Improvement in the Enantioselectivity of the Hydrogen Transfer with NADH Models Bearing Amino Alcohols as Chiral Auxiliaries

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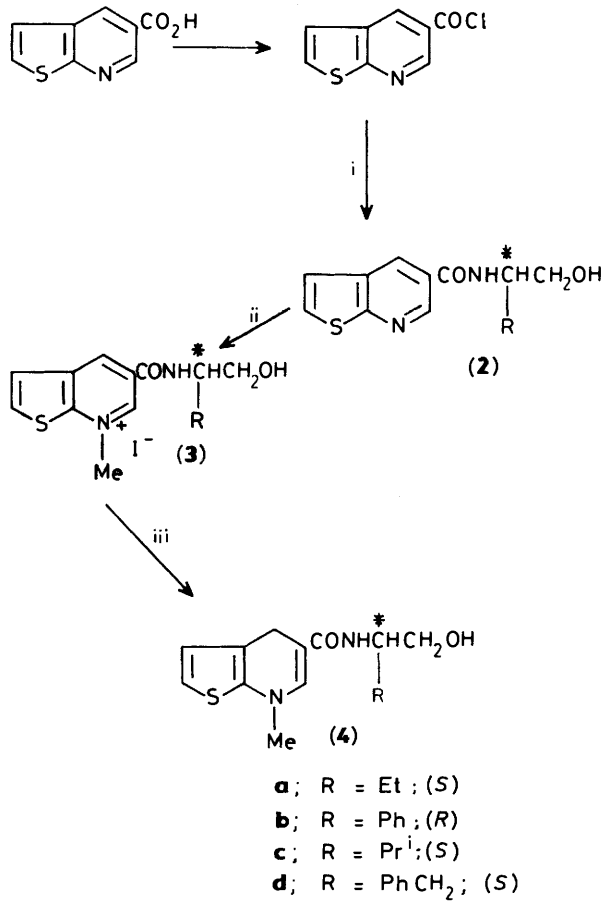
Chiral amino alcohols have been linked to the γ-carbonyl group of the 5,7-dihydrothieno[2,3-*b*]pyridines (**4a**—**d**). These models are much more easily handled in mild conditions than common NADH models. The factors affecting enantiomeric excess have been studied, *e.g.* influence of temperature, polarity of solvents, magnesium concentration, and hydrogen bonding. By appropriate modifications of the chiral auxiliary, the rigidity of the ternary complex: model–Mg^{2+}–substrate involved has been enhanced. In this way a high enantiomeric excess has been obtained.

NADH models bearing a chiral auxiliary have been widely studied in asymmetric synthesis, some of them producing a high enantiomeric excess.[1] A chiral auxiliary can be introduced at several positions on the 1,4-dihydropyridine structure. For example, many models have been synthesized with a chiral auxiliary on the amide part of the 1,4-dihydronicotinamide structure. In our laboratory, we chose to introduce chirality with a 2-amino alcohol, used only once before.[2] We hoped that the geometry of the 'ternary complex' formed by the dihydropyridine, magnesium ions, and the substrate could be strongly influenced by the chelation of Mg^{2+} with the amide moiety enhanced by the chelation caused by the alcoholic oxygen near the amide. In a preliminary study we have shown that this type of substituent induces the asymmetric reduction of methyl benzoylformate efficiently. Moreover we observed an interesting inversion in the enantioselectivity of reductions performed with models bearing the same chiral auxiliary which depended on the function of the amino alcohol which is linked to the dihydropyridine.[3] This behaviour is essentially a consequence of the fundamental role played by the ternary complex as can be seen in Figure 1. From previously reported work,[1] it can be assumed that the phenyl and 1,4-dihydropyridine rings are facing each other and that the carbonyl groups of the ketone and the amide are also facing each other *via* complexation of the magnesium ion. This rigidity is aided by additional complexation of the oxygen atom of the alcohol, possibly reinforced by the ability to form a hydrogen bond.

However with simple pyridine ring models the reduction of substrate competes with important secondary reactions caused by the presence of traces of water which affect the 5,6 double-bond of the 1,4-dihydropyridine structure.[4] The presence of a hydrophilic substituent on the model reinforces the pernicious role of water which is very difficult to eliminate totally. Thus, with the simple pyridine model, the chemical yield was only 60%.

Previously, we synthesized annelated NADH models where a thiophenic ring protects the 5,6 double-bond.[5] These models are much more useful for synthetic purposes since the experimental conditions are milder and yields are higher. The 5,7-dihydrothieno[2,3-*b*] structure was therefore used to study the following factors which can enhance enantiomeric excess in the reduction of methyl benzoylformate by models bearing an amino alcohol as a chiral auxiliary: influence of steric hindrance caused by variation of the amino alcohol, influence of physical parameters, role of the alcohol hydrogen atom and magnesium ion concentration; modification of the interaction between the dihydro-thienopyridine structure and the substituent of the chiral auxiliary with a view to enhancing the rigidity of the ternary complex.

(1) *Influence of steric hindrance caused by variation of the amino alcohol.* Four amino alcohols were used: (*S*)-2-amino-butan-1-ol (obtained from commercial sources), (*R*)-phenylglycinol, (*S*)-valinol, and (*S*)-phenylalaninol (obtained after reduction of the corresponding amino acids with $AlLiH_4$).[6] The compounds were obtained by the route outlined in Scheme 1.



Scheme 1. *Reagents:* i, R*CH(NH_2)CH_2OH; ii, MeI; iii, $Na_2S_2O_4$

The condensation between thienol [2,3-*b*] pyridinecarbonyl chloride and amino alcohols must be performed at low temperature (to avoid the double condensation of the amine and alcohol functions). The dihydropyridine derivatives were

Table 1. Reduction of methyl benzoylformate with various models

Model	Yield (%)	E.e.	Configuration of major enantiomer
(**1**)	60	50	*R*
(**4a**)	100	42	*R*
(**4b**)	100	34	*R*
(**4c**)	100	46	*S*
(**4d**)	100	53	*R*

Table 2. Influence of temperature

Temp (°C)	Reaction time (h)	Yield (%)	E.e.
65	24	100	53
20	72	100	58
0	96	68	60

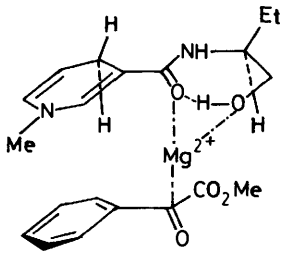


Figure 1.

obtained by quaternization and then subjected to regioselective reduction with sodium dithionite. I.r. and ^{1}H n.m.r. spectral data were consistent with the structures proposed.

The reduction of methyl benzoylformate was performed with 1 equiv. of each reagent (model, magnesium perchlorate, substrate, in acetonitrile as solvent at 65 °C for 24 h). The results are summarized in Table 1.

Since the e.e.'s with (**1**) and (**4a**) were similar and the chiral auxiliary is the same, it is clear that the annelated thiophene ring does not disturb the efficiency of the enantioselectivity of the hydrogen transfer. Moreover, the chemical yields were quantitative with (**4a**). This confirms the superiority of annelated models in synthesis.

An *R*-amino alcohol gives preferentially the *S*-mandelate. The stereochemical course of the reduction can be easily rationalized by the geometry of the ternary complex as already discussed. The substituent of the chiral auxiliary blocks selectively one of the faces of the model and hydrogen transfer occurs at the other face. The benzyl group ensures maximum steric hindrance, so it was used exclusively in the following experiments.

(2) *Influence of temperature, solvent and* Mg^{2+} *concentration.* The steric course of the asymmetric reduction can be explained by the difference of the free activation energy in the transfer of the *pro R* or the *pro S* hydrogen. This energy can be modified by the temperature, by the polarity of the solvent, and by the concentration of magnesium ions. Several experiments were performed with (**4d**) and the results are summarised in Tables 2, 3, and 4.

Several important features were noted. The e.e. is greatest at room temperature but the reaction time is longer. The following experiments were carried out at 20 °C. With 20% of a non polar solvent (cyclohexane), the interactions between the different partners are not modified (use of more cyclohexane was precluded by the insolubilities of the magnesium perchlorate and the model).

Table 3. Influence of solvent (at 20 °C)

Solvent	Yield (%)	E.e.
MeCN	100	58
MeCN:*cyclo*-C_6H_{12} = 4:1	100	58

Table 4. Influence of $Mg(ClO_4)_2$ concentration

Mg^{2+}:model	Yield (%)	E.e.
0.5	100	43
1	100	58
2	100	60

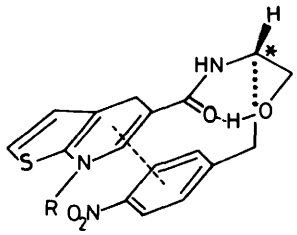


Figure 2.

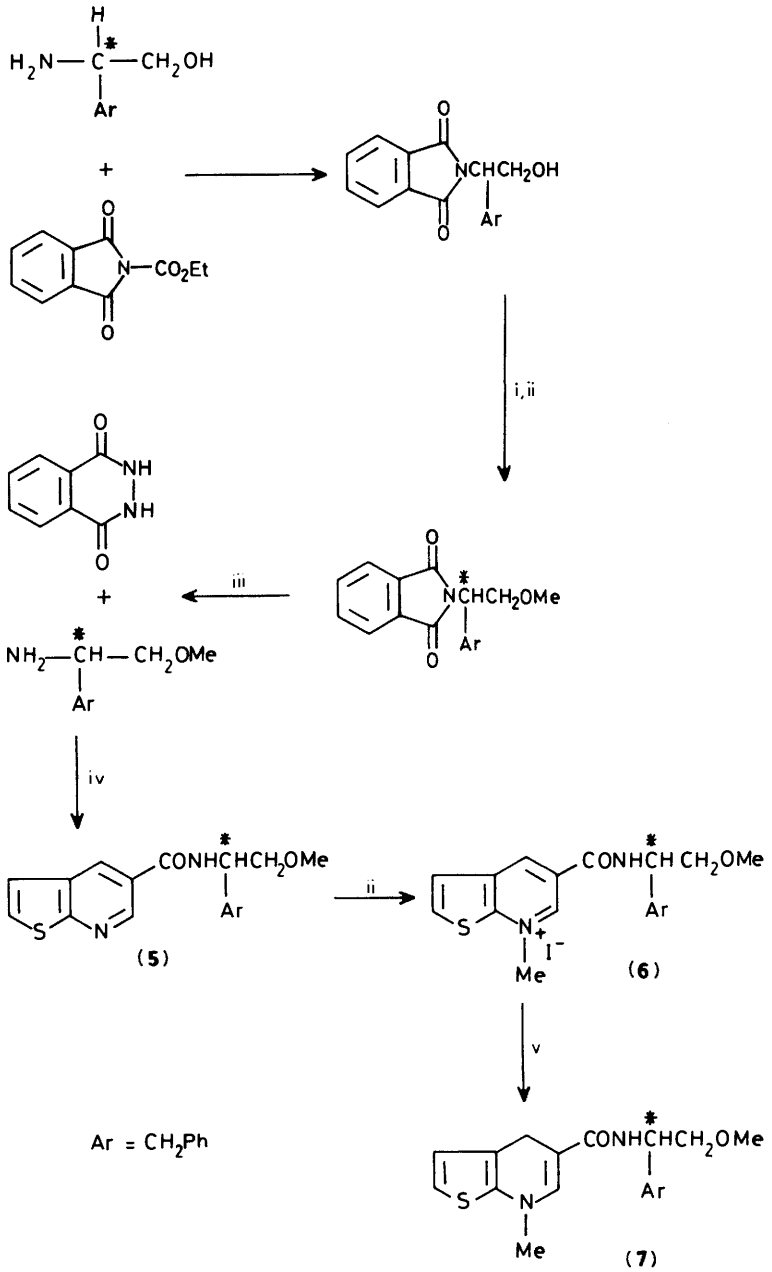
The influence of the concentration of magnesium ions is more difficult to explain although similar observations were made with other models. Although the structure of the ternary complex may be dependent on the amount of magnesium ions, the best e.e. is obtained with 1 equiv. of Mg^{2+} (no significant change with 2 equiv.).

(3) *Rigidity of the ternary complex.* The rigidity of the complex is certainly due, in part, to the occurrence of a hydrogen bond between the hydroxy hydrogen and the carbonyl function (see Figure 1). In order to examine this effect, we synthesized the *O*-methylated derivative (**7**) by the following scheme (Scheme 2).

The amino ether precursor was obtained by protection of the amine function of phenylalaninol by *N*-ethoxycarbonylphthalimide,[7] methylation of the alcoholate with MeI in the presence of 18-crown-6-ether, and subsequent deprotection with hydrazine. Access to the dihydropyridine structure was obtained in the usual way.

With this compound the reduction of methyl benzoylformate gave a 41% e.e. in methyl mandelate, in contrast to 58% with model (**4d**). The decreased e.e. in the former experiment indicates that the most important factor in the geometry of the ternary complex is the complexation of the magnesium ion with the carbonyl group and with the alcohol or ether oxygen. With model (**4d**) the occurrence of a hydrogen bond reinforces the rigidity of the complex only to a minor extent.

A more important factor could be involved in the geometry of the complex. As can be seen in Figure 2, interactions (charge-transfer complex), can be established between the π-electron excessive system of the model and the π-electron system of the phenyl ring of phenylalaninol. If this charge-transfer interaction was reinforced, the geometry of the ternary complex could become more rigid and, as a consequence, the enantioselectivity of the hydrogen transfer would be enhanced. In order to realize this situation an electron withdrawing substituent was introduced on the phenyl ring of the amino alcohol. The synthesis of the nitrophenyl model (**10**) is outlined in Scheme 3.



Scheme 2. *Reagents:* i, KH/18-crown ether; ii, MeI; iii, NH_2NH_2; iv, thieno[2,3-*b*]pyridine-5-carbonyl chloride; v, $Na_2S_2O_4$

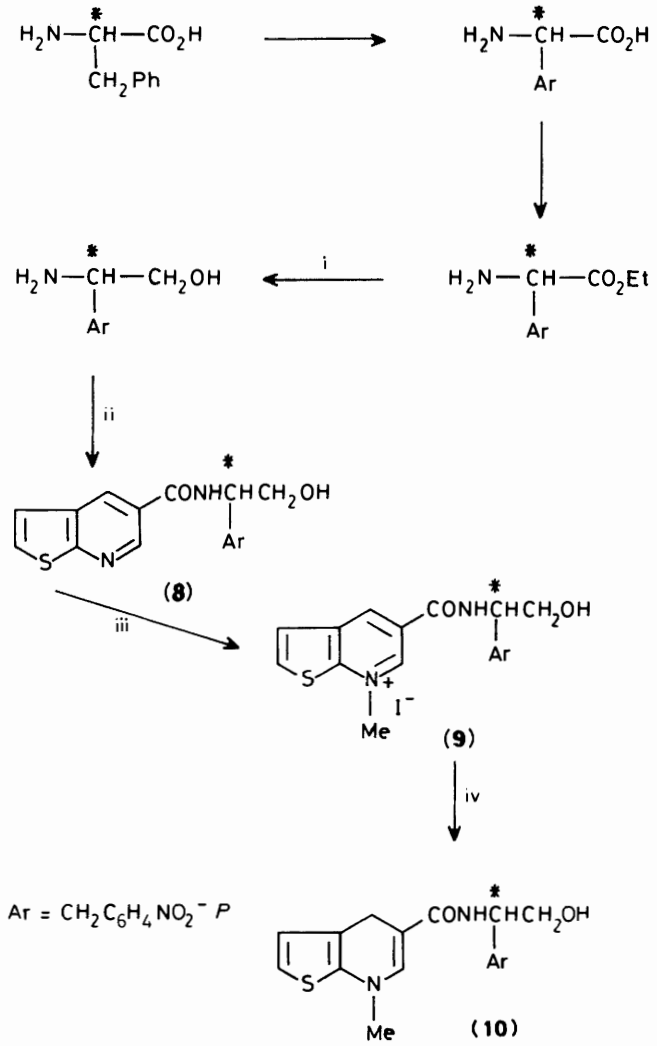
p-Nitrophenylalaninol was obtained by careful nitration of (*S*)-phenylalanine,[8] followed by esterification and reduction of the ester function (a stoicheiometric amount of $AlLiH_4$ must be used to avoid simultaneous reduction of the nitro group). The crude enantiomerically pure *p*-nitrophenylalaninol was used to obtain compounds (**8**) and (**9**). Sodium dithionite could not be used to reduce the pyridinium salt because a partial simultaneous reduction of the nitro group occurred. The regioselective reduction of the pyridinium salt was therefore performed with BNAH (1-benzyl-1,4-dihydronicotinamide).[9] This reaction was easier than similar reductions performed on the thieno[2,3]pyridinium structure without substitution on the amide.[5]

With this model the reduction of methyl benzoylformate gave a 75% e.e. This result supports the hypothesis concerning the establishment of a π complex interaction in the ternary complex. Moreover, this high e.e. was obtained with an easily handled NADH model which gave a chemical yield of 100% under classical laboratory conditions.

Experimental

M.p.s were determined on a Kofler block I.r. spectra were obtained on a Beckman IR 4250 spectrophotometer. N.m.r. spectra were recorded on a Varian E.M. 360 L apparatus. Microanalyses were obtained from a Carlo Erba 1106 apparatus. Optical rotations were determined on a Perkin-Elmer 241 micropolarimeter or by h.p.l.c. by using a Waters apparatus and a L.K.B. enantiopac as chiral column.

Chiral 2-Amino Alcohols.—(*a*) (*S*)-(+)-2-Aminobutan-1-ol (R = Et) was purchased from the 'Société Chimique de la



Scheme 3. *Reagents:* i, $LiAlH_4$, ii, thieno[2,3-*b*]pyridine-5-carbonyl chloride; iii, MeI; iv, BNAH

Grande Paroisse', $[\alpha]_D^{22}$ +9.8° (neat) [lit.,[10] +12.5 (*c* 2 in EtOH)]. Other amino alcohols were obtained after reduction of the corresponding amino acids with $LiAlH_4$.[6]

(*b*) (*S*)-(+)-Valinol (R = Pr^i), $[\alpha]_D^{22}$ +14.6° (*c* 8 in EtOH) [lit.,[10] +16° (neat)].

(*c*) (*R*)-(−)-Phenylglycinol (R = Ph), $[\alpha]_D^{22}$ −26.0 (*c* 6.6 in MeOH) [lit.,[10] −25° (*c* 6.0 in MeOH)].

(*d*) (*S*)-(−)-Phenylalaninol (R = $PhCH_2$), $[\alpha]_D^{22}$ −21.5° (*c* 1.15 in EtOH) [lit.,[10] −23° (*c* 5.0 in EtOH)].

(*e*) (*S*)-(−)-2-Amino-3-(4-nitrophenyl)propan-1-ol. (*S*)-Phenylalanine (10.0 g) dissolved in concentrated sulphuric acid (22 ml) was treated with fuming nitric acid (3 ml; *d* 1.52 g cm^{-3}) at <15 °C. The solution was stirred for 15 min at room temperature and then poured on ice–water (500 ml). The solution was neutralized with concentrated ammonia and water was evaporated until the appearance of a precipitate. After being left overnight in a refrigerator, the product was filtered off, washed with water, and dried, (10.4 g, 82%); $\nu_{max.}$ 1 700, 1 535, and 1 350 cm^{-1}; δ_H ([$^2H_6$]DMSO + CF_3CO_2H) 8.15 (d, 2 H), 7.2 (d, 2 H), 4.25 (m, 1 H), and 3.25 (d, 2 H). The crude acid (10.5 g) was refuxed in ethanol through which HCl was bubbled. After 3 h, the cold mixture was filtered. The precipitate was taken up in water (100 ml) and ether (130 ml). The pH was adjusted to 6.5. The phases were separated and the aqueous phase was extracted with ether (3 × 50 ml). The organic fractions were dried and evaporated and the residual oil distilled (b.p. 160 °C/2 mmHg) to give ethyl-(*S*)-2-amino-3-(4-nitrophenyl)propionate (9.5 g, 80%); $\nu_{max.}$ 1 735, 1 520, and 1 350 cm^{-1}; $\delta_H(CDCl_3)$ 8.15 (d, 2 H), 4.0 (d, 2 H), 4.2 (q, 2 H), 3.9—3.6 (m, 1 H), 3.4—2.7 (m, 2 H), 1.7 (s, 2 H), and 1.25 (t, 3 H). To a solution of the above ester (7.5 g) in anhydrous ether (800 ml) was slowly added a suspension of $LiAlH_4$ (1.19 g) in anhydrous ether (200 ml). The mixture was stirred for 1 h at room temperature and then hydrolysed with water (10 ml). After extraction with ether, the aluminium salts were separated by decantation. The ethereal phases were dried and evaporated under reduced pressure and the resulting (S)-(−)-2-*amino*-3-(4-*nitrophenyl*)*propan*-1-*ol* (5.5 g, 69%) was stored in the dark; m.p. 144—145 °C; $[\alpha]_D^{22}$ −26.4° (*c* 2.2 in MeOH); $\nu_{max.}$ 3 400, 1 520, and 1 345 cm^{-1}; δ_H ([$^2H_6$]DMSO) 8.1 (d, 2 H), 7.5 (d, 2 H) and 3.4—2.3 (m, 8 H) (Found: C, 55.6; H, 5.7; N, 14.2. $C_9H_{12}N_2O_3$ requires C, 55.10; H, 6.12, N; 14.28).

(*f*) (*S*)-(−)-Methoxy-3-phenylpropane-2-amine. Ethoxycarbonylphthalimide was obtained from phthalimide and ethyl chloroformate by the procedure described in the literature.[7] This compound was treated with *S*-phenylalaninol leading to (*S*)-2-phthalamido-3-phenylpropan-1-ol. To a suspension of NaH (2.1 g) in anhydrous THF (115 ml) and 18-crown-6 ether (0.25 g), was added the above product (13.0 g). After being stirred for 1 h at room temperature, the mixture was cooled to 0 °C. IMe (9.6 g) was added and the mixture was then stirred at room temperature for 2 days. The remaining hydride was destroyed by addition of methanol (10 ml). Volatile compounds were eliminated and the residue was taken up in water (100 ml) and then extracted with ether. After drying and concentration, the residue was purified by chromatography on silica [ether–hexane (1:1) + 3% MeOH] to give (*S*)-(−)-2-phthalimido-1-methoxy-3-phenylpropane (7.5 g, 55%); m.p. 91—92 °C; $[\alpha]_D^{22}$ = −139° (*c* 0.28 in MeOH) $\nu_{max.}$ 1 710, 1 750, and 1 770 cm^{-1}; $\delta_H(CDCl_3)$: 7.85—7.45 (m, 4 H), 7.20 (s, 5 H), 5, 10—4.55 (m, 1 H), 4.25—3.50 (m, 2 H), 3.4—3.0 (m, 2 H), and 3.35 (s, 3 H) (Found C, 73.3; H, 5.9; N, 4.8. $C_{18}H_{17}NO_3$ requires C, 73.22; H, 5.76; N, 4.74).

To a suspension of the above compound (2.15 g) in ethanol (15 ml), was added anhydrous hydrazine (1 ml). The mixture was stirred for 3 h at room temperature and then acidified with HCl (10%). Ethanol was evaporated and the precipitate filtered off. The solution was made basic by addition of dilute KOH, the aqueous phase extracted with ether and after evaporation of the solvent the residue was distilled yielding (S)-(−)-2-*amino*-1-*methoxy*-3-*phenylpropane* (1.1 g, 91%); b.p. 70 °C/5 mmHg; $[\alpha]_D^{22}$ −10.3 (*c* 1.80 in $CHCl_3$); $\delta_H(CDCl_3)$ 7.20 (s, 5 H), 3.55—3.0 (m, 3 H), 3.30 (s, 3 H), 3.0—2.2 (m, 2 H), and 1.30 (s, 2 H) (Found C, 72.5; H, 9.3; N, 8.2. $C_{10}H_{15}NO$ requires C, 72.72; H, 9.09; N, 8.48).

Condensation of Amino Alcohols: General Procedure.—The chloride of thieno[2,3-*b*]pyridine-5-carboxylic acid was obtained after refluxing the acid (3.6 g) in thionyl chloride (40 ml) during 12 h. After cooling, the volatile products were eliminated and the residue was dissolved in CH_2Cl_2 (40 ml) and retained.

A mixture of CH_2Cl_2 (40 ml), anhydrous Et_3N (2.04 g), and the amino alcohol (20.2 mmol) was cooled to −20 °C under an argon atmosphere and the above solution of the acid chloride was then introduced with a syringe at a temperature between −20 and −10 °C. After 1 h at −20 °C, the mixture was stirred for 24 h at room temperature. The precipitate was filtered off and the organic phase washed with water (3 × 40 ml) and evaporated. The solid was collected then purified. The following were prepared in this way.

(S)-(−)-2-(*Thieno*[2,3-b]*pyridine*-5-*carbonylamino*)*butan*-1-*ol* (**2a**) (2.1 g, 42%), m.p. 125—126 °C (H_2O–EtOH, 8:2); $[\alpha]_D^{22}$

−31.1° (*c* 2.5 in EtOH); $\nu_{max.}$ 3 260 and 1 660 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.0 (d, 1 H), 8.7 (d, 1 H), 8.3 (1 H, NH), 7.9 (d, 1 H), 7.5 (d, 1 H), 4.7 (m, 1 H), 4.25—3.65 (m, 1 H), 3.5 (d, 2 H), 1.85—1.3 (m, 2 H), and 0.9 (t, 3 H) (Found C, 57.4; H, 5.5; N, 10.8. $C_{12}H_{14}N_2O_2S$ requires C, 57.60; H, 5.60; N, 11.20).

(R)-(+)-N-(*Thieno*[2,3-b]*pyridine-5-carbonyl*)*phenylglycinol* (**2b**) (4.0 g, 67%), m.p. 146—147 °C (toluene); $[\alpha]_D^{22}$ +68.3 (*c*. 2.4 in EtOH); $\nu_{max.}$ 3 360 and 1 635 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.0 (d, 1 H), 8.95 (m, 1 H), 8.7 (d, 1 H), 7.9 (d, 1 H), 7.5 (d, 1 H), 7.45—7.05 (m, 5 H), 5.35—4.85 (m, 2 H), and 3.85—3.5 (m, 2 H) (Found C, 64.0; H, 4.7; N, 9.3. $C_{16}H_{14}N_2O_2S$ requires C, 64.42; H, 4.70; N, 9.39).

(S)-(+)-N-(*Thieno*[2,3-b]*pyridine-5-carbonyl*)*valinol* (**2c**) (2.2 g, 42%), m.p. 162 °C (H_2O–EtOH, 7:3); $[\alpha]_D^{22}$ −27° (*c* 2.5 in EtOH); $\nu_{max.}$ 3 290 and 1 635 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.0 (d, 1 H), 8.7 (d, 1 H), 8.25 (m, 1 H), 7.95 (d, 1 H), 7.5 (d, 1 H), 4.65 (m, 1 H), 4.1—4.35 (m, 3 H), 2.15—1.45 (m, 1 H), and 0.95 (d, 6 H) (Found C, 58.9; H, 6.1; N, 10.3. $C_{13}H_{16}N_2O_2S$ requires C, 59.09; H, 6.06; N, 10.60).

(S)-(−)-N-(*Thieno*[2,3-b]*pyridine-5-carbonyl*)*phenylalaninol* (**2d**) (4.6 g, 73%), m.p. 178—179 °C (purified by chromatography on silica with 5% MeOH–EtOAc as eluant); $[\alpha]_D^{22}$ −84.9° (*c* 1.45 in EtOH); $\nu_{max.}$ 3 290 and 1 640 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 8.9 (d, 1 H), 8.6 (d, 1 H), 8.45 (m, 1 H), 7.9 (d, 1 H), 7.45 (d, 1 H), 7.2 (s, 5 H), 4.5—3.85 (m, 1 H), 3.55 (d, 2 H), and 2.9 (m, 2 H) (Found C, 65.0; H, 5.0; N, 8.8. $C_{17}H_{16}N_2O_2S$ requires C, 65.38; H, 5.13; N, 8.97).

(S)-(−)-1-*Methoxy*-3-*phenyl*-N-(*thieno*[2,3-b]*pyridine-5-carbonyl*)*propane-2-amine* (**5**) (1.4 g, 30%), m.p. 144—145 °C (purified by chromatography on silica with CH_3CO_2Et–hexane, 4:6 as eluant); $[\alpha]_D^{22}$ −56° (*c* 1.4 in EtOH); $\nu_{max.}$ 3 360 and 1 640 cm^{-1}; $\delta_H[^2H_6]DMSO)$ 8.85 (d, 1 H), 8.40 (d, 1 H), 7.75 (d, 1 H), 7.25 (m, 6 H), 6.65 (m, 1 H), 4.75—4.25 (m, 1 H), 3.55—3.30 (s + d, 5 H), and 3.0 (d, 2 H). (Found: C, 66.8; H, 5.5; N, 8.55. $C_{18}H_{19}N_2O_2S$ requires C, 66.05; H, 5.81; N, 8.56).

(S)-3-(4-*Nitrophenyl*)-2-(*thieno*[2,3-b]*pyridine-5-carbonylamino*)*propan-1-ol* (**8**) (4.0 g, 55%), m.p. 186—187 °C (purified by chromatography on silica with 5% MeOH–EtOAc as eluant); $\nu_{max.}$ 3 240, 1 635, 1 520, and 1 350 cm^{-1}; δ_H ($[^2H_6]DMSO$) 8.8 (d, 1 H), 8.5 (d, 1 H), 8.45 (d, 1 H), 8.05 (d, 2 H), 7.9 (d, 1 H), 7.5 (d, 2 H), 7.45 (d, 1 H), 4.9 (m, 1 H), 4.6—4.0 (m, 1 H), 3.65—3.25 (m, 2 H), and 3.15—2.8 (m, 2 H) (Found C, 57.15; H, 4.1; N, 11.5. $C_{17}H_{15}N_3O_4S$ requires C, 57.14; H, 4.20; N, 11.76).

Quaternization: General Procedure.—The above amide (1.0 g) was refluxed for 8 h in acetonitrile (20 ml) and MeI (2 ml). After elimination of volatile compounds, the following pyridinium salts were obtained quantitatively.

(S)-5-(1-*Ethylhydroxymethylcarbamoyl*)-7-*methylthieno*[2,3-b]*pyridinium iodide* (**3a**). $\nu_{max.}$ 3 280 and 1 660 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.6 (s, 1 H), 9.4 (s, 1 H), 8.6 (d, 1 H), 8.35 (d, 1 H), 7.9 (d, 1 H), 4.85—4.45 [m + s, (4.55), 4 H], 3.6—3.25 (m, 2 H), 1.85—1.3 (m, 2 H), and 0.85 (t, 3 H) (Found C, 39.9; H, 4.4; N, 7.2. $C_{13}H_{17}IN_2O_2S$ requires C, 39.79; H, 4.34; N, 7.14).

(R)-5-(1-*Hydroxymethylphenylcarbamoyl*)-7-*methylthieno*-[2,3-b]*pyridinium iodide* (**3b**). $\nu_{max.}$ 3 350 and 1 670 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.6 (s, 1 H), 9.45 (s, 1 H), 9.3 (d, 1 H), 8.3 (d, 1 H), 7.9 (d, 1 H), 5.25—4.8 (m, 5 H), 4.55 (s, 3 H), and 3.85—3.55 (m, 2 H) (Found C, 46.0; H, 3.8; N, 6.2. $C_{17}H_{17}IN_2O_2S$ requires C, 46.36; H, 3.86; N, 6.36).

(S)-5-(1-*Hydroxymethylisopropylcarbamoyl*)-7-*methylthieno*-[2,3-b]*pyridinium iodide* (**3c**) $\nu_{max.}$ 1 665 cm^{-1}; $\delta_H([^2H_6]DMSO$ 9.6 (m, 1 H), 9.4 (m, 1 H), 8.55 (m, 1 H), 8.35 (d, 1 H), 7.9 (d, 1 H), 4.6 (s, 3 H), 4.05—3.3 (m, 3 H), 2.15—1.45 (m, 1 H), and 0.9 (d, 6 H) (Found C, 41.2; H, 4.8; N, 7.0. $C_{14}H_{19}IN_2O_2S$ requires C, 41.37; H, 4.68; N, 6.70).

(S)-5-(1-*Benzylhydroxymethylcarbamoyl*)-7-*methylthieno*-[2,3-b]*pyridinium iodide* (**3d**). $\nu_{max.}$ 1 670 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.55 (s, 1 H), 9.35 (s, 1 H), 8.8 (m, 1 H), 8.35 (d, 1 H), 7.9 (d, 1 H), 7.2 (s, 5 H), 4.55 (s, 3 H), 4.55—4.3 (m, 1 H), 3.5 (m, 2 H), and 2.85 (m, 2 H). (Found C, 47.35; H, 4.2; N, 6.35. $C_{18}H_{19}IN_2O_2S$ requires C, 47.57; H, 4.18; N, 6.17).

(S)-5-(1-*Benzylmethoxymethylcarbamoyl*)-7-*methylthieno*-[2,3-b]*pyridinium iodide* (**6**). $\nu_{max.}$ 1 665 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.55 (s, 1 H), 9.35 (s, 1 H), 8.95 (m, 1 H), 8.3 (d, 1 H), 7.9 (d, 1 H), 7.3 (s, 5 H), 4.6 (s, 3 H), 4.6—4.15 (m, 1 H), 3.45 (d, 2 H), 3.3 (s, 3 H), and 2.85 (d, 2 H). (Found C, 48.3, H, 4.6, N, 5.9. $C_{19}H_{22}IN_2O_2S$ requires C, 48.61; H, 4.69; N, 5.97).

(S)-5-[1-*Hydroxymethyl*(p-*nitrobenzyl*)*carbamoyl*]-7-*methylthieno*[2,3-b]*pyridinium iodide* (**9**). $\nu_{max.}$ 3 400, 1 665, 1 515, and 1 350 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 9.45 (s, 1 H), 9.35 (s, 1 H), 8.85 (d, 1 H), 8.3 (d, 1 H), 8.05 (d, 2 H), 7.9 (d, 1 H), 7.5 (d, 2 H), 4.55 (s, 3 H), 4.5—4.0 (m, 1 H), 3.5 (d, 2 H), 3.2—2.8 (m, 2 H) (Found C, 43.5; H, 3.5; N, 8.6. $C_{18}H_{18}IN_3O_4S$ requires C, 43.28; H, 3.61; N, 8.42).

Reduction of Thienopyridinium Salts (**3a**) *and* (**3b**).—Compound (**3a**) (1.0 g) in deoxygenated water (40 ml) was treated in the dark with $Na_2CO_3 \cdot 10H_2O$ (2.0 g) and then $Na_2S_2O_4$ (2.0 g). After the mixture had been stirred for 15 min at room temperature, the oil was extracted with CH_2Cl_2 (3 × 60 ml). The organic phases were washed with water (2 × 25 ml), dried, and evaporated to give (*S*)-2-(*N*-methyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbonyl)aminobutan-1-ol, (**4a**) (0.55 g, 78%). (The crude product was not further purified because of its instability.) $\nu_{max.}$ 3 340 and 1 655 cm^{-1}; $\delta_H(CDCl_3)$, 7.05 (s, 1 H), 6.6 (s, 2 H), 5.6 (d, 1 H), 4.45—3.4 (m, 6 H), 3.05 (s, 3 H), 1.45 (q, 2 H), and 0.85 (t, 3 H).

The pyridinium salt (**3b**) (1.5 g) was added to a solution of $Na_2CO_3 \cdot 10H_2O$ (3.0 g) and $Na_2S_2O_4$ (3.0 g) in deoxygenated water (100 ml) in the dark. After cooling the precipitate was filtered off and dried to give (*S*)-*N*-(*N*-methyl-4,7-dihydrothieno[2,3-*b*]pyridine-5-carbonyl)phenylglycinol (**4b**) (0.75 g, 70%), which was further purified by crystallization from H_2O–EtOH (4:6), m.p. 195 °C (decomp.); $\nu_{max.}$ 3 330 and 1 655 cm^{-1}; $\delta_H(CDCl_3)$ 7.35 (s, 5 H), 7.1 (s, 1 H), 6.65 (s, 2 H), 6.1 (m, 1 H), 5.1 (t, 1 H), 3.9 (d, 2 H), 3.75 (s, 2 H), and 3.2 (s, 3 H).

Reduction of Pyridinium Salts (**3c**, (**3d**), *and* (**6**).—The pyridinium salt (1.0 g) in methanol (10 ml) was poured into a solution of $Na_2CO_3 \cdot 10H_2O$ (2.0 g) and $Na_2S_2O_4$ (2.0 g) in deoxygenated water (40 ml). After 20 min the mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the organic phase was dried and evaporated. The crude products were not further purified. (S)-N-(N-*Methyl*-4,7-*dihydrothieno*[2,3-b]*pyridine-5-carbonyl*)*valinol* (**4c**) (0.54 g, 78%), $\nu_{max.}$ 3 360 and 1 650 cm^{-1}; $\delta_H(CDCl_3)$ 7.1 (s, 1 H), 6.65 (s, 2 H), 5.65 (m, 1 H), 4.55—3.5 (m, 6 H), 3.15 (s, 3 H), 2.3—1.55 (m, 1 H), and 0.95 (d, 6 H).

(S)-N-(N-*Methyl*-4,7-*dihydrothieno*[2,3-b]*pyridine-5-carbonyl*)*phenylalaninol* (**4d**) (0.70 g, 94%), $\nu_{max.}$ 3 380 and 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 7.25 (s, 5 H), 7.05 (s, 1 H), 6.6 (s, 2 H), 5.65 (m, 1 H), 4.55—3.45 (m, 6 H), 3.15 (s, 3 H), and 2.9 (d, 2 H).

(S)-1-*Methoxy*-2-(N-*methyl*-4,7-*dihydrothieno*[2,3-b]*pyridine-5-carbonylamino*)-3-*phenylpropane* (**7**) (0.70 g, 97%), $\delta_H(CDCl_3)$ 7.3 (s, 5 H), 7.1 (s, 1 H), 6.65 (s, 2 H), 5.7 (m, 1 H), 4.7—4.1 (m, 1 H), 3.65 (s, 2 H), 3.35 (s + d, 5 H), 3.15 (s, 3 H), and 2.9 (d, 2 H).

Reduction of the Pyridinium Salt (**9**).—A mixture of the pyridinium salt (**9**) (1.0 g) and BNAH (0.54 g) in methanol was stirred for 4 h at room temperature. Methanol was evaporated and the residue taken in a mixture of water (80 ml) and CH_2Cl_2 (150 ml). The organic phase was dried and evaporated to give (S)-2-(N-*methyl*-4,7-*dihydrothieno*[2,3-b]*pyridine-2-carbonylamino*-3-(4-*nitrophenyl*)*propan-1-ol* (**10**) (0.54 g, 72%), $\nu_{max.}$ 1 650, 1 550, 1 515, and 1 340 cm^{-1}; $\delta_H([^2H_6]DMSO)$ 8.05 (d, 2 H), 7.5 (d, 2 H), 6.9 (s, 1 H), 6.8 (d, 1 H), 6.65 (d, 1 H), 4.45—3.75 (m, 1 H), and 3.75—2.7 (m + s, 10 H).

Reduction of Methyl Benzoylformate with Models bearing a Chiral Auxiliary.—The model (0.33 mmol), Mg $(ClO_4)_2$ (0.33 mmol, 74.3 mg), and methyl benzoylformate (0.33 mmol, 54.7 mg) were dissolved in acetonitrile (5 ml). The flask was stoppered with a septum and flushed with argon. The mixture was stirred for 72 h in the dark and then poured into a mixture of water (10 ml) and ether (90 ml). The ethereal phase was dried and evaporated. The residue was weighed and analyzed by ^1H n.m.r. spectroscopy. Methyl mandelate was purified by t.l.c. (silica, elution with ether–hexane, 1:2). The enantiomeric excess was determined by polarimetry or by h.p.l.c.

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