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Chiral biomimetic NADH models in the benzo[*b*]-1,6-naphthyridine series. A novel class of stable, reactive and highly enantioselective NADH mimics

Jean-Luc Vasse, Vincent Levacher,* Jean Bourguignon and Georges Dupas

Laboratoire de Chimie Organique Fine et Hétérocyclique associé au CNRS, IRCOF-INSA. B.P. 08 F-76131 Mont Saint Aignan Cédex, France

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Abstract—The preparation of a new class of tricyclic models **1** based on a Friedländer reaction between chiral piperidine-2,4-diones **2** and azomethine **3** is reported. Alkylation of the lactam allowed to install various pendant arms on the chiral cyclic inducer. The so-obtained mimics **1a**,**d**,**f**,**g**,**h**,**k** were involved in the reduction of methyl benzoylformate to furnish methyl mandelate in 4–87% ee (*R*). The presence of a coordinating pendant arm proved to be essential to reach optimum results in terms of enantioinduction. Asymmetric reduction of 2-benzoylpyridine with mimics **1d**,**f**,**g** produced α-phenyl-2-pyridinemethanol in 30–84% ee (*R*).

1. Introduction

Considerable effort has been devoted to elucidating the stereospecificity of NADH coenzyme in biological reduction processes. In the past two decades, the design and synthesis of biomimetic NADH models has largely contributed to define the role played by the nicotinamide moiety of the coenzyme in the stereospecificity of biological redox processes.[1] Although some of these models exhibit high performance in terms of enantioselectivity,[2] most of them did not find application in asymmetric reduction due to their poor stability. Indeed, simple NADH mimics undergo numerous parasites reactions which limit seriously the perspective to regenerate these reagents. To improve the stability of these reagents we developed, with success, the synthesis of annulated NADH models (**I**).[3] The second important aim from the outset of this work was to develop highly stereoselective NADH models. To this end, various models (**II**) bearing aminoalcohols as chiral auxiliaries were prepared and displayed high stereoselectivities during the reduction of methyl benzoylformate.[4] The chiral cyclic inducer of models (**II**) was designed to examine the role of a *syn* orientation of the carbonyl moiety on the stereochemical outcome of biomimetic reductions. Although the good performances of these models is thought to arise partly from the *syn* orientation of the carbonyl group, the presence of the complexing alcohol function at the exocyclic nitrogen substituent has been shown to be essential to achieve high stereoselectivities.[5] Biomimetic reductions are usually performed in the presence of magnesium perchlorate. This metal salt is involved in the formation of a ternary complex mimic/Mg^{2+}/substrate activating both partners of the reduction. A detailed NMR study of these models (**II**) in the presence of magnesium perchlorate highlighted the formation of a chelate between the alcohol chain and the C═O lactam.[5c] In our continuous effort to develop this biomimetic chemistry, we have linked the stability of annulated models (**I**) and the good stereoselectivity of model (**II**) to report herein the synthesis of a new chiral NADH quinoline-type models **1** (Fig. 1). Some aspects of this work have been briefly reported recently.[6]

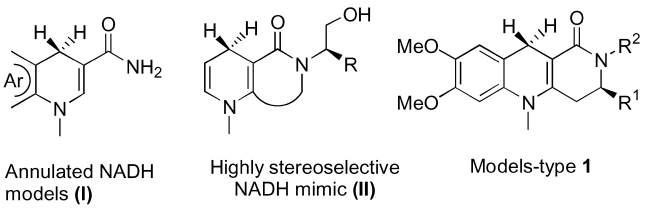

Figure 1. New chiral annulated NADH mimics **1**.

2. Results and discussion

2.1. Design of the tricyclic models-type 1

These biomimetic NADH models-type **1** are composed of three modules. Module *A* protects the reagent against electrophilic attacks on the 5,6-enamine double bond, encountered with simple NADH models (**I**). As a result of this protection, the reducing properties of annulated NADH

Keywords: Friedländer reaction; enantioinduction; asymmetric reduction; biomimetic NADH models.

* Corresponding author. Tel.: +33-2-35-52-24-85; fax: +33-2-35-52-29-62; e-mail: vincent.levacher@insa-rouen.fr

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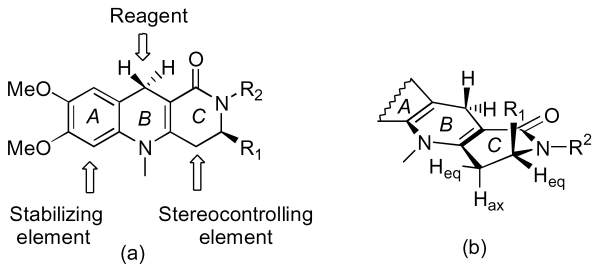


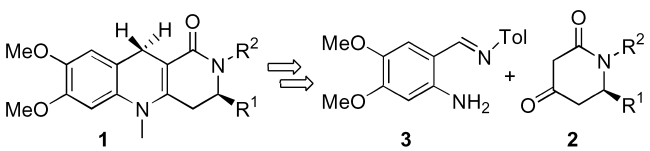
Figure 2. (a) Design of a new tricyclic model **1**. (b) Conformational analysis of the stereocontrolling element (module *C*).

models are significantly altered. To overcome this side effect, the electron donating methoxy groups on module *A* are expected to restore the reactivity of the reagent. The active part of the model (module *B*) is annulated by a second module *C* to ensure the stereocontrol of reduction (Fig. 2(a)). A straightforward conformational analysis prompted us to install the chirality on the cyclic module *C*. As a consequence of strong eclipsing interactions with the neighboring *N*-alkyl substituent R^2, we anticipated that R^1 would adopt a pseudo-axial position (Fig. 2(b)). This hypothesis is supported by molecular modeling[7] and is consistent with conformational analysis of 2-substituted-3,4-dihydroisoquinoline-1-ones previously reported in the literature.[8] We reasoned that, in pseudo-axial position, R^1 would exert a good stereodifferentiation of both diastereotopic faces of the tricyclic model **1**. In addition, the design of this new chiral cyclic inducer *C*, offers the possibility to install various substituents R^2 to sharpen the role of the alcohol function, on the origin of the stereoselectivity with the previously reported NADH models **II**.

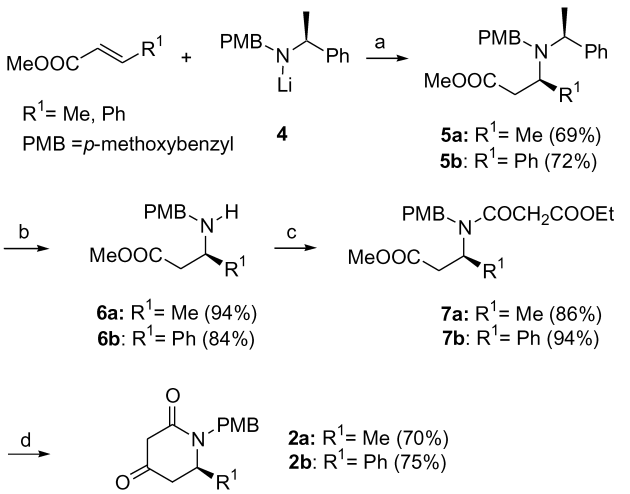
2.2. Synthesis of the tricyclic models-type 1

Our synthetic approach is based on a Friedländer-type reaction between piperidine-2,4-diones **2** and Schiff base **3** of the corresponding *o*-aminobenzaldehyde (Scheme 1).

An examination of the literature relating to the preparation of piperidine-2,4-diones reveals that asymmetric synthesis of this class of compounds bearing a stereogenic center at C-6 has been rarely reported.[9] We undertook to develop a Dieckmann cyclization of compounds **7a**,**b** intermediates, easily accessible via diastereoselective conjugated addition of (*R*)-lithium amide **4** to methyl crotonate or methyl cinnamate (Fig. 3). Following this strategy, β-amino esters **5a**,**b** are obtained in 69 and 72% yields, respectively, in up to 95% de in both cases (Scheme 2). According to literature reports, the absolute configuration of the newly created stereogenic center was assigned as (*S*).[10] Selective reductive cleavage of the chiral auxiliary afforded β-aminoesters **6a**,**b** in 94 and 84% yields which were subsequently condensed with ethyl malonyl chloride to produce β-(acylamino)esters



Scheme 1. Retrosynthesis of the tricyclic models-type **1**: Friedländer approach.

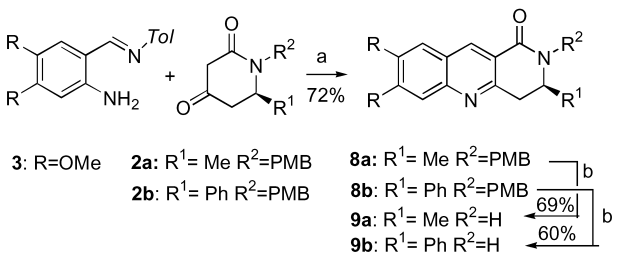


Scheme 2. Synthesis of the piperidine-2,4-diones **2**. *Reagents and conditions*: (a) THF/−78°C; (b) H_2/Pd(OH)$_2$; (c) $ClCOCH_2COOEt/NEt_3/CH_2Cl_2$; (d) NaOMe/THF.

7a,**b** in excellent yields. Dieckmann cyclization furnished the required chiral piperidine-2,4-diones **2a**,**b** in 70 and 75%, respectively.

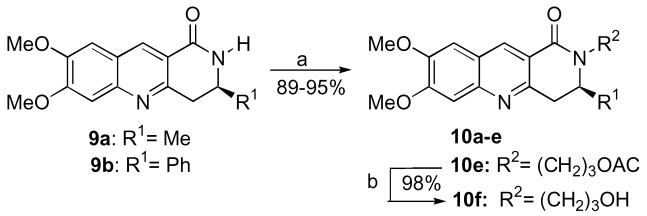
In a first attempt to prepare the desired benzo[*b*]-1,6-naphthyridines **8a** and **8b**, piperidine-2,4-diones **2a** and **2b** were reacted with 3,4-dimethoxy *ortho*-aminobenzaldehyde.[11] Whatever the reaction conditions used, the cyclization products **8a** and **8b** were obtained in modest yield (<20%) along with large amounts of unidentified products. The major limitation of this procedure lies with the ease at which *ortho*-aminobenzaldehydes undergo self-condensation. To circumvent this problem we made use of the Borsche modification[12] employing arylimine **3**[11] instead of 3,4-dimethoxy *ortho*-aminobenzaldehyde. The main advantage of this procedure is to dispose large amounts of stable azomethine **3** and to scale up the preparation of **8a** and **8b** to a multi-gram scale in good yield. Thus, piperidine-2,4-diones **2a** and **2b** reacted with azomethine **3** in the presence of piperidine in refluxing ethanol to give **8a** and **8b** in 68 and 78% yields, respectively. Oxidative cleavage of **8a** and **8b** in the presence of CAN afforded the corresponding benzo[*b*]-1,6-naphthyridines **9a** and **9b** in 69 and 60% yield, respectively (Scheme 3).

Alkylation of lactams **9a** and **9b** allowed to install a wide choice of substituents, offering the opportunity to investigate the influence of the N-substituent on the performance of these models. According to a literature procedure,[13] alkylation of lactams **9a**,**b** is performed in DMSO in the

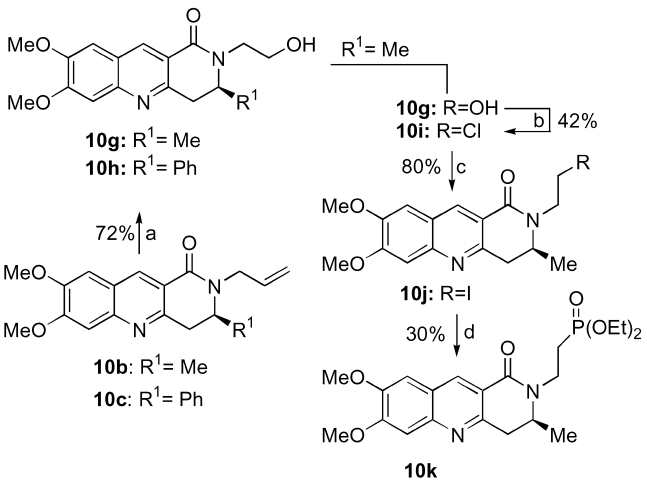


Scheme 3. *Reagents and conditions*: (a) piperidine/EtOH/reflux; (b) CAN/CH_3CN/H_2O.

Table 1. *Reagents and conditions*: (a) RX/KOH/DMSO; (b) NaOH



Entry	Compound	R^2X	Product	Yield (%)
1	**9a**	$PhCH_2Br$	**10a**: R^1=Me	92
2	**9a**	CH_2=$CHCH_2Br$	**10b**: R^1=Me	95
3	**9b**	CH_2=$CHCH_2Br$	**10c**: R^1=Ph	97
4	**9a**	$MeOCH_2CH_2I$	**10d**: R^1=Me	89
5	**9a**	$AcO(CH_2)_3I$	**10e**: R^1=Me	73



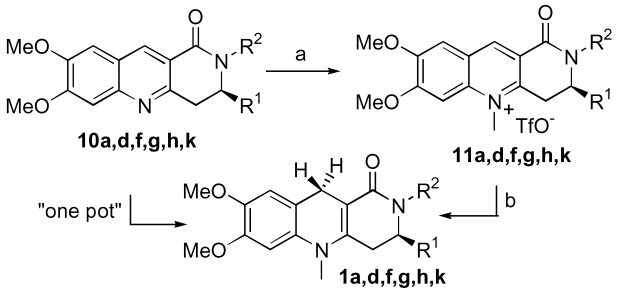
Scheme 4. *Reagents and conditions*: (a) OsO4/THF–H_2O/$NaIO_4$ then $NaBH_4$; (b) TsCl/NEt_3/CH_2Cl_2; (c) NaI/acetone; (d) $NaPO(OEt)_2$/THF.

presence of KOH to give **10a**-**e** in 73–97% yields (Table 1). Treatment of **10b**,**c** with osmium tetroxide, followed by reduction of the intermediate aldehyde with sodium borohydride afforded the corresponding alcohols **10g**,**h**, in 72% yield in both cases (Scheme 4).

The good affinity of the magnesium ion for the phosphonate function prompted us to incorporate a phosphonate chain. To this end, treatment of **10g** with *p*-toluenesulphonyl chloride afforded **10i** in 59% yield which was cleanly converted into the iodo derivative **10j** in 80% yield by treatment with sodium iodide in acetone. Many attempts to introduce a phosphonate chain by means of Arbuzov reaction failed, leading in most cases to the starting material. Alternatively, the phosphonate chain could be introduced by reacting **10j** with diethylphosphite sodium salt affording **10k**, however, with a modest yield of 30% (Scheme 4).[14]

Quaternization of **10a**,**d**,**f**,**g**,**h**,**k** with methyl trifluoromethanesulfonate afforded the corresponding quinolinium salts **11a**,**d**,**f**,**g**,**h**,**k** in nearly quantitative yield. Subsequent regioselective reduction of the former quinolinium salts with sodium dithionite gave the desired models **1a**,**d**,**f**,**g**,**h**,**k** in 81–98% yields. Alternatively, a simplified one pot

Table 2. *Reagents and conditions*: (a) $TfOMe/CH_2Cl_2$; (b) $Na_2S_2O_4/Na_2CO_3$



Entry	Compound	R^2, R^1	Product	Yield[a] (%)
1	**10a**	$PhCH_2$, Me	**1a**	95
2	**10d**	$(CH_2)_2OMe$, Me	**1d**	98
3	**10f**	$(CH_2)_3OH$, Me	**1f**	90
4	**10g**	$(CH_2)_2OH$, Me	**1g**	81
5	**10h**	$(CH_2)_2OH$, Ph	**1h**	90
6	**10k**	$(CH_2)_2PO(OEt)_2$, Me	**1k**	91

[a] Overall yield (**10**⟶**1**).

procedure was developed from **10a**,**d**,**f**,**g**,**h**,**k**, providing models **1** with comparable overall yields (Table 2).

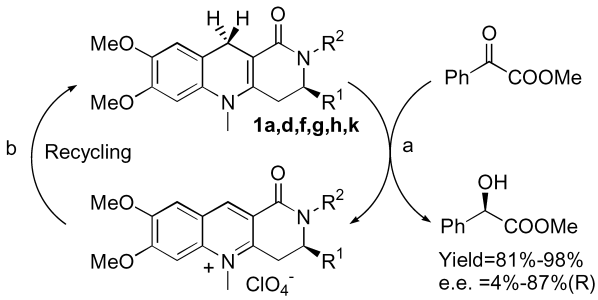
2.3. Reduction of methyl benzoylformate with NADH mimics 1a,d,f,g,h,k

Models **1a**,**d**,**f**,**g**,**h**,**k** were involved in the asymmetric reduction of methyl benzoylformate in the presence of magnesium perchlorate in acetonitrile at room temperature. This metal salt, involved in the formation of a ternary complex mimic/Mg^{2+}/substrate, activates both partners of the reduction. The enantioselectivities observed ranged from 4 to 87% (*R*) and in 90% yield in most cases. It is interesting to note that quinolinium perchlorate salts could be cleanly recovered and subsequently reduced in high yield. The so-recycled NADH mimics could be used in a second reduction process to give methyl mandelate with comparable yields without erosion of the enantioinduction. As can be seen from Table 1, the presence of an additional binding element on the lactam chain (R^2) appears to be crucial to attain high level of asymmetric induction. While **1a** afforded methyl mandelate in 4% ee (Table 3, entry 1), all other models **1d**,**f**,**g**,**h**,**k**, bearing an additional coordinating site, yielded methyl mandelate in 71–87% ee (Table 3, entries 2–6). Lastly, comparison of the performance of **1g** and **1h** reveals that changing the substituent R^1 did not result in any further improvement in the enantioselection (Table 3, entries 4 and 5).

2.4. Conformational analysis and mechanistic aspect of the stereoselective hydrogen transfer

A detailed NMR study throws light on the conformation adopted by the chiral cyclic inducer. As expected, measurement of the coupling constants between H-3′ and the two H-4′ protons, demonstrated that R^1 adopts a pseudo-axial position in **8a** and **8b**. The same set of coupling constants was observed in model **1a**, indicating that the methyl group occupies a pseudo-axial position as well. Further support for this assignment came from a NOESY experiment of **8a**, showing a strong dipolar interaction

Table 3. Reduction of methyl benzoylformate with models **1a**,**d**,**f**,**g**,**h**,**g**. *Reagents and conditions*: (a) $Mg(ClO_4)_2/CH_3CN$/rt/24 h; (b) $Na_2S_2O_4/Na_2CO_3$/rt



Entry	Compound	R^2, R^1	Yield (%)	e.e. (*R*) (%)
1	**1a**	$PhCH_2$, Me	95	4
2	**1d**	$(CH_2)_2OMe$, Me	98	71
3	**1f**	$(CH_2)_3OH$, Me	90	81
4	**1g**	$(CH_2)_2OH$, Me	81	86
5	**1h**	$(CH_2)_2OH$, Ph	90	84
6	**1k**	$(CH_2)_2PO(OEt)_2$, Me	91	87

between R^1 (CH_3) and H-4′ equatorial. Molecular modeling[5] confirms this finding and shows a dihedral angle (α) of about 15° (Fig. 4(a)). As a result of the preferential stabilization of R^1 in pseudo-axial conformation, the carbonyl lactam slightly oriented out-of-plane of the dihydroquinoline, would in turn promote the complexation of magnesium ion on one face of models **1**. According to this scenario, the lactam carbonyl would act as a 'chiral relay' in the diastereofacial discrimination of both faces of the model to promote H^{syn} transfer.[15] Although this chiral relay may induce the stereodiscrimination of the two diastereotopic H-4, the poor performance of **1a** (Table 3, entry 1) discloses that incorporation of a second binding site (R^2) is necessary to ensure the stereodifferentiation of both faces of MBF. One can assume that this supplementary binding site participates with the lactam carbonyl in the formation of a chelate as illustrated in Figure 4(b). These considerations led us to propose the ternary complex depicted in Figure 4(b) which accounts for the formation of (*R*)-methyl mandelate.

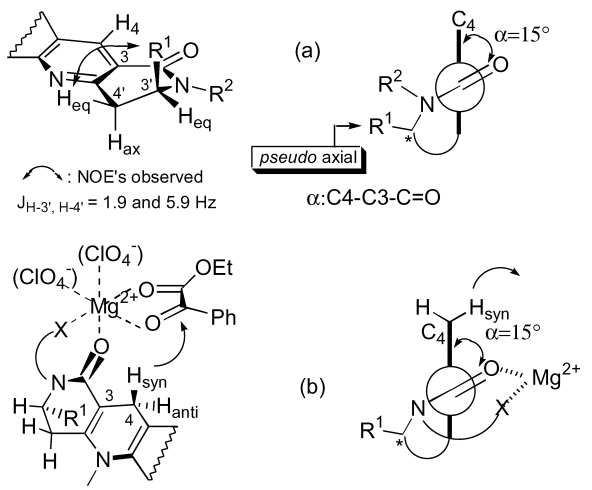
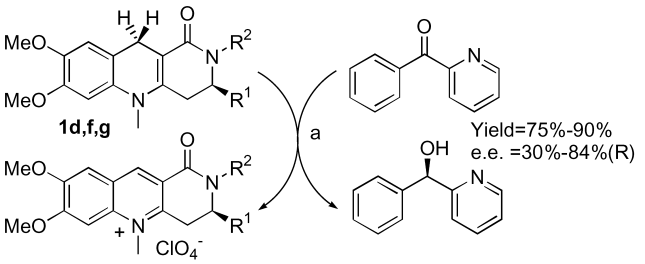


Figure 4. (a) Conformational analysis of the chiral cyclic inducer in **8a** and **8b**. (b) Binding sites for magnesium ion and proposed ternary complex Model/Mg^{2+}/MBF.

Table 4. Reduction of 2-benzoylpyridine with NADH mimics **1d**,**f**,**g**. *Reagents and conditions*: (a) $Mg(ClO_4)_2/CH_3CN$/rt/24 h



Entry	Compound	R^2, R^1	Yield (%)	e.e. (*R*) (%)
1	**1d**	$(CH_2)_2OMe$, Me	90	30
2	**1f**	$(CH_2)_3OH$, Me	95	84
3	**1g**	$(CH_2)_2OH$, Me	85	35

2.5. Reduction of 2-benzoylpyridine with NADH mimics 1d,f,g

To further explore the potential of these new biomimetic models **1**, we next investigated the reduction of 2-benzoylpyridine. Asymmetric reduction of diarylketones remains poorly explored and only few papers deal with the stereoselective preparation of α-phenyl-2-pyridinemethanol.[16] Under the same conditions, i.e. in acetonitrile in the presence of magnesium perchlorate, α-phenyl-2-pyridinemethanol was obtained in 75–90% yield and in 30–84% ee. While the best enantioselectivity (ee=84%) is reached with model **1f** (Table 4, entry 2), it decreased strongly (30–35% ee) when the coordinating pendant arm (R^2) turned out to be shorter (Table 4, entries 1 and 3).

Comparison of the sign of the specific rotation value with literature data reveal that (*R*)-α-phenyl-2-pyridinemethanol was obtained in all cases. By analogy to the ternary complex proposed for the reduction of MBF (Fig. 4(b)), one could anticipate the sense of induction during the reduction of 2-benzoylpyridine. Indeed, the ketone displays two binding sites, as in MBF, which would coordinate magnesium ions as outlined in Figure 5.

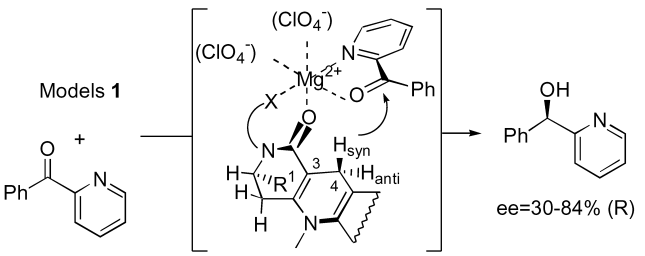


Figure 5. Reduction of 2-benzoylpyridine with models **1**: proposed ternary complex.

3. Conclusion

We have reported with success the preparation of a new class of NADH quinoline-type models **1** which rely on a Friedländer reaction between chiral piperidine-2,4-diones **2** and an *o*-aminobenzaldehyde derivative. Various coordinating pendant arms could be introduced on the lactam nitrogen to probe the influence of a supplementary binding site on the

enantioselectivity of these new biomimetic models **1**. We could conclude that the cyclic chiral inducer (C) would participate in the stereodifferentiation of both diastereotopic faces of the mimics **1**, whereas the complexing chain proved to be essential to ensure the stereodifferentiation of both prochiral faces of the substrate. The possibility to install various pendant arms (R^2) offers the opportunity, to some extent, to tune the stereoselectivity of the model to a given substrate. The screening of these various mimics, allowed to select **1k**, as the most efficient model towards the reduction of methyl benzoylformate. Methyl mandelate was obtained in 87% ee (*R*). In the case of 2-benzoylpyridine, the best level of asymmetric induction is attained with model **1f** affording α-phenyl-2-pyridinemethanol in 84% ee (*R*).

4. Experimental

4.1. General methods

The infra-red spectra were recorded on a Beckmann IR 4250 spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a 200 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuteriodimethylsulfoxide (DMSO-d_6). Chemical shift are given in ppm with TMS or HMDS as internal reference. Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless otherwise stated, were used without further purification. Flash chromatography was performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica Plate (Merck, Kieselgel 60 F_{254}). The following compounds were prepared by literature methods: 3,4-dimethoxy *ortho*-aminobenzaldehyde,[11] 6-(*p*-tolylaminomethylidene)-3,4-dimethoxyaniline **3**.[11]

4.1.1. (*S*)-*N*-*p*-Methoxybenzyl-1-phenylethylamine (4). A solution of (*S*)-1-phenylethylamine (20 g, 165.2 mmol) and *p*-anisaldehyde (22.45 g, 165.2 mmol) in methanol (100 mL) was stirred at room temperature for 2 h. Sodium borohydride (5 g, 129 mmol) was slowly added to the solution at 0°C. The solution was stirred at room temperature for 2 h. Methanol was evaporated, the residue was diluted with water and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give **4** as a colorless liquid (96%). The crude product is pure enough to be used in the next step without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (3H, d, *J*=6.5 Hz), 3.57 (1H, d, *J*=15.9 Hz), 3.64 (1H, d, *J*=15.9 Hz), 3.83 (1H,q, *J*=6.5 Hz), 3.85 (3H, s), 6.89 (2H, d, *J*=8.4 Hz), 7.23 (2H, d, *J*=8.4 Hz), 7.40–7.25 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.80, 51.34, 55.56, 57.69, 114.06, 127.01, 127.21, 128.77, 129.60, 133.08, 145.93, 158.85. IR (neat) 3323, 2960, 2931, 2834, 1611, 1513, 1453, 1246, 1174, 1114, 1035, 822, 762, 701 cm^{-1}. MS (EI, 70 eV): 241.

4.1.2. Methyl (3*S*,α*S*)-3-(*N*-*p*-methoxybenzyl-*N*-α-methylbenzylamino) butyrate (5a). A solution of *n*-butyllithium in hexane (8.52 mL, 2.5 M, 21.3 mmol) was added to a solution of **4** (5.1 g, 21.3 mmol) in THF (15 mL) at 0°C. The solution was cooled at −70°C and *trans*-methylcrotonate (2.56 g, 25.6 mmol) was added dropwise. After stirring for 30 min at −70°C, a saturated aqueous solution of ammonium chloride (10 mL) was added at −50°C. The aqueous layer was extracted with diethylether. The organic phase was dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash chromatography (SiO_2/diethylether–cyclohexane 1:5) to give **5a** in 69% yield as a colorless liquid. ^1H NMR δ 1.15 (3H, d, *J*=6.6 Hz), 1.37 (3H, d, *J*=6.9 Hz), 2.13 (1H, dd, *J*=14.2, 7.6 Hz), 2.38 (1H, dd, *J*=14.2, 6.5 Hz), 3.45 (1H, q, *J*=7.3 Hz), 3.51 (3H, s), 3.67 (2H, s), 3.82 (3H, s), 3.90 (1H, q, *J*=6.9 Hz), 6.88 (2H, d, *J*=8.6 Hz), 7.36–7.21 (7H, m). ^{13}C NMR δ 18.32, 26.77, 39.81, 48.63, 49.50, 51.19, 55.09, 56.90, 113.41, 126.44, 127.63, 127.81, 129.32, 133.26, 144.13, 158.27, 172.59. IR (neat): 2970, 1736, 1511, 1250, 1036, 702 cm^{-1}. HRMS (FAB): calcd for $C_{21}H_{28}NO_3$ [$(M+H)^+$]: 342.2069. Found: 342.2065.

4.1.3. Methyl (3*S*,α*S*)-3(*N*-*p*-methoxybenzyl-*N*-α-methylbenzyl)amino-3-phenylpropanoate (5b). According to the procedure used to prepare **5a** from *trans*-methylcinnamate (1.78 g, 11 mmol), butyllithium in hexane (4 mL, 2.5 M, 10 mmol) and **4** (2.4 g, 10 mmol). Purification by flash chromatography (SiO_2/diethylether–cyclohexane 1:9) afforded **5b** in 72% yield as a colorless oil. ^1H NMR δ (200 MHz, $CDCl_3$) 1.24 (3H, d, *J*=6.9 Hz), 2.59 (1H, dd, *J*=14.9, 9.0 Hz), 2.73 (1H, dd, *J*=14.9, 6.1 Hz), 3.50 (3H, s), 3.63 (1H, d, *J*=14.4 Hz), 3.74 (1H, d, *J*=14.4 Hz), 3.81 (3H, s), 4.04 (1H, q, *J*=6.8 Hz), 4.47 (1H, dd, *J*=9.0, 6.1 Hz), 6.85 (2H, d, *J*=8.6 Hz), 7.23 (2H, d, *J*=8.6 Hz), 7.27–7.46 (10H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.59, 37.34, 49.85, 51.31, 55.07, 56.20, 58.79, 113.44, 126.65, 127.06, 127.68, 127.86, 127.95, 128.13, 129.06, 133.02, 141.68, 143.99, 158.27, 172.11. IR (neat) 2950, 2838, 1737, 1611, 1511, 1452, 1249, 1170, 1035, 760, 735, 701 cm^{-1}. HRMS (FAB): calcd for $C_{26}H_{30}NO_3$ [$(M+H)^+$] 404.2226. Found: 404.2234.

4.1.4. Methyl (3*S*)-3-(*N*-*p*-methoxybenzyl)amino butyrate (6a). A mixture of β-amino ester **5** (6.82 g, 20 mmol), 20% $Pd(OH)_2/C$ (1.75 g, 2.5 mmol) and concentrated HCl (4.8 mL) in methanol (100 mL) was stirred under 1 atm of hydrogen overnight at room temperature. The mixture was then filtered through a plug of celite. The methanol was evaporated under vacuum and the resultant acidic aqueous layer was neutralized with 10% aqueous K_2CO_3. Extraction with CH_2Cl_2 (3×50 mL), drying ($MgSO_4$) and evaporation of the solvent gave **6** in 94% yield as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (3H, d, *J*=6.4 Hz), 2.41 (1H, dd, *J*=15.4, 6.2 Hz), 2.56 (1H, dd, *J*=15.4, 6.6 Hz), 2.81 (1H, s), 3.17 (1H, sept, *J*=6.4 Hz), 3.67 (3H, s), 3.75 (2H, d, *J*=7.4 Hz), 3.79 (3H, s), 6.86 (2H, d, *J*=8.6 Hz), 7.26 (2H, d, *J*=8.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.29, 41.20, 49.41, 50.78, 51.32, 55.65, 110.84, 111.16, 119.95, 132.82, 147.79, 148.78, 172.62. IR (neat) 3327, 2954, 1732, 1514, 1248, 825 cm^{-1}. HRMS (FAB): calcd for $C_{13}H_{20}NO_3$ [$(M+H)^+$] 238.1443. Found: 238.1437.

4.1.5. Methyl (3*S*)-3-(*N*-*p*-methoxybenzylamino)-3-phenylpropanoate (6b). According to the above procedure used to prepare **6a** from β-amino ester **5b** (8.05 g, 20 mmol). Amino ester **6b** was obtained in 84% yield as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 2.00 (1H, broad), 2.63 (1H, dd, *J*=15.6, 5.5 Hz), 2.75 (1H, dd, *J*=15.6,

8.5 Hz), 3.49 (1H, d, *J*=12.9 Hz), 3.62 (1H, d, *J*=12.9 Hz), 3.65 (3H, s), 3.81 (3H, s), 4.12 (1H, dd, *J*=8.5, 5.5 Hz), 6.86 (2H, d, *J*=8.6 Hz), 7.20 (2H, d, *J*=8.6 Hz), 7.29–7.37 (5H, m). HRMS (FAB): calcd for $C_{18}H_{22}NO_3$ [(M+H)$^+$] 300.1600. Found: 300.1605.

4.1.6. Methyl (3*S*)-3-(*N*-*p*-methoxybenzylamino-*N*-ethoxycarbonylacetyl)-3-butyrate (7a). To a stirred solution of ethyl malonyl chloride (4.98 g, 37.0 mmol) in CH_2Cl_2 (40 mL) was added dropwise a solution of β-amino ester **6a** (8.77 g, 37.0 mmol) and triethylamine (7.48 g, 37.0 mmol) in CH_2Cl_2 (40 mL). The stirring was continued for an additional 4 h. After addition of water (100 mL), the organic layer was washed with water (3×20 mL) and with 10% aqueous K_2CO_3 (2×20 mL). The organic phase was dried ($MgSO_4$) and evaporated under vacuum. The resultant crude product was purified by chromatography (SiO_2/cyclohexane–EtOAc 7:3) affording **7a** as a yellow oil in 86% yield. Compound **7a** is obtained as a mixture of two rotamers which interconvert by rotation about the amide N–C═O bond. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (1.5H, d, *J*=6.8 Hz), 1.24 (1.5H, d, *J*=6.9 Hz), 1.27 (1.5H, t, *J*=7.1 Hz) 1.32 (1.5H, t, *J*=7.2 Hz), 2.35 (0.5H, dd, *J*=15.5, 6.2 Hz), 2.54 (0.5H, dd, *J*=15.5, 7.8 Hz), 2.58 (0.5H, dd, *J*=15.5, 7.3 Hz), 2.82 (0.5H, dd, *J*=15.6, 6.9 Hz), 3.39 (1H, s), 3.89 (0.5H, d, *J*=15.8 Hz), 3.64 (0.5H, d, *J*=15.8 Hz), 3.57 (1.5H, s), 3.66 (1.5H, s), 3.78 (1.5H, s), 3.81 (1.5H, s), 4.18 (1H, q, *J*=7.1 Hz), 4.23 (1H, q, *J*=7.1 Hz), 4.39 (0.5H, d, *J*=15.3 Hz), 4.65 (0.5H, d, *J*=15.3 Hz), 4.46 (1H, s), 4.42 (0.5H, m), 4.59 (0.5H, m), 6.81 (1H, d, *J*=8.6 Hz), 6.90 (1H, d, *J*=8.5 Hz), 7.15 (1H, d, *J*=8.6 Hz), 7.18 (1H, d, *J*=8.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.36, 16.30, 20.29, 21.80, 41.00, 41.90, 43.99, 44.50, 45.73, 51.74, 52.10, 53.06, 53.91, 54.03, 57.44, 57.52, 63.60, 63.68, 115.98, 116.51, 129.74, 130.50, 130.98, 132.84, 160.70, 161.31, 168.96, 169.85, 170.22, 173.30, 174.07. IR (neat) 2992, 2954, 1738, 1650, 1514, 1248, 1176, 1033 cm^{-1}. HRMS (FAB): calcd for $C_{18}H_{26}NO_6$ [(M+H)$^+$] 352.1760. Found 352.1743.

4.1.7. Methyl (3*S*)-3-(*N*-*p*-methoxybenzyl-*N*-ethoxycarbonylacetylamino)-3-phenyl-propanoate (7b). According to the procedure used to prepare **7a** from **6b** (4.0 g, 15 mmol), triethylamine (2.29 mL, 16.5 mmol) and ethyl malonyl chloride (2.48 g, 16.5 mmol). Compound **7b** was obtained in 94% yield as a mixture of two rotamers. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (1.8H, t, *J*=7.2 Hz), 1.29 (2H, t, *J*=7.6 Hz), 2.90 (2H, m), 3.38 (1H, s), 3.51 (1H, s), 3.59 (1.8H, s), 3.76 (3H, s), 3.86 (1.2H, s), 4.11–4.43 (2.4H, m), 4.39 (0.6H, d, *J*=7.0 Hz), 5.03 (0.4H, d, *J*=6.5 Hz), 5.28 (0.4H, t, *J*=7.3 Hz), 6.20 (0.6H, t, *J*=7.7 Hz), 6.74–6.81 (2H, m), 6.92 (1.2H, d, *J*=8.5 Hz), 7.01 (0.8H, d, *J*=8.4 Hz), 7.26–7.32 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.44, 171.30, 168.26, 167.93, 167.82, 159.40, 158.95, 138.57, 138.02, 130.76, 129.42, 129.20, 129.02, 128.40, 127.85, 127.22, 114.58, 114.11, 61.95, 61.85, 57.92, 55.68, 55.64, 55.06, 52.29, 48.76, 45.89, 42.54, 42.08, 37.65, 36.78, 14.48. IR (neat) 2934, 1731, 1651, 1513, 1246, 1176, 1032, 733, 700 cm^{-1}. HRMS (FAB): calcd for $C_{23}H_{28}NO_6$ [(M+H)$^+$] 414.1917. Found: 414.1923.

4.1.8. (6*S*)-1-(*p*-Methoxybenzyl)-6-methyl-piperidin-2,4-dione (2a). To a solution of sodium methoxide (0.97 g, 17.9 mmol) in dry THF (25 mL) was added compound **7a** (5.0 g, 14.9 mmol). After refluxing for 2 h, THF was evaporated under vacuum to give a slightly yellow solid. After addition of 6N HCl (6 mL) at room temperature, the resulting suspension was heated at reflux for 2 h. After cooling, the solution was neutralized with aqueous 10% Na_2CO_3 (pH=8). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL) and the combined organic phases were dried (Na_2SO_4). Evaporation of CH_2Cl_2 under vacuum gave **2a** as a white solid in 70% yield after recrystallization in ethanol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, d, *J*=6.7 Hz), 2.46 (1H, dd, *J*=15.9, 2.5 Hz), 2.65 (1H, dd, *J*=15.9, 5.8 Hz), 3.38 (2H, m), 3.74 (1H, m), 3.80 (3H, s), 4.04 (1H, d, *J*=14.7 Hz), 5.25 (1H, d, *J*=14.7 Hz), 6.88 (2H, d, *J*=8.7 Hz), 7.23 (2H, d, *J*=8.7 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.84, 46.50, 47.13, 48.04, 48.81, 55.63, 114.55, 129.11, 129.81, 159.60, 166.36, 204.21. IR (neat) 2969, 2907, 1654, 1556, 1492, 1356, 1237, 1027 cm^{-1}. Mp=142°C. Anal. calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.84; H, 6.91 N, 5.62.

4.1.9. (6*S*)-6-Phenyl-1-*p*-methoxybenzylpiperidine-2,4-dione (2b). According to the above procedure used to prepare **2a** from compound **7b** (1.97 g, 5.3 mmol) and sodium methoxide (0.37 g, 6.6 mmol). Compound **2b** was obtained in 75% yield as a colorless oil, after purification by flash chromatography (SiO_2/EtOAc–cyclohexane 1:5) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.77 (1H, d, *J*=12.8 Hz), 2.86 (1H, dd, *J*=12.8, 2.9 Hz), 3.31 (1H, d, *J*=20.4 Hz), 3.46 (1H, d, *J*=20.4 Hz), 3.61 (1H, d, *J*=14.6 Hz), 3.77 (3H, s), 4.75 (1H, dd, *J*=5.1, 3.9 Hz), 5.59 (1H, d, *J*=14.6 Hz), 6.84 (2H, d, *J*=8.5 Hz), 7.06 (2H, dd, *J*=7.6, 1.6 Hz), 7.15 (2H, d, *J*=8.5 Hz), 7.29–7.40 (3H, m). IR (neat) 2934, 1731, 1651, 1513, 1246, 1176, 1032, 733, 700 cm^{-1}. Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.66; H, 6.02; N, 4.46.

4.1.10. (3*S*)-2-*p*-Methoxybenzyl-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (8a). A mixture of piperidin-2,4-dione **2a** (4.39 g, 17.8 mmol), Schiff base **3** (5.04 g, 18.7 mmol) and a few drops of piperidine in ethanol (60 mL) was stirred at room temperature for 24 h. The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2/EtOAc–cyclohexane 3:7) to give 2.66 g (68%) of **8a** as a beige solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (3H, d, *J*=6.6 Hz), 2.98 (1H, dd, *J*=16.1, 1.9 Hz), 3.41 (1H, dd, *J*=16.1, 5.9 Hz), 3.80 (3H, s), 3.85 (m, 1H); 4.02 (3H, s), 4.03 (3H, s), 4.09 (1H, d, *J*=14.6 Hz), 5.48 (1H, d, *J*=14.6 Hz), 6.89 (2H, d, *J*=8.5 Hz), 7.16 (1H, s), 7.31 (2H, d, *J*=8.5 Hz), 7.38 (1H, s), 8.74 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.80, 38.57, 48.08, 50.28, 55.61, 56.50, 56.57, 106.51, 107.53, 114.43, 121.32, 123.06, 129.73, 130.08, 135.45, 146.89, 150.11, 154.38, 154.38, 159.41, 163.56. IR (neat) 2966, 2933, 1644, 1504, 1249 cm^{-1}. Anal. calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.34; H, 6.23; N, 7.04.

4.1.11. (3*S*)-2-*p*-Methoxybenzyl-7,8-dimethoxy-1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (8b). According to the above procedure used to prepare **8a** from piperidine-2,4-dione **2b** (1.73 g, 5.6 mmol) and Schiff base **3** (1.51 g, 5.6 mmol). Compound **8b** was obtained in

78% yield after purification by flash chromatography (SiO_2/EtOAc–cyclohexane 1:3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.23 (1H, dd, J=16.1, 1.8 Hz), 3.66 (1H, d, J=14.6 Hz), 3.78 (1H, dd, J=16.1, 7.2 Hz), 3.71 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.77 (1H, dd, J=6.8, 1.8 Hz), 5.78 (1H, d, J=14.6 Hz), 6.78 (2H, d, J=8.6 Hz), 6.97 (2H, d, J=8.6 Hz), 7.05–7.18 (7H, m), 8.71 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.77, 48.44, 55.70, 56.56, 56.60, 57.71, 106.55, 107.64, 114.55, 121.71, 123.13, 126.61, 128.16, 129.24, 129.29, 129.76, 135.37, 139.87, 147.05, 150.22, 153.28, 154.48, 159.57, 164.74. IR (neat) 2925, 1648, 1502, 1249, 1154, 1031, 1010, 849, 737, 700 cm^{-1}. Anal. calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.02; H, 5.69; N, 6.02.

4.1.12. (3*S*)-7,8-Dimethoxy-3-methyl-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (9a). A solution of CAN (3.29 g, 6 mmol) in H_2O–MeCN (1:9) (20 mL) was added dropwise to a solution of **8a** (0.78 g, 2 mmol) in H_2O–MeCN (1:9) (15 mL) at room temperature. The mixture was stirred vigorously for 5 h, then diluted with NaOH (2N, 12 mL). After stirring for 30 min, the mixture was filtered. The filtrate was extracted with CH_2Cl_2 (4×20 mL). The resultant organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was solubilized in CH_2Cl_2 (5 mL). After addition of Et_2O (45 mL), **9a** precipitates as white needles (0.375 g, 69%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (3H, d, J=6.4 Hz), 3.05 (1H, dd, J=15.9, 10.0 Hz), 3.32 (1H, dd, J=15.9, 4.6 Hz), 3.95–4.05 (1H, m), 4.03 (3H, s), 4.05 (3H, s), 5.97 (1H, s, broad), 7.14 (1H, s), 7.39 (1H, s), 8.69 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.95, 39.39, 46.39, 56.00, 56.13, 105.95, 107.12, 120.10, 122.50, 134.91, 146.61, 149.74, 154.20, 155.04, 165.53. IR (neat): 3201, 3065, 1709, 1649, 1515, 1432, 1408, 1384, 1309, 1277, 998 cm^{-1}. Mp 214°C. Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.03; H, 5.81; N, 10.26.

4.1.13. (3*S*)-7,8-Dimethoxy-1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (9b). According to the above procedure used to prepare **9a** from **8b** (0.61 g, 1.33 mmol), CAN (2.19 g, 4 mmol). Compound **9b** was obtained in 60% yield as white needles after recrystallization in ethanol. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.46 (2H, m), 4.03 (6H, s), 5.00 (1H, t, J=7.2 Hz), 6.32 (1H, s broad), 7.14 (1H, s), 7.36–7.39 (6H, m), 8.73 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.41, 55.17, 56.03, 56.16, 105.99, 107.17, 120.15, 122.59, 126.19, 128.31, 128.98, 135.00, 140.54, 146.76, 149.82, 154.28, 154.39, 165.80. IR (neat) 3175, 3056, 1675, 1603, 1497, 1425, 1249 cm^{-1}. Mp 238°C. Anal. calcd for $C_{20}H_{18}N_2O_3$: C,71.84; H, 5.43; N, 8.38. Found: C, 71.73; H, 5.30; N, 8.27.

4.1.14. General procedure A: (3*S*)-2-benzyl-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10a). To a solution of powdered KOH (0.224 g, 4 mmol) in DMSO (2 mL) was added **9a** (0.272 g, 1 mmol) and benzyl bromide (238 μL, 2 mmol). After stirring for 1 h at room temperature the mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with water (5×10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2/EtOAc–cyclohexane 3:7) to give **10a** in 92% yield as a thick oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, d, J=6.6 Hz), 2.99 (1H, dd, J=16.0, 2.0 Hz), 3.46 (1H, dd, J=16.0, 5.8 Hz), 3.86 (1H, qdd, J=6.6, 5.8, 2.0 Hz), 4.03 (3H, s), 4.04 (3H, s), 4.10 (1H, d, J=14.9 Hz), 5.56 (1H, d, J=14.9 Hz), 7.17 (1H, s), 7.29–7.38 (6H, m), 8.75 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.32, 154.05, 154.03, 149.77, 146.55, 137.70, 135.15, 128.72, 128.36, 127.96, 122.71, 120.88, 107.14, 106.18, 56.59, 56.51, 50.63, 48.73, 38.58, 18.85. Anal. calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.85; H, 6.20; N, 7.63.

4.1.15. (3*S*)-2-Allyl-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10b). According to the general procedure (A) used for the preparation of **10a** using allyl bromide as an electrophile (173 μL, 2 mmol). Compound **10b** was obtained in 95% yield as a yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (3H, d, J=6.6 Hz), 3.04 (1H, dd, J=16.0, 2.0 Hz), 3.53 (1H, dd, J=16.0, 6.0 Hz), 3.64 (1H, ddt, J=15.3, 6.9, 1.4 Hz), 3.91 (1H, quint-t, J=6.4, 2.0 Hz), 4.00 (3H, s), 4.02 (3H, s), 4.82 (1H, ddt, J=15.3, 4.8, 1.7 Hz), 5.23 (1H, dd, J=17.1, 1.3 Hz), 5.28 (1H, dd, J=10.0, 1.3 Hz), 5.91 (1H, dddd, J=17.1, 10.0, 1.4, 1.7 Hz), 7.13 (1H, s), 7.36 (1H, s), 8.67 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.94, 31.06, 47.95, 50.55, 56.29, 56.36, 106.25, 107.32, 117.61, 121.10, 122.83, 133.76, 146.67, 149.92, 154.20, 154.23, 163.05. IR (neat) 3369, 3264, 2967, 2933, 1650, 1505, 1253 cm^{-1}. Anal. calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.12; H, 6.50; N, 8.86.

4.1.16. (3*S*)-2-Allyl-3-phenyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10c). According to the general procedure (A) used for the preparation of **10a** from compound **9b** (0.33 g, 1 mmol) and allyl bromide as an electrophile (173 μL, 2 mmol). Compound **10c** was obtained in 97% yield as yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.84 (1H, dd, J=16.2, 6.8 Hz), 3.39 (1H, dd, J=16.2, 2.0 Hz), 3.33 (1H, dd, J=15.3, 7.4 Hz), 3.96 (3H, s), 3.98 (3H, s), 4.96–5.27 (4H, m), 5.91 (1H, m), 7.04–7.27 (7H, m), 8.75 (1H, s). Anal. calcd for $C_{23}H_{22}N_2O_3$: C,73.78; H, 5.92; N, 7.48. Found: C, 73.75; H, 5.85; N, 7.35.

4.1.17. (3*S*)-2-(2-Methoxyethyl)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10d). According to the general procedure (A) used for the preparation of **10a** using 2-iodo-1-methoxyethane (0.74 g, 2 mmol) as an electrophile. Compound **10d** was obtained in 89% yield as a yellow solid after purification by flash chromatography (SiO_2/EtOAc–cyclohexane 4:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (3H, d, J=6.7 Hz), 3.00 (1H, dd, J=16.0, 2.0 Hz), 3.18 (1H, ddd, J=13.8, 7.1, 5.2 Hz), 3.36 (3H, s), 3.52–3.68 (3H, m), 3.99 (3H, s), 4.01 (3H, s), 4.04 (1H, m), 4.23 (1H, dt, J=14.0, 4.4 Hz), 7.15 (1H, s), 7.39 (1H, s), 8.68 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.20, 38.41, 46.36, 53.02, 56.51, 56.60, 59.38, 71.88, 106.55, 107.53, 121.04, 123.04, 135.14, 146.81, 150.12, 154.39, 154.69, 163.58. IR (neat) 3374, 2936, 2832, 1644, 1601, 1506, 1254 cm^{-1}. Anal. calcd for $C_{18}H_{22}N_2O_4$: C,65.44; H, 6.71; N, 8.48. Found: C, 65.37; H, 6.53; N, 8.31.

4.1.18. (3*S*)-2-(3-Propyl acetate)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10e). According to the general procedure (A) used for the preparation of **10a** using 3-iodo-propyl-acetate (0.74 g, 2 mmol) as electrophile. Compound **10e** was obtained in 65% yield as a colorless oil after flash chromatography (SiO_2/EtOAc–cyclohexane 4:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (3H, d, J=6.6 Hz), 2.07 (3H, s), 2.08 (2H, m), 3.02–3.14 (2H, m), 3.58 (1H, dd, J=16.0, 6.0 Hz), 3.90 (1H, t, J=5.5 Hz), 4.02 (3H, s), 4.04 (3H, s), 4.20 (2H, t, J=6.2 Hz), 4.22 (1H, m), 7.14 (1H, s), 7.38 (1H, s), 8.67 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.90, 20.87, 27.61, 38.08, 43.07, 51.72, 56.03, 56.11, 62.07, 106.04, 107.03, 120.80, 122.58, 134.72, 146.39, 149.69, 153.75, 153.96, 163.12, 170.95. IR (neat) 2968, 1732, 1634, 1504, 1253, 753 cm^{-1}. Anal. calcd for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.25; H, 6.58; N, 7.39.

4.1.19. (3*S*)-2-(3-Hydroxypropyl)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10f). To a stirred solution of **10e** (0.32 g, 0.87 mmol) in ethanol (5 mL) was added a solution of KOH (63 mg, 1.1 mmol) in ethanol (5 mL). After stirring for 30 min, the mixture was poured into water (10 mL). After extraction with dichloromethane, the combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford **10f** (98%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.7 Hz), 1.88 (2H, m), 3.07 (1H, dd, J=16.0, 2.0 Hz), 3.31 (1H, dt, J=14.1, 5.3 Hz), 3.58 (1H, dd, J=16.0, 5.3 Hz), 3.62 (2H,m), 3.90 (1H, m), 4.01 (3H, s), 4.04 (3H, s), 4.19 (1H, ddd, J=14.0, 9.2, 4.6 Hz), 7.13 (1H, s), 7.37 (1H, s), 8.65 (1H, s). ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.93, 30.66, 37.97, 42.06, 51.53, 56.01, 56.10, 58.09, 106.00, 106.95, 120.34, 122.53, 134.83, 146.37, 149.75, 153.60, 154.08, 164.21. HRMS (FAB): calcd for $C_{18}H_{23}N_2O_4$ [(M+H)$^+$]: 331.1658. Found: 331.1655.

4.1.20. (3*S*)-2-(2-Hydroxyethyl)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10g). To a stirred solution of **10b** (0.36 g, 1.15 mmol) in THF–H_2O (1:1) (18 mL) was added osmium tetraoxide (4 wt% solution in water, 0.705 mL, 0.115 mmol), giving initially a clear solution which darkened rapidly. The solution was stirred for 15 min, at which time sodium periodate (0.747 g, 3.45 mmol) was added in one portion affording a white precipitate. After 1 h, methanol (9 mL) was added, the mixture was cooled at 0°C, and sodium borohydride (0.086 g, 2.3 mmol) was added in one portion. The resultant black mixture was vigorously stirred at 0°C for 30 min and then poured into a saturated $NaHCO_3$ aqueous solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (4×30 mL), the combined organic phases were dried over Na_2SO_4 and concentrated to give after flash chromatography (SiO_2/EtOAc–EtOH 95:5) the desired compound **10g** (0.261 g, 72%) as a white solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.8 Hz), 3.05 (1H, dd, J=16.0, 1.8 Hz), 3.41 (1H, ddd, J=14.1, 6.2, 3.8 Hz), 3.65 (1H, dd, J=16.0, 6.0 Hz), 3.97 (2H, m), 4.00 (1H, m), 4.02 (3H, s), 4.04 (3H, s), 4.15 (1H, ddd, J=14.1, 6.2, 3.8 Hz), 7.14 (1H, s), 7.39 (1H, s), 8.67 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.00, 38.01, 50.27, 53.45, 56.02, 5611, 62.57, 106.02, 107.05, 120.44, 122.51, 134.72, 146.53, 149.74, 153.75, 154.09, 164.88. IR (neat) 3193, 1649, 1506, 1258 cm^{-1}. Mp 197°C. Anal. calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.22; H, 6.18; N, 8.69.

4.1.21. (3*S*)-2-(2-Hydroxyethyl)-3-phenyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10h). According to the above procedure used to prepare **10g** from **10c** (0.35 mg, 1.08 mmol), osmium tetraoxide (4 wt% solution in water, 0.705 mL, 0.115 mmol), sodium periodate (0.70 g, 3.24 mmol), sodium borohydride (81 mg, 2.15 mmol). Compound **10h** was obtained in 72% yield as a white solid after purification by chromatography (SiO_2/EtOAc–EtOH 99:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.25 (1H, ddd, J=14.2, 6.2, 4.7 Hz), 3.29 (1H, dd, J=16.2, 2.3 Hz), 3.87 (2H, m), 3.94–4.00 (7H, m), 4.21 (1H, ddd, J=14.2, 5.7, 4.3 Hz), 5.06 (1H, dd, J=6.8, 2.3 Hz), 7.04–7.25 (7H, m), 8.70 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.29, 50.56, 56.04, 56.08, 60.93, 62.07, 106.03, 107.10, 120.92, 122.51, 125.96, 127.78, 128.75, 134.53, 139.46, 146.59, 149.76, 152.68, 154.08, 165.85. Anal. calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.75; H, 5.82; N, 7.33.

4.1.22. (3*S*)-2-(2-Chloroethyl)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10i). To a stirred solution of **10g** (2.0 g, 6.3 mmol) in CH_2Cl_2 (20 mL) and triethylamine (900 μL, 6.9 mmol) was added dropwise a solution of *p*-toluenesulphonyl chloride (1.32 g, 6.9 mmol) in CH_2Cl_2 (20 mL). After stirring for 8 h, water (20 mL) was added. After phase separation, the organic layer was washed with water (10 mL) dried over $MgSO_4$ and evaporated under vacuum. The crude product was purified by chromatography (SiO_2/cyclohexane–EtOAc 7:3) to obtain **10i** as a yellow solid (42%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J=6.7 Hz), 3.07 (1H, dd, J=16.1, 1.5 Hz), 3.24 (1H, ddd, J=17.2, 8.8, 5.6 Hz), 3.70 (1H, dd, J=16.1, 5.9 Hz), 3.83 (2H, m), 4.03 (3H, s), 4.05 (3H, s), 4.08 (1H, m), 4.51 (1H, dt, J=13.8, 4.7 Hz), 7.15 (1H, s), 7.40 (1H, s), 8.67 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.90, 37.78, 42.38, 48.47, 53.43, 56.05, 56.15, 106.03, 107.10, 120.56, 122.54, 134.71, 146.54, 149.75, 153.96, 154.08, 163.41. Anal. calcd for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; N, 8.37. Found: C, 60.75; H, 5.55; N, 8.18.

4.1.23. (3*S*)-2-(2-Iodoethyl)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10j). A solution of **10i** (723 mg, 2.16 mmol) and sodium iodide (1 g, 6.5 mmol) in dry acetone (15 mL) was heated to reflux for 16 h. Filtration of sodium chloride and evaporation of the solvent afforded a slightly yellow solid. The crude product was dissolved in dichloromethane and washed with saturated aqueous Na_2SO_3. The organic phase was dried (Na_2SO_4) and evaporation of the solvent furnished **10i** in 85% yield as a yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J=6.7 Hz), 3.09 (1H, dd, J=16.0, 1.5 Hz), 3.24–3.56 (4H, m), 3.73 (1H, dd, J=16.0, 5.9 Hz), 4.03 (3H, s), 4.05 (3H, s), 4.52 (1H, ddd, J=13.4, 6.9, 3.9 Hz), 7.15 (1H, s), 7.39 (1H, s), 8.67 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.98, 26.76, 37.97, 49.10, 52.88, 56.05, 56.15, 106.04, 107.11, 120.53, 122.56, 125.36, 134.77, 146.58, 153. 88, 154.09, 163.25. IR (neat) 1650, 1499, 1254 cm^{-1}. HRMS: calcd for $C_{17}H_{19}IN_2O_3$ (M$^+$): 426.0440. Found: 426.0437.

4.1.24. (3*S*)-2-(2-Ethyl-diethylphosphonate)-3-methyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridine (10k). To a suspension of NaH (24 mg, 1 mmol) in THF (5 mL) was added dropwise a solution of diethylphosphite in THF (5 mL) at 0°C. The solution was stirred for 30 min at room temperature. A solution of **10j** (213 mg, 0.5 mmol) in THF (5 mL) was added. The mixture was stirred for a further 6 h, then quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$, filtered and evaporated. The crude product was purified by chromatography (SiO_2/EtOAc–EtOH 98:2) to obtain **10k** as a colorless oil (30%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J=6.6 Hz), 1.34 (6H, q, J=6.8 Hz), 2.30 (2H, m), 3.05 (1H, d, J=16.0 Hz), 3.33 (1H, m), 3.63 (1H, dd, J=16.0, 6.0 Hz), 3.95 (1H, m) 4.03 (3H, s), 4.05 (3H, s), 4.14 (4H, qd, J=7.1, 8.0 Hz), 4.34 (1H, m), 7.14 (1H, s), 7.39 (1H, s), 8.66 (1H, s). ^{31}P NMR δ 29.38. ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.25 (d, J=2.5 Hz), 16.37 (d, J=1.9 Hz), 19.05, 24.87 (d, J=138 Hz), 38.04, 41.25, 52.38, 56.01, 56.10, 61.71 (d, J=6.5 Hz), 106.00, 107.06, 120.58, 122.51, 134.53, 134.70, 146.47, 149.69, 153.89, 153.99, 163.13. HRMS: calcd for $C_{21}H_{29}N_2O_6P$ (M^+): 436.1763. Found: 436.1760.

4.1.25. General procedure (B): (3*S*)-2-benzyl-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo-[*b*]-1,6-naphthyridinium triflate (11a). To a solution of **10a** (362 mg, 1 mmol) in CH_2Cl_2 (5 mL), was added a solution of methyl trifluoromethane sulfonate (180 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere. The solution was stirred for 1 h, the solvent was evaporated to give tetrahydrobenzo-naphthyridium salt **11a** as a yellow solid in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (3H, d, J=6.6 Hz), 3.54 (1H, dd, J=18.0, 3.6 Hz), 3.65 (1H, dd, J=18.0, 6.3 Hz), 3.94 (1H, m), 4.00 (3H, s), 4.14 (3H, s), 4.16 (1H, d, J=15.0 Hz), 4.45 (3H, s), 5.36 (1H, d, J=15.0 Hz), 7.32 (5H, m), 7.42 (1H, s), 7.69 (1H, s), 9.30 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$,) δ 19.31, 34.13, 40.41, 48.53, 49.10, 56.69, 57.99, 99.07, 107.75, 121.92, 124.36, 127.85, 127.94, 128.89, 136.14, 139.48, 141.98, 151.95, 153.37, 159.27, 159.52. HRMS (FAB): calcd for $C_{23}H_{25}N_2O_3$ (M^+): 377.1865. Found: 377.1862.

4.1.26. (3*S*)-2-(2-Methoxyethyl)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridinium triflate (11d). According to the general procedure (B) used to prepare **11a** from **10d** (330 mg, 1 mmol). Tetrahydrobenzo-naphthyridium salt **11d** was obtained as yellow solid in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J=6.7 Hz), 3.22 (1H, m), 3.30 (3H, s), 3.57 (2H, m), 3.62 (1H, dd, J=17.8, 2.5 Hz), 3.82 (1H, dt, J=17.8, 6.0 Hz), 4.02 (3H, s), 4.12 (1H, m), 4.18 (3H, s), 4.22 (1H, m), 4.56 (3H, s), 7.34 (1H, s), 7.65 (1H, s), 9.15 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.97, 34.46, 40.90, 46.16, 51.49, 57.11, 58.50, 59.375, 71.19, 99.62, 108.09, 122.58, 124.71, 139.88, 142.08, 152.39, 154.11, 159.67, 159.72. ^{19}F NMR δ −78.76. Mp 208°C. HRMS (FAB): calcd for $C_{19}H_{25}N_2O_4$ (M^+): 345.1814. Found: 345.1812.

4.1.27. (3*S*)-2-(2-Hydroxypropyl)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridinium triflate (11f). According to the general procedure (B) used to prepare **11a** from **10f** (330 mg, 1 mmol). Tetrahydrobenzo-naphthyridium salt **11f** was obtained as yellow solid in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (3H, d, J=6.6 Hz), 1.80 (2H, m), 3.25–3.95 (7H, m), 3.94 (3H, s), 4.24 (3H, s), 4.57 (3H, s), 7.35 (1H, s), 7.64 (1H, s), 9.21 (1H, s). ^{19}F NMR δ −78.76. ^{13}C NMR (50 MHz, CD_3OD) δ 161.59, 160.48, 155.40, 153.31, 143.08, 140.72, 126.10, 123.23, 109.74, 99.86, 60.27, 58.10, 57.98, 51.87, 44.41, 40.16, 34.92, 32.01, 19.78. HRMS (FAB): calcd for $C_{19}H_{25}N_2O_4$ (M^+): 345.1814. Found 345.1812.

4.1.28. (3*S*)-2-(2-Hydroxyethyl)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridinium triflate (11g). According to the general procedure (B) used to prepare **11a** from **10g** (316 mg, 1 mmol). Tetrahydrobenzo-naphthyridium salt **11g** was obtained as a yellow solid in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, d, J=6.5 Hz), 3.17 (1H, m), 3.55 (1H, d, J=18.4 Hz), 3.78 (3H, m), 4.08 (3H, s), 4.21 (3H, s), 4.25 (1H, m), 4.49 (3H, s), 7.46 (1H, s), 7.59 (1H, s), 9.14 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) 160.21, 159.47, 154.75, 152.29, 142.20, 139.64, 124.74, 122.83, 108.45, 99.11, 61.15, 58.26, 57.22, 51.74, 49.25, 40.52, 34.45, 20.28. HRMS (FAB): calcd for $C_{18}H_{23}N_2O_4$ (M^+): 331.1658. Found 331.1645.

4.1.29. (3*S*)-2-(2-Hydroxoxyethyl)-5-methyl-7,8-dimethoxy-1-oxo-3-phenyl-1,2,3,4-tetrahydrobenzo[*b*]-1,6-naphthyridinium triflate (11h). According to the general procedure (B) used to prepare **11a** from **10h** (378 mg, 1 mmol). Tetrahydrobenzo–naphthyridium salt **11h** was obtained as a yellow solid in a quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.01 (2H, m,), 3.63 (2H, m), 3.99 (3H, s), 4.12 (3H, s), 4.15 (2H, m), 4.34 (3H, s), 5.42 (1H, m), 7.20–7.30 (5H, m), 7.66 (1H, s), 8.03 (1H, s), 9.43 (1H, s). ^{19}F NMR δ −78.74. HRMS (FAB): calcd for $C_{23}H_{25}N_2O_4$ (M^+): 393.1814. Found 393.1816.

4.1.30. (3*S*)-2-(2-Ethyl-diethylphosphonate)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4-tetrahydrobenzo-[*b*]y1,6-naphthyridinium triflate (11k). According to the general procedure (B) used to prepare **11a** from **10k** (436 mg, 1 mmol). Tetrahydrobenzo-naphthyridium salt **11k** was obtained as yellow solid in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25–1.39 (9H, m), 2.22 (2H, m), 3.30 (1H, m), 3.65 (1H, dd, J=17.9, 2.4 Hz), 3.96–4.26 (13H, m), 4.59 (3H, s), 7.37 (1H, s), 7.72 (1H, s), 9.20 (1H, s). ^{19}F NMR δ −78.72. Anal. calcd for $C_{22}H_{32}N_2O_6P$: C, 58.53; H, 7.14; N, 6.20. Found: C, 58.43; H, 7.23; N, 6.24.

4.1.31. General procedure (C): (3*S*)-2-benzyl-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4,5,10-hexahydro-benzo[*b*]-1,6-naphthyridine (1a). To a solution of tetrahydrobenzo-naphtyridinium salt **11a** (378.5 mg, 1 mmol) in water (15 mL), were added in one portion sodium dithionite (174 mg, 1 mmol) and sodium carbonate (106 mg, 1 mmol). After stirring for 1 h under a nitrogen atmosphere, $Na_2S_2O_4$ (174 mg, 1 mmol) and Na_2CO_3 (106 mg, 1 mmol) were added. After stirring for 1 h, $Na_2S_2O_4$ (174 mg, 1 mmol) was added and stirring was continued for an additional 1 h. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL),

the combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to give **1a** in 95% yield as a red oil. NMR (200 MHz, $CDCl_3$) δ 1.29 (3H, d, J=6.5 Hz), 2.13 (1H, d, J=16.0 Hz), 2.50 (1H, dd, J=15.6, 4.5 Hz), 3.14 (3H, s), 3.43 (1H, m), 3.60 (1H, d, J=18.5 Hz), 3.84 (1H, d, J=18.5 Hz), 3.86 (3H, s), 3.87 (3H, s), 4.11 (d, 1H, J=15 Hz), 5.44 (d, 1H, J=15 Hz), 6.42 (1H, s), 6.68 (1H, s), 7.31 (5H, m). HRMS (FAB): calcd for $C_{23}H_{27}N_2O_3$ [(M+H)$^+$]: 379.2022. Found: 379.2018.

4.1.32. (3*S*)-2-(2-Methoxyethyl)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridine (1d). According to the general procedure (C) from **11d** (346 mg, 1 mmol) affording **1d** as an orange solid in 98% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (3H, d, J=6.5 Hz), 2.34 (1H, dd, J=16.1, 2.5 Hz), 2.88 (1H, dd, J=14.1, 5.9 Hz), 2.99 (1H, ddd, J=14.2, 6.8, 5.8 Hz), 3.21 (3H, s), 3.35 (3H, s), 3.54 (2H, dd, J=6.1, 4.7 Hz), 3.62 (1H, m), 3.69 (1H, m), 3.78 (1H, m), 3.84 (3H, s), 3.88 (3H, s), 4.10 (1H, dt, J=14.1, 4.6 Hz), 6.43 (1H, s), 6.65 (1H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.39, 25.83, 32.32, 33.45, 50.93, 56.68, 56.75, 59.30, 72.49, 98.61, 99.08, 113.01, 116.14, 134.91, 145.02 (2C), 147.86, 166.02. HRMS (FAB): calcd for $C_{19}H_{27}N_2O_4$ [(M+H)$^+$]: 347.1971. Found: 347.1968.

4.1.33. (3*S*)-2-(3-Hydroxypropyl)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridine (1f). According to the general procedure (C) from **11f** (346 mg, 1 mmol) affording **1f** (90%) as a pink solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, d, J=6.5 Hz), 1.58–1.89 (2H, m), 2.29 (1H, dd, J=16.3, 3.4 Hz), 2.81 (1H, dd, J=16.3, 6.6 Hz), 3.14 (1H, dt, J=14.6, 1.8 Hz), 3.22 (3H, s), 3.52–3.76 (5H, m), 3.84 (3H, s), 3.88 (3H, s), 4.08 (1H, dt, J=14.6, 1.8 Hz), 4.52 (1H, broad), 6.44 (1H, s), 6.63 (1H, s). HRMS (FAB): calcd for $C_{19}H_{27}N_2O_4$ [(M+H)$^+$]: 347.1971. Found: 347.1973.

4.1.34. (3*S*)-2-(2-Hydroxyethyl)-7,8-dimethoxy-3,5-dimethyl-1-oxo-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridine (1g). According to the general procedure C from **11g** (332 mg, 1 mmol) affording **1g** (81%) as an orange solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (3H, d, J=6.5 Hz), 2.37 (1H, dd, J=15.7, 2.6 Hz), 2.90 (1H, dd, J=15.7, 6.6 Hz), 3.17 (1H, m), 3.20 (3H,s), 3.63 (1H, m), 3.66 (1H, m), 3.69 (1H, m), 3.78 (2H, m), 3.83 (3H, s), 3.86 (3H, s), 3.87 (1H, m), 6.42 (1H, s), 6.61 (1H, s). HRMS (FAB): calcd for $C_{18}H_{25}N_2O_4$ [(M+H)$^+$]: 333.1814. Found 333.1812.

4.1.35. (3*S*)-2-(2-Hydroxyethyl)-7,8-dimethoxy-5-methyl-1-oxo-3-phenyl-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridine (1h). According to the general procedure C from **11h** (394 mg, 1 mmol) affording **1h** (90%) as an orange solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.71 (1H, dd, J=16.1, 4.3 Hz), 3.01 (1H, dt, J=14.3, 4.7 Hz), 3.04 (3H, s), 3.09 (1H, ddt, J=16.1, 7.1, 1.4 Hz), 3.53–3.71 (4H, m), 3.76–3.81 (7H, m), 4.66 (1H, dd, J=7.4, 4.3 Hz), 6.26 (1H, s), 6.53 (1H, s), 7.10–7.25 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.78, 33.42, 34.17, 50.41, 56.64, 56.71, 60.23, 63.37, 98.58, 99.30, 112.94, 115.90, 127.13, 128.40, 129.28, 134.33, 140.92, 144.85, 145.29, 147.88, 169.64. HRMS (FAB): calcd for $C_{23}H_{27}N_2O_4$ [(M+H)$^+$]: 395.1971. Found: 395.1973.

4.1.36. (3*S*)-2-(2-Ethyl-diethylphosphonate)-3,5-dimethyl-7,8-dimethoxy-1-oxo-1,2,3,4,5,10-hexahydrobenzo[*b*]-1,6-naphthyridine (1k). According to the general procedure C from **11k** (452 mg, 1 mmol) affording **1k** (91%) as a red oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (3H, d, J=6.7 Hz), 1.33 (6H, q, J=6.2 Hz), 2.05 (2H, m), 2.35 (1H, dd, J=16.4, 1.8 Hz), 2.87 (1H, dd, J=16.4, 5.8 Hz), 3.07 (1H, m), 3.21 (3H, s), 3.58 (1H, d, J=18.9 Hz), 3.63–3.83 (2H, m), 3.86 (3H, s), 3.88 (3H, s), 4.02–4.18 (5H, m), 6.42 (1H, s), 6.63 (1H, s). ^{31}P NMR δ 30.14. HRMS (FAB): calcd for $C_{22}H_{34}N_2O_6P$ [(M+H)$^+$]: 453.2155. Found: 453.2150.

4.1.37. One pot procedure for the preparation of NADH models 1 from compounds 10. To a stirred solution of **10** (1 mmol) in CH_2Cl_2 (5 mL) was added a solution of methyl trifluoromethane sulfonate (180 mg, 1.1 mmol) in CH_2Cl_2 (5 mL). After stirring under nitrogen for 1 h at room temperature, a solution of sodium dithionite (174 mg, 1 mmol) and sodium carbonate (106 mg, 1 mmol) in water (15 mL) were added. After stirring for 1 h under nitrogen atmosphere, $Na_2S_2O_4$ (174 mg, 1 mmol) and Na_2CO_3 (106 mg, 1 mmol) were added in one portion. After stirring for 1 h, $Na_2S_2O_4$ (174 mg, 1 mmol) was added and stirring was continued for an additional 1 h. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were dried over Na_2SO_4 and evaporated under vacuum to give the corresponding model **1** in 81–98% yield (see Table 2).

4.1.38. General procedure for the reduction of methyl benzoylformate with NADH mimics 1a,d,f,g,h,k. In a flask, flushed with argon, were introduced model **1** (1 mmol), acetonitrile (3 mL), methyl benzoylformate (142 μL, 1 mmol) and magnesium perchlorate (224 mg, 1 mmol). The resulting solution was stirred at room temperature for 24 h in the dark. After addition of water (10 mL), the organic solvent was evaporated under reduced pressure and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). After drying ($MgSO_4$) and evaporation of CH_2Cl_2, the residue was chromatographed on silica gel (eluent Et_2O–cyclohexane 2:1). Yield: 81–98%. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μl (0.5 mg of methyl mandelate in 10 mL of hexane). Eluent: hexane–2-propanol 90:10. Flow rate: 1 mL/min. Pressure: 300 psi. Temperature: 22°C. UV detection: λ=235 nm. Retention time: 9.2 min [(*S*)-enantiomer] and 14.8 min [(*R*)-enantiomer].

4.1.39. General procedure for the reduction of 2-benzoylpyridine with NADH mimics 1d,f,g. Model **1** (1 mmol), acetonitrile (3 mL), 2-benzoylpyridine (183 mg, 1 mmol) and magnesium perchlorate (224 mg, 1 mmol) were introduced in a flask flushed with argon. The resulting solution was stirred at room temperature for 24 h in the dark. After addition of water (10 mL), the organic solvent was evaporated under reduced pressure and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). After drying ($MgSO_4$) and evaporation of CH_2Cl_2, the residue was purified by flash chromatography (SiO_2/EtOAc–cyclohexane 1:4) affording 2-(α-hydroxybenzyl)-pyridine in 75–90% yield as a beige solid. ^{1}H NMR

(200 MHz, $CDCl_3$) δ 5.40 (1H, s, broad, D_2O exchangeable), 5.77 (1H, s), 7.15–7.27 (2H, m), 7.30–7.43 (5H, m), 7.63 (1H, td, J=7.6, 1.7 Hz), 8.57 (1H, dt, J=4.7, 1.4 Hz). IR ($CHCl_3$) 3119, 1594, 1050, 756, 696 cm^{-1}. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD (250×4.6 mm; 10 μm). Chromatographic conditions: injection: 20 μl [0.5 mg of 2-(α-hydroxybenzyl)pyridine in 10 mL of hexane]. Eluent: hexane–2-propanol 98:2. Flow rate: 1 mL/min. Pressure: 61 psi. Temperature: 19°C. UV detection: λ=230 nm. Absolute configuration was determined by comparison with the sign of the optical rotation known in literature.[16a]

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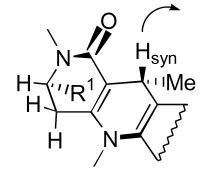
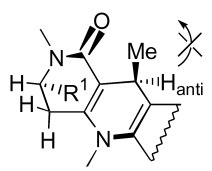
14. At this stage of the synthesis, it was important to make sure that deprotection and alkylation steps are performed under non-racemizing conditions. To this end, oxidative cleavage of *rac*-**8a**, followed by alkylation of the resulting lactam *rac*-**9a** with allyl bromide furnished *rac*-**10b**. The enantioseparation of *rac*-**10b** by chiral HPLC allowed us to conclude that no racemization occurs when the same deprotection–alkylation sequence is achieved starting from (*S*)-**8a**. Chromatographic conditions: Chiralcel OD (250×4.6 mm, 10 μm), injection: 20 μl (0.5 mg of *rac*-**10b** in 10 mL of hexane); Eluent: heptane/2-propanol: 80/20; Flow rate: 1 mL/min. Pressure: 455 psi. Temperature: 18.5°C. UV detection: λ=230 nm. Retention time: 13.25 min [(*R*)-enantiomer] and 15.64 min [(*S*)-enantiomer].
15. We previously showed (Ref. 6) with similar models that only H_{syn} is transferred to the substrate. Indeed, from a mixture of both models (A) and (B), only the diastereoisomer (A) placing H-4 in a *syn* position with respect to the carbonyl moiety is transferred to MBF to yield methyl mandelate in 4% ee (*R*)



Reactive diastereoisomere (A)



Unreactive Diastereoisomere (B)

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