, 1 H, C-9H, system, J = 5.6 Hz).

6a: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.49 (s, 3 H), 1.60 (s, 3 H), 4.56 (s, 1 H), 5.40 (br s, 1 H), 5.81 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.84 (d, 1 H, C-9H, AB system, J = 5.6 Hz).

6b: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.50 (s, 3 H), 1.67 (s, 3 H), 4.54 (s, 1 H), 5.56 (s, 1 H), 5.78 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.85 (d, 1 H, C-9H, AB system, J = 5.6 Hz).

7: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.49 (s, 3 H), 1.63 (s, 3 H), 4.56 (s, 1 H), 5.45 (br s, 1 H), 5.78 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.85 (d, 1 H, C-9H, AB system, J = 5.6 Hz).

8: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.49 (s, 3 H), 1.66 (s, 3 H), 3.54 (m, 1 H), after irradiation of H(5) became a broad singlet, 4.47 (s, 1 H), 5.28 (br d, 1 H, J = 4.0 Hz), 5.80 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.81 (d, 1 H, C-9H, AB system, J = 5.6 Hz).

9: ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.49 (s, 3 H), 1.66 (s, 3 H), 4.47 (s, 1 H), 5.28 (s, 1 H), 5.80 (d, 1 H, C-9H, AB system, J = 5.6 Hz), 5.81 (d, 1 H, C-9H, AB system, J = 5.6 Hz).

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Registry No. **1**, 99277-03-9; **2a**, 76468-87-6; **2b**, 74772-33-1; **3**, 76517-03-8; **4a**, 75722-94-0; **4b**, 74772-35-3; **5**, 69388-93-8; **6a**, 116724-90-4; **6b**, 116724-92-6; **8a**, 116724-91-5; **8b**, 116724-93-7; $RhCl(PPh_3)_3$, 14694-95-2.

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[21] (a) For examples involving thioethers as coordinative ligands, see: Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry, 5th ed.*; Wiley: New York, 1988; p 532 and references therein. (b) For a review on the directing effect in homogeneous hydrogenation, see: Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

[22] Setti, E. L.; Mascaretti, O. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2059 and references therein.

[23] For the synthesis and applications of [6α-^{3}H]-6β-bromopenicillanic acid, see: (a) Loosemore, M. J.; Cohen, S. A.; Pratt, R. F. *Biochemistry* **1980**, *19*, 3990. (b) Cohen, S. A.; Pratt, R. F. *Ibid.* 3996.

[24] For an example of the use of monodeuteriated penicillanic acid sulfone in mechanistic studies of β-lactamase inhibition, see: Brenner, D. G.; Knowles, J. R. *Biochemistry* **1981**, *20*, 3680.

[25] For a recent review, see: Knowles, J. R. *Acc. Chem. Res.* **1985**, *18*, 97.

[26] Setti, E. L.; Mascaretti, O. A. *J. Org. Chem.* **1986**, *51*, 3217.

[27] Kemp, J. K. G.; Closier, M. D.; Narayanaswuami, S.; Stefaniak, M. H. *Tetrahedron Lett.* **1980**, *21*, 2991.

[28] Biemann, K. *Mass Spectrometry*; McGraw-Hill: New York, 1962; p 223.

Highly Chemoselective and Stereocontrolled Catalytic Hydrogenolysis of the Carbon-6-Halogen Bond of (Pivaloyloxy)methyl 6,6-Dihalo- and 6-Halopenicillanates by 5% Palladium on Calcium Carbonate and 5% Rhodium on Alumina

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Introduction

Although the hydrogenolysis of carbon–halogen bonds, also termed dehalogenation or reductive dehalogenation, has been extensively investigated,[2] the mechanism of the

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