Synthesis of Optically Active α-Aminophosphinic Acids by Catalytic Asymmetric Hydrogenation in Organic Solvents and Aqueous Micellar Media**

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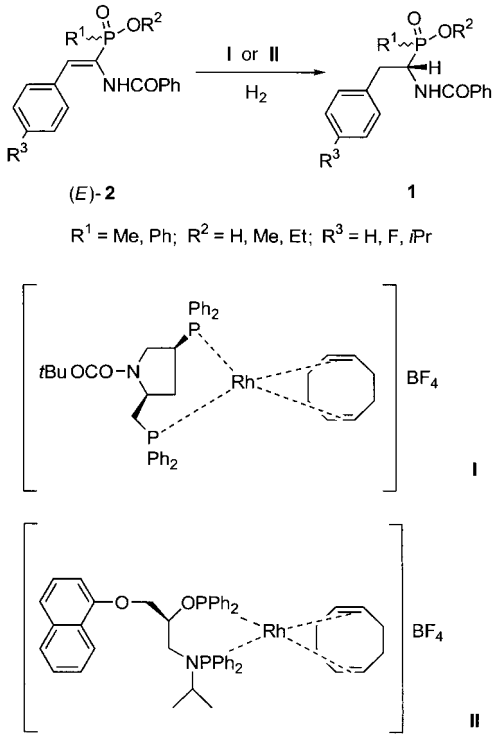
Dedicated to Professor Hanswalter Krause on the occasion of his 70th birthday

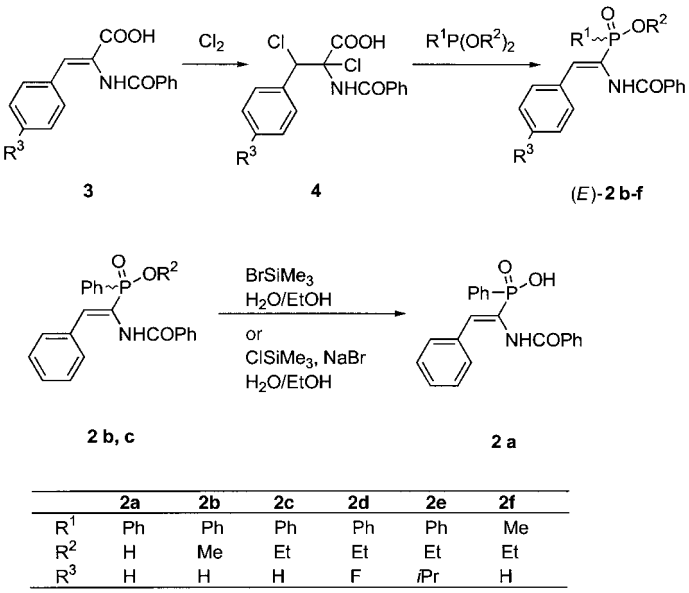
As structural analogues of α-aminocarboxylic acids, α-aminophosphinic acids can have interesting biological properties and serve as active substances in herbicides, bactericides, and antibiotics.[1] The synthesis of optically active α-aminophosphinic acids and their derivatives by means of catalytic asymmetric reactions is hitherto unknown. Only the diastereoselective addition of phosphonites to imines to form chiral α-aminophosphinic esters was described by Afarinkia et al.[2] Martin et al.[3] obtained an optically pure acylated α-aminophosphinic acid by resolution of racemic 1-*N*-carbobenzoxyamino-2-phenylethylphosphonous acid with α-phenylethylamine according to Baylis et al.[4] and subsequent alkylation. We were now able for the first time to synthesize optically active α-aminophosphinic acid derivatives **1** from the unsaturated precursors **2** with high enantioselectivities by catalytic asymmetric hydrogenations with rhodium(I) complexes **I**[5] and **II**[6] (Scheme 1). The reactants **2** can be obtained in two steps from the dehydroamino acids **3** according to the method of Brovarets et al.[7] (Scheme 2).

The ^{1}H NMR spectrum (^3J(P,CH) ≈ 20 Hz) shows that the substrates thus synthesized possess an *E* configuration. According to HPLC analyses of the α-benzamidodehydrophosphinic acid esters **2**, two enantiomers are present in which the phosphorus atoms are the centers of chirality. In contrast, acid **2a** is a racemate owing to the tautomerism of the POOH structure.

As shown in Table 1, optically active acylated α-aminophosphinic acid derivatives are available from suitable precursors by means of catalytic hydrogenations under varying conditions with cationic, optically active rhodium complexes such as **I** and **II** containing a seven-membered chelating ring. The activities of **I** and **II** (represented here by the reaction half-time $t_{1/2}$) are lower than for the hydrogenations of amino acid[8] and aminophosphonic acid precursors,[9] and decrease as expected when the ratio of substrate to catalyst is increased (Table 1, entries 3 and 4). Greater enantiomeric excesses are obtained with **I** (79–98% *ee*) than with **II** (31–79% *ee*). The hydrogenation of **2a** in methanol is less enantioselective than that of esters **2b** and **2c**. The methyl ester **2b** is hydrogenated at a higher reaction rate than the ethyl ester **2c**, but the enantioselectivities are almost identical. In contrast to **I**, hydrogenations with **II**, which contains the ligand PROPRAPHOS (see Scheme 1 for the structure), are more strongly dependent on changes in the reaction condi-



Scheme 1. Catalytic asymmetric hydrogenation of the α-benzamidodehydrophosphinic acids **2** to **1** with the catalysts **I** and **II**.



	2a	2b	2c	2d	2e	2f
R^1	Ph	Ph	Ph	Ph	Ph	Me
R^2	H	Me	Et	Et	Et	Et
R^3	H	H	H	F	*i*Pr	H

Scheme 2. Syntheses of the substrates **2**.

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Table 1. Results of the asymmetric hydrogenation of the substrates **2a–f**.

Entry	Substrate				Catalyst[a]				Remarks
					I		II		
	R^1	R^2	R^3		$t_{1/2}$[b] [min]	ee_C [%]	$t_{1/2}$[b] [min]	ee_C [%]	
1	Ph	H	H	**2a**	16	81	14	56	
2	Ph	Me	H	**2b**	8	86	38	76	
3	Ph	Et	H	**2c**	15	87	70	75	
4	Ph	Et	H	**2c**	95	86	131	71	C:S = 1:100[d]
5	Ph	Et	F	**2d**	20	87	60	64	
6	Ph	Et	*i*Pr	**2e**	20	87	141	60	
7	Ph	Et	H	**2c**	30	91	40	31	in benzene
8	Ph	Et	H	**2c**	16	79	40	79	in CH_2Cl_2
9	Ph	Et	H	**2c**	13	96	–	–	in water[c]
10	Me	Et	H	**2f**	8	93	20	77	
11	Me	Et	H	**2f**	6	98	–	–	in water[c]

[a] Reaction conditions: 0.5 mmol of substrate, 0.01 mmol of catalyst, 7.5 ml of methanol, 25 °C, 0.1 MPa of hydrogen. [b] Reaction half-time. [c] Catalyst:substrate:SDS = 1:50:100. [d] C = catalyst, S = substrate.

tions. An influence of the substituents at the β phenyl ring (**2d**, **2e**) on the rate of hydrogenation ($t_{1/2} = 60$, 70, 141 min for entries 5, 3, 6) as well as a strong solvent dependence of the enantioselectivities (MeOH: 75% *ee*, C_6H_6: 31% *ee*, CH_2Cl_2: 79% *ee* for entries 3, 7, 8) are clear. The highest enantioselectivity was obtained in water with added sodium dodecyl sulfate (SDS; Table 1, entries 9, 11) with 96 and 98% *ee*, respectively. In addition, the aqueous micellar system is extremely efficient because of the high activities. The substituents at the phosphorus atom seem to have an influence on the rates of the reaction with the two catalysts (**2c** (R^1 = Ph): 15 and 70 min, respectively; **2f** (R^1 = Me): 8 and 20 min, respectively), but only to a much lesser degree on the selectivities (**2c**: 87 and 75% *ee*, respectively; **2f**: 93 and 77% *ee*, respectively), which we currently ascribe to steric effects. The *ee* values with respect to the α-C atom (ee_C) can be determined from the enantiomeric excesses of the diastereomer pairs of the ester.[10]

After the hydrogenation (Table 1, entry 9), the diastereomeric ester **1c** was hydrolyzed with hydrochloric acid, and the phosphinic acid formed thereby was recrystallized from 50% acetic acid. The optical purity of the α-*N*-benzoylamino-β-phenylethylphenylphosphinic acid **1a** was 99% *ee* according to a capillary electrophoretic analysis. X-ray structure analysis revealed an *S* configuration for the new center of asymmetry[11] (Figure 1). With the catalytic synthetic pathway described here, these enantiomerically pure α-aminophosphinic acids can now be synthesized in a novel way.

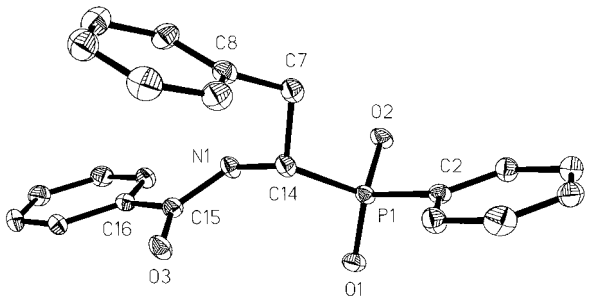

Figure 1. View of the structure of **1a** in the crystal.

Experimental Section

The (*E*)-α-*N*-benzoylamino-β-phenylethenephosphinic acid esters **2b–f** were prepared according to reference [7].

2a: **2b** or **2c** (10 mmol) was stirred with bromotrimethylsilane (20 mmol) in 20 ml of $CHCl_3$ (10 mmol) or with chlorotrimethylsilane (10 mmol) and NaBr (10 mmol) in 20 ml of acetonitrile for 30 min at room temperature. The solution was then concentrated in vacuo, mixed with EtOH/water, and stirred for 5 min. Upon evaporation of the solvent, the acid precipitated in the form of colorless crystals (74% yield).

1a–f: In the presence of catalyst **I** or **II** (0.01 mol) and in the strict absence of oxygen, compounds **2** (0.5 mmol) in 7.5 ml of methanol (or in water with 1 mmol of SDS, see Table 1) were hydrogenated at 25 °C and a hydrogen pressure of 0.1 MPa up to the theoretical hydrogen uptake.[12] Then the solvent was removed in vacuo, and the residue was dissolved in a little CH_2Cl_2/MeOH (29/1) and filtered through a 3-cm plug of silica gel in order to remove the rhodium complex quantitatively. After concentration of the filtrate, the product was obtained in 96% yield. The enantiomeric excess with respect to the center of chirality formed was determined with HPLC (chiral stationary phase: Chiralpak AD (column: 250×4.6 mm^2, DAICEL), eluent: hexane/ethanol (9/1), Liquid Chromatograph 1090, Hewlett-Packard) and, in the case of (S_C)-α *N*-benzoylamino-β-phenylethylphosphinic acid, capillary electrophoretically (boric acid buffer, 10 mM β-cyclodextrin, 0.05% polyvinyl alcohol, pH 9.6, $U = 15$ kV, capillary: 30 cm $\times$ 50 μm, BioFocus 3000 Capillary Electrophoresis system, BIO-RAD).

All isolated compounds were characterized with elemental analysis, NMR and IR spectroscopy, and mass spectrometry.

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[10] HPLC analyses of the dehydroaminophosphinic esters (enantiomeric ratio 1:1) and the diastereomeric pairs of enantiomers (ee_1 und ee_2) lead to a system of equations for the proportions of the four isomers obtained after hydrogenation (A: (S_C,S_P); B: (R_C,R_P); C: (S_C,R_P); D: (R_C,S_P)): A+D = 50, B+C = 50, A/B = (100+ee_1)/(100 – ee_1) and C/D = (100 + ee_2)/(100 – ee_2). Solving this system of equations and combining the calculated values with identical C configurations provides the desired ee_C value after subtraction.
[11] Crystal structure analysis of **1a**: CAD4 diffractometer, graphite-monochromatized Cu $_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, structure solution with direct methods (SHELXS-86: G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467.), full-matrix least-squares refinement against F^2 (SHELXL-97: G. M. Sheldrick, not yet published), structure representation: XP (Siemens); crystal dimensions: $1.10 \times 0.25 \times 0.20$ mm^3, colorless prisms, space group $P2_1$, monoclinic, $a = 12.850(5)$, $b =$

5.293(1), $c = 13.741(3)$ Å, $\beta = 108.69(4)^\circ$, $V = 885.3(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.371$ g cm^{-3}, 4036 measured reflections, 2022 symmetry-independent reflections, of which 1858 were observed ($I = 2\sigma(I)$), $R = 0.046$, wR^2 (all data) $= 0.096$, 239 parameters, Flack parameter 0.01(3). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-101627. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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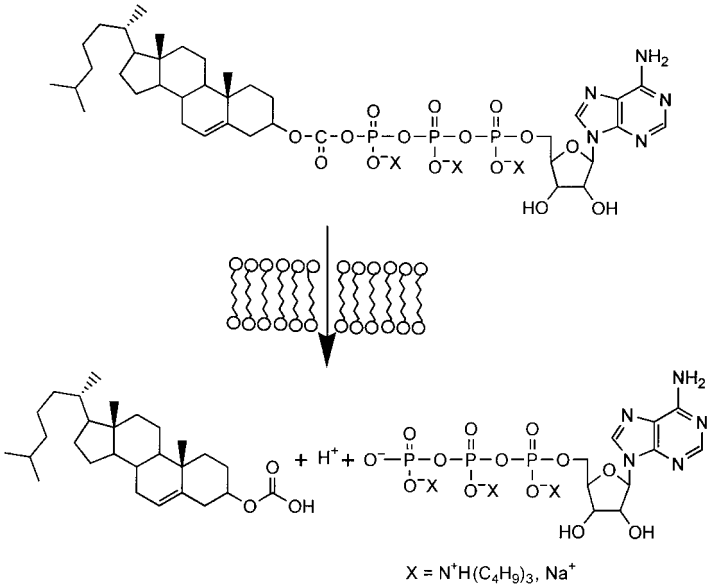

Scheme 1. Schematic representation of the transfer of Chol-ATP across the membrane and the release of ATP by hydrolysis.

Transmembrane Transport of Adenosine 5′-Triphosphate Using a Lipophilic Cholesteryl Derivative**

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Numerous studies to find prodrugs of nucleoside 5′-monophosphates have been reported.[1] However, little work has been described on synthetic carrier systems for nucleoside 5′-triphosphates.[2] To our knowledge no nucleotide derivatives currently exist that are capable of effecting the transfer across membranes with subsequent release of the parent nucleoside 5′-triphosphate. For instance a phospholipid ester of 3′-azido-3′-deoxythymidine (AZT) 5′-triphosphate has been shown to be an effective anti-HIV agent in vitro, but required liposomal formulation; its intracellular hydrolysis led to AZT 5′-monophosphate instead of AZT 5′-triphosphate.[3]

We have recently described the synthesis of acyl nucleoside 5′-di- and 5′-triphosphates as potential membrane-permeable prodrugs.[4, 5] Further development of this work led us to synthesize derivatives of adenosine 5′-triphosphate (ATP). Herein, we present the results of a ^{31}P NMR based study of the transfer of cholesteryloxycarbonyl-ATP (Chol-ATP) (Scheme 1) as a model of a lipophilic nucleotide.

Chol-ATP was synthesized in one step from ATP and cholesteryl chloroformate.[5] A suitable method to investigate the transmembrane transport of liponucleotide conjugates is ^{31}P NMR spectroscopy since it allows both the monitoring of ATP release after internalization of Chol-ATP into liposomes and the distinction between external and internal species in a well-compartmented system.[6, 7] Moreover, ^{31}P NMR resonances are highly sensitive probes of local pH changes.[8] Our approach consists of recording ^{31}P NMR spectra of Chol-ATP in the presence of small unilamellar vesicles (SUV) in a phosphate-buffered system using a pH gradient to distinguish between resonances of ATP molecules located inside and/or outside the liposomes.

Essential requirements of such an experiment are that the compound of interest does not act as a detergent damaging the liposomal structure, and that its hydrolysis kinetic is compatible with the incubation time in the presence of the vesicles.[9] In order to observe the resonances of ATP at different pH values, the liposomes must be able to maintain the proton gradient (ΔpH) across the membrane within the required acquisition time of the ^{31}P NMR spectrum (one hour). To monitor Chol-ATP transport through membranes and the subsequent ATP release, the specific pattern of a ^{31}P NMR spectrum of ATP entrapped in liposomes was first characterized. For this purpose, we prepared vesicles containing ATP. Figure 1 shows ^{31}P NMR spectra of ATP (internal concentration 50 mM) entrapped in liposomes prepared in a phosphate-buffered medium recorded at different times. The comparison of these spectra provided three important pieces of information: a) The appearance of an inorganic phosphate peak, at a resonance frequency identical to the initial step before the pH jump, indicates the preservation of the pH 5 in the inner volume of the liposomes during the acquisition time. This, and the fact that no extravesicular ATP resonances occurred, demonstrates the integrity of the vesicles (Figure 1b). b) After the pH jump the integral value for the two inorganic phosphate resonances gives an accurate determination of the distribution between the inner (6%) and outer volume (94%). As a result, the concentration of internal ATP was equivalent to 3 mM with respect to the total volume. c) A direct comparison of the lineshapes of intra- and extravesicular ATP resonances, while

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