NAD(P)$^+$–NAD(P)H Models. 86. Nonsteric Stereochemistry in Hydride-Transfer to Sulfinylpyridinium Ion

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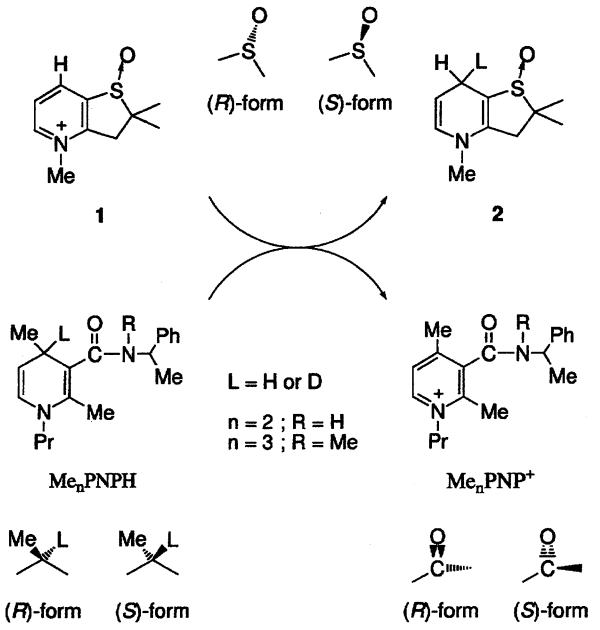
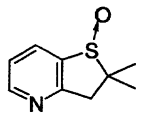
The molecular structure of an enantiomer of nicotinamide coenzyme analog **1** has been determined by X-ray crystallography with the absolute configuration being established by the anomalous dispersion effects of all non-hydrogen atoms: (+)-**1** exhibits (*S*)-form sticking the sulfinyl S–O out of the *re* face. The stereochemistry of the hydride-transfer reaction between the chiral coenzyme analogs, **1** and Me$_n$PNPH, was studied. The hydride from (*S*)- or (*R*)-Me$_n$PNPH, respectively, transfers to (*S*)- or (*R*)-**1**, affording the dihydropyridine compound *syn*-**2** predominantly: That is, the reaction takes place in the face occupied by the sulfinyl oxygen. On the other hand, the transfer to (*R*)- or (*S*)-**1** mainly takes place so as to afford *anti*-**2**. It has been deduced that (*S*)-**1** reacts with (*S*)-Me$_n$PNPH more than twice as fast as (*R*)-**1** does or vice versa. It has also been elucidated that the amide oxygen in Me$_n$PNPH points to **1** exclusively at the transition state of the reaction, regardless the configuration of the reagents. The intermolecular arrangement at the transition state of the reaction is discussed.

Based on the experimental results, we reported that there is a series of reactions in which the stereochemistry is controlled by the orientation of a carbonyl dipole instead of a steric hindrance exerted by substituents in the molecules. Before the proposal of this electronically oriented, or nonsteric, stereochemistry is established, it is necessary to investigate the effect of other dipolar functions as well; we thus employed a sulfinyl group in place of a carbonyl function as one of the dipolar functions. A sulfinyl group has an advantage over a carbonyl group in that the former has a configurationally stable structure, whereas the latter is often unstable configurationally, resulting in rapid racemization at room temperature.[1)]

In principle, there are four possible diastereomeric conformations for the transition state of a reaction between two enantiomeric reagents. A hydride-transfer reaction between chiral analogs of the nicotinamide coenzyme is one example. In a previous paper we reported on the stereochemistry associated with the reduction of 2,3-dihydro-2,2,4-trimethylthieno[3,2-*b*]pyridinium 1-oxide[2)] (**1**) with various achiral reducing agents, and proposed that the orientation of the sulfinyl dipole plays an important role in determining the stereochemical course of the reaction:[3)] The hydride mainly transfers to the same face of **1** as that occupied by the sulfinyl oxygen. This observation has the same tendency as that observed with carbonyl compounds.[1,4)] As the second stage of investigation, it is interesting and quite important to study the molecular arrangement at the transition state of the reaction in order to understand the stereochemical preferency; we thus studied the reaction of **1** with a chiral dihydropyridine derivative, 3-[*N*-(α-methylbenzyl)carbamoyl]-2,4-dimethyl-1-propyl-1,4-dihydronicotinamide (Me$_2$PNPH) and its *N*-methylcarbamoyl homolog (Me$_3$PNPH). With respect to the relative arrangement of the pyridinium ion/dihydropyridine moieties, the arrangements are symbolized by *exo* or *endo*. At the same time, with respect to the relative positions of the side chains, they are referred to as *cis* or *trans*. Finally, we define *syn* and *anti* arrangements with respect to the relative orientation of the carbon–hydrogen bond at the 7-position and the sulfinyl dipole in the side chain of 2,3,4,7-tetrahydro-2,2,4-trimethylthieno[3,2-*b*]pyridine 1-oxide (**2**), one of reaction products (Schemes 1 and 2). Thus, either a *syn* or *anti* product is afforded when the reducing agent attacks **1** from the same or the other face that includes the sulfinyl oxygen, respectively.

Molecular orbital calculations based on AM1 and MNDO procedures by Bodor et al. predict that the *endo-cis* arrangement is reasonable for the transition state of the reaction between a protonated pyridinium ion and 1,4-dihydronicotinamide.[5,6)] However, recent and more sophisticated ab initio molecular orbital calculations propose that the *endo-trans-syn* arrangement is most favored.[7)] Experimentally, assuming a linear transition state, Verhoeven et al. report that the reaction of 1-benzyl-1,4-dihydronicotin-





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Scheme 1.

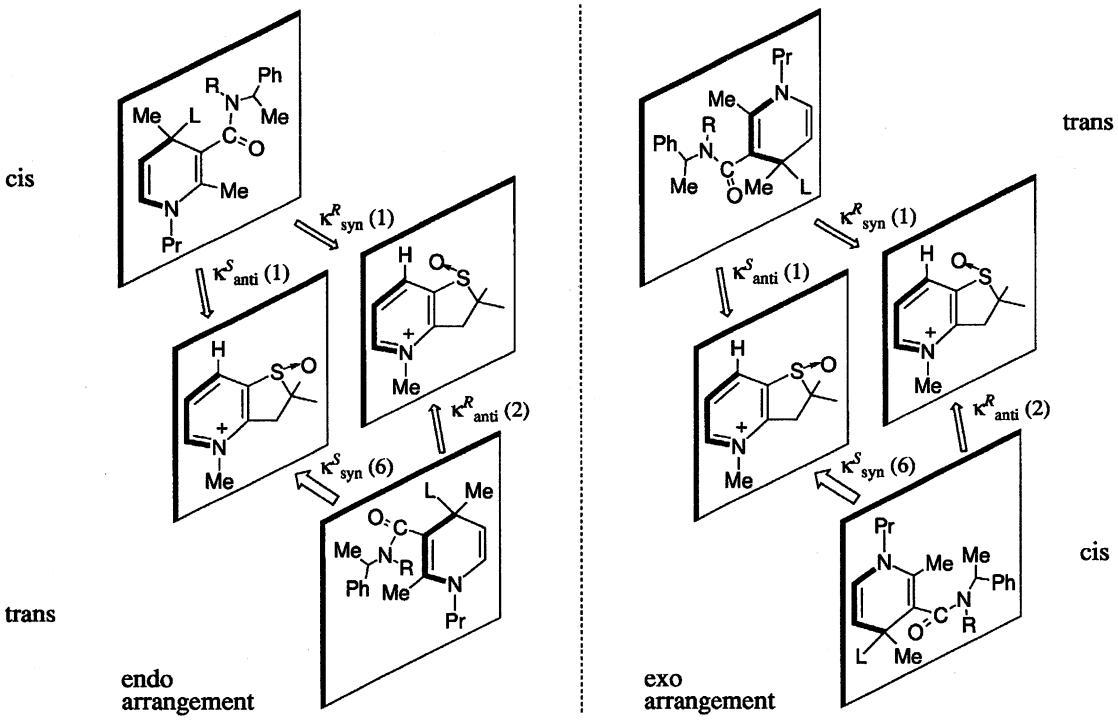
amide (BNAH) with 10-methyl-9-phenylacridinium favors the *exo* arrangement.[8,9] On the other hand, a bent transition state is proposed by Powell and Bruice with the preference of the *endo* arrangement.[10] A bent transition state has also been suggested theoretically for a hydride transfer by Huskey and Schowen.[11] Previous reports from our laboratory have predicted the preferency of the *endo-cis* arrangement for a neutral substrate[12,13] and the *endo-trans* arrangement for a positively charged substrate.[4] The present reaction belongs to the category in which a pyridinium ion is reduced.

Results and Discussion

Absolute Configuration of Chiral 1. As noted in the preceding report,[3] optically pure **1** was obtained by Menschutkin methylation of its precursor, optically pure **3**. Racemic **3** was separated to two enantiomers with an HPLC equipped with a chiral column (DAICEL CHIRALCEL AS). Circular dichroism (CD) spectra of the chiral iodide salt of **1** in H_2O and **3** in CH_3OH are shown in Figs. 1 and 2, respectively. The similarity of these two spectra proves that the absolute configuration of **3** is not affected by methylation to afford **1**.

Despite our best effort, the crystallographic data did not converge to afford an *R* value less than 8%, which is not satisfactorily small to discuss on the molecular structure of (+)-**1** in detail. However, undoubtedly, anomalous dispersion effects in the crystallography[14] reveal that the oxygen atom of (+)-**1** exists in the *re* face, or the molecule has the *S* configuration. At the same time, the crystallography guarantees that the ring system in the molecule is set in almost a planar configuration. A perspective view of (*S*)-(+)-**1** is presented in Fig. 3 and the crystallographic parameters are listed in Table 1.

Consequently, it has been elucidated that (+)-**3** also has



Scheme 2.

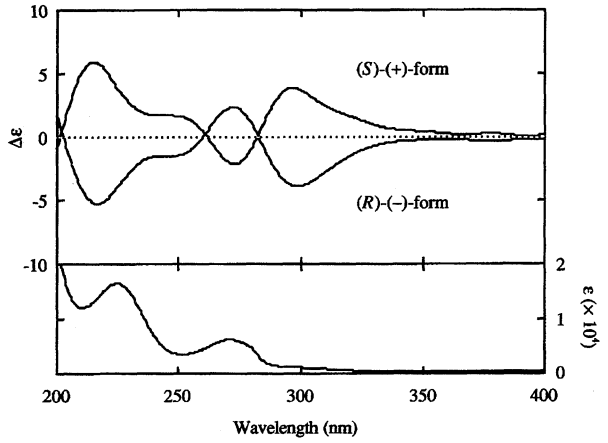


Fig. 1. CD and UV spectra of iodide salt of (*S*)-(+)- and (*R*)-(−)-**1** in water.

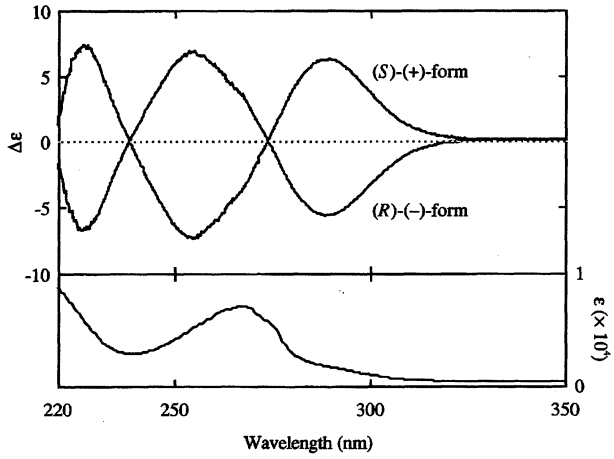


Fig. 2. CD and UV spectra of (*S*)-(+)- and (*R*)-(−)-**3** in methanol.

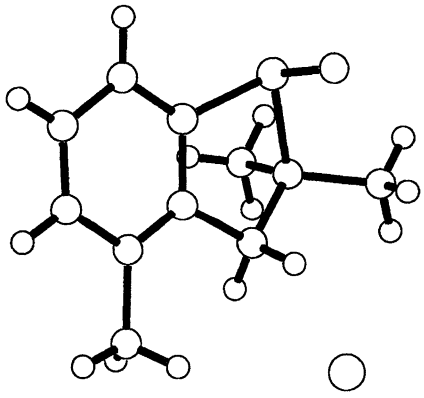


Fig. 3. A perspective view of an iodide salt of (*S*)-(+)-**1**.

the *S* configuration.

Stereochemistry of Hydride Transfer. The reaction was run using Me_2PNPH-4-*d* or Me_3PNPH-4-*d* in order to elucidate the reacting face of **1** by analyzing the stereochemistry of the proton at the 7-position of **2**, the reduction product, by means of ^{1}H NMR spectroscopy. Table 2 summarizes the *syn*/*anti* stereospecificities of the reactions shown in Scheme 1. The fact that both Me_2PNPH-4-*d* and Me_3PNPH-4-*d* result in essentially the same *syn*/*anti* ratio clearly indicates that the amide hydrogen in Me_2PNPH-4-*d* does not play a role to control the stereochemistry of reaction by forming a hydrogen bond with the sulfinyl oxygen in **1**.

Table 1. Crystallographic Parameters of Iodide Salt of (*S*)-(+)-**1**

Empirical formula		$C_{10}H_{14}INOS$
Formula weight		323.19
Cryst color, habit		Yellow, prismatic
Cryst dimens/mm		0.40 × 0.40 × 0.60
Cryst system		Monoclinic
Space group		$P2_1$ (#4)
Lattice type		Primitive
Lattice params	*a*/Å	6.817(3)
	b/Å	12.390(2)
	c/Å	7.734(2)
	β/°	108.56(2)
V/Å^3		619.2(3)
Z value		2
D_{calcd}/g cm^{-3}		1.733
Radiation		Cu *Kα* (*λ* = 1.54178 Å)
μ/cm^{-1}		216.53
Scan type		*ω*–2*θ*
$2\theta_{max}$/°		120.0
Refinement		Full-matrix least-squares
No. of measd reflcns		2025
No. of indep reflcns (I > 3.00*σ*(I))		1923
R		0.087
R_w		0.106
Goodness of fit indicator		4.66
Max peak in final diff map/e Å^{-3}		1.91
Min peak in final diff map/e Å^{-3}		−1.85

Table 2 reveals that racemic **1** affords *syn*-**2** predominantly regardless of the configuration of Me_nPNPH-4-*d* (*n* = 2 or 3) employed for the reaction, whereas *syn*- or *anti*-**2** is obtained predominantly depending on the combination of (4*R*)- or (4*S*)-Me_nPNPH-4-*d* (*n* = 2 or 3) and (*R*)- or (*S*)-**1**.

Although it is difficult to follow the kinetics of the hydride-transfer reactions quantitatively, because of interference by undesired side reaction(s),[3] the relative facility of the reactions with each combination of reagents can be estimated by comparing the stereochemistry of the reactions of chiral **1** with that of racemic **1**: in the case of the reaction of (4*S*)-Me_2PNPH-4-*d*, for example,[15]

$$(0.86\varkappa^S + 0.38\varkappa^R) : (0.14\varkappa^S + 0.62\varkappa^R) = 72 : 28$$

$$\therefore\ \varkappa^S : \varkappa^R \approx 7 : 3,$$

where $\varkappa^S$ and $\varkappa^R$ are the reactivities of (*S*)- and (*R*)-**1**, respectively. Thus, (*S*)-**1** reacts with (4*S*)-Me_2PNPH-4-*d* more than twice as fast as (*R*)-**1** does. Moreover, each reactivity can be divided into *syn*- and *anti*-counterparts ($\varkappa = \varkappa_{syn} + \varkappa_{anti}$); then, from the data listed in Table 2,

$$\varkappa^S_{syn} : \varkappa^S_{anti} : \varkappa^R_{syn} : \varkappa^R_{anti} \approx 6 : 1 : 1 : 2.$$

The ratios from the reactions with (4*R*)-Me_2PNPH-4-*d*, of course, appear similarly:

Table 2. *Syn/Anti* Stereoselectivity in the Reduction of 2,3-Dihydro-2,2,4-trimethylthieno-[3,2-*b*]pyridinium 1-Oxide with Me_nPNPH ($n=2$ or 3)

1	(*R*)-Me_2PNPH[a)]	(*S*)-Me_2PNPH[a)]	(*R*)-Me_3PNPH[b)]	(*S*)-Me_3PNPH[b)]
Racemic	70/30	72/28	75/25	78/22
(*R*)-	87/13	38/62	85/15	35/65
(*S*)-	38/62	86/14	29/71	87/13

a) Errors are ±3. b) Errors are ±5.

$$\varkappa^R_{syn} : \varkappa^R_{anti} : \varkappa^S_{syn} : \varkappa^S_{anti} \approx 6 : 1 : 1 : 2.$$

The thus-obtained relative importance of each process is indicated in Scheme 2 by the number in parentheses.

When Me_3PNPH is employed as the reducing agent, its oxidized form, Me_3PNP^+, maintains the axial chirality with respect to its C_3–$C_{carbonyl}$ bond.[16—19] Since (4*R*)-Me_3PNPH-4-*d* affords (*S*)-Me_3PNP^+ and vice versa, it has been confirmed that the transferring hydrogen is set in the same face of the molecule as where the carbonyl oxygen exists, or the configuration of Me_3PNPH at the transition state of the reaction is syn with respect to the carbonyl oxygen. In other words, it has been confirmed that both oxidizing and reducing agents accept or release a *syn*-hydrogen with respect to the orientation of a dipolar functional group.

Molecular Arrangement at the Transition State. A combination of (4*R*)-Me_nPNPH ($n=2$ or 3) and (*R*)- or (*S*)-**1** affords the same result as that obtained by a combination of (4*S*)-Me_nPNPH ($n=2$ or 3) and (*S*)- or (*R*)-**1**, respectively; we discuss on the latter pair only for simplicity, as depicted in Scheme 2. In addition, for a hydride-transfer reaction between a pyridinium and dihydropyridine derivatives, isotope scrambling must be taken into account in principle, because these two species form a complex in which the intermolecular transfer of a hydride takes place.[20] However, we confirmed that this process is very much slower than the redox reaction.

Since the intermolecular arrangement is not firmly fixed in the present reaction system, the present result does not contribute evidence concerning the preferency of the *exo* or *endo* arrangement unambiguously. Therefore, we have to assume a preference based on a certain scientifically reasonable prediction. There remains no doubt that the *syn* process is more facile than the *anti* process from the viewpoint of the classical steric effect. However, we are not convinced at this stage whether the *syn* selectivity is the most important factor to overwhelm any other stereo-controlling effects, and we have to inspect them one by one.

When the *exo* arrangement is chosen as the preferable arrangement at the transition state, the experimentally observed predominance of the *cis-syn* process (Scheme 2) predicts that the *syn* arrangement is a predominating factor to control the stereochemistry of the reaction. It is conceivable that the *syn* selectivity overwhelms any steric interference stemming from the side-chain carbamoyl group. Such a strong preference of the *syn* arrangement might result in a *trans-syn* arrangement as the second, or even the first, choice of preferency, where no steric effect is anticipated. This argument does not coincide with the experimental result. It should be noted that the transferring *syn*-hydrogen always suffers from a steric interference by the carbonyl oxygen in Me_nPNPH ($n=2$ or 3).[21]

On the other hand, when one assumes that the *cis* arrangement is a dominant factor to control the stereochemistry under the restriction of an *exo* arrangement, and that other effects are overwhelmed by this factor, the *syn* and *anti* arrangements as the first and second choices due to the orientation effected by the sulfinyl dipole is a reasonable result. However, previously reported[4] and unpublished[22] results from our laboratory predict that the *cis* arrangement cannot explain all of the evidence so far obtained. Moreover, the *cis* arrangement violates the traditional idea of a steric hindrance. Consequently, we prefer to choose the *endo* arrangement as the basis of our discussion.

The predominance of the *endo-trans-syn* arrangement is a reasonable result: The process is most plausible not only from the viewpoint of *syn* selectivity, but also from the viewpoint of the classical steric effect. The fact that the second choice (experimentally observed) is the *endo-trans-anti* arrangement reveals that the classical steric effect predominates over the *syn* selectivity stemming from the orientation of the dipole. Thus, the importance of stereo-controlling effects decreases in the order: π–π *endo*-stacking effect>classical steric hindrance>dipole-controlled orientation.

Previously, we report evidence for the contribution of a π–π stacking interaction in similar reaction systems.[20]

The highest reactivity for the *endo-trans-syn* arrangement is in excellent agreement with the result from the ab initio molecular orbital calculations; this arrangement inevitably predicts that a bent transition state is favored over a linear one for a hydride-transfer reaction.[7]

Experimental

Instruments. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR 200 FT-NMR spectrometer. The optical rotations were measured on a JASCO DIP-181 digital polarimeter. The circular dichroism spectra were collected on a JASCO J-720W spectropolarimeter.

Materials. Acetonitrile was distilled over calcium hydride under an atmosphere of argon before use. An iodide salt of racemic **1**[3] and (*S*)- and (*R*)-Me_nPNPH ($n=2$ or 3)[9,23] were prepared according to literature procedures.

Optically pure **1** was obtained from optically pure **3** by the same method as described for preparing racemic **1** from racemic **3**.[3] Racemic **3** was separated to two enantiomers using an HPLC equipped with a chiral column (DAICEL CHIRALCEL AS, 2 cm $\phi \times 25$ cm) eluted with 2-propanol/hexane (1/1) at 3 mL min^{-1} and

monitored at 254 nm. The CD spectra of two enantiomers of **1** and **3** are shown in Figs. 1 and 2, respectively.

The iodide salt of (*R*)-(−)-**1**: $[\alpha]_D^{22}$ −92.0° (*c* 0.631, water), the iodide salt of (*S*)-(+)-**1**: $[\alpha]_D^{22}$ 91.9° (*c* 0.650, water), (*R*)-(−)-**3**: $[\alpha]_D^{18}$ −157° (*c* 0.760, chloroform), (*S*)-(+)-**3**: $[\alpha]_D^{17}$ 158° (*c* 0.835, chloroform).

Crystallographic Study. A yellow prismatic crystal with approximate dimensions (0.40×0.40×0.60 mm) of an optically pure iodide salt of (+)-**1** was used for data collection. All of the measurements were made on a Rigaku AFC7R diffractometer with Cu $K\alpha$ radiation and a 12-kW rotating anode generator. Based on the systematic absences (0*k*0: $k \neq 2n$), packing considerations, a statistical analysis of the intensity distribution, and a successful solution and refinement of the structure, the space group was determined to be $P2_1$. Two-thousand-and-twenty-five reflections were recorded for the $(+h \pm k \pm l)$ octant using the ω–2θ scan technique to a maximum 2θ value of 120.0°. An empirical absorption correction using the program DIFABS[24] was applied, which resulted in transmission factors ranging from 0.50 to 1.40. The data were corrected for both Lorentz and polarization effects.

The structure was solved by direct methods (SIR88),[25] and expanded using Fourier techniques (DIRDIF92).[26] Anomalous dispersion effects for all non-hydrogen atoms were included in F_c. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but not refined. For the structure having the *S* configuration (Fig. 3) the final cycle of a full-matrix least-squares refinement was based on 1923 observed reflections ($I > 4.00\sigma(I)$) and 126 variable parameters, and converged with the factors of R=0.087 and R_w=0.106. The configuration is correct rather than the opposite enantiomorph converging to R=0.113. A comparison of the observed and calculated values of Bijvoet differences ($||F_{hkl}| - |F_{\bar{h}\bar{k}\bar{l}}||$) also confirmed the assignment. All of the calculations were performed using a TEXSAN crystallographic software package developed by Molecular Structure Corp. (1985 and 1992). A perspective view is presented in Fig. 3, and the crystallographic parameters are listed in Table 1. Atomic coordinates, thermal parameters, bond lengths, bond angles, and torsion angles have been deposited as Document No. 69016 in the Office of the Editor of Bull. Chem. Soc. Jpn.

Reactions. All of the reactions were performed under an atmosphere of argon in the dark at 25 °C. As a typical example, acetonitrile (1 mL) was added to a mixture of an iodide salt of (*R*)-, (*S*)-, or racemic **1** (16.2 mg, 0.05 mmol) and a deuterated form of (*R*)- or (*S*)-Me_3PNPH (6.1 mg, 0.02 mmol) in a 20 mL round-bottomed flask equipped with a magnetic stirrer. The reaction mixture was stirred for 2 h. The acetonitrile was evaporated under reduced pressure to give a residue, which was then roughly purified by flash-column chromatography on activated neutral alumina eluted with dichloromethane. Removal of the solvent under reduced pressure gave a residue, which was then dissolved in $CDCl_3$ and subjected to ^{1}H NMR spectroscopy to elucidate the stereospecificities of the products, **2**[3] and Me_3PNP^+.[9,27,28]

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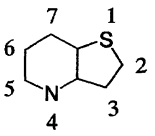

Chart 1.

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