Pergamon

Tetrahedron 57 (2001) 3087–3098

TETRAHEDRON

Stable annelated chiral NADH models with a rigidified amide part in the quinoline series: synthesis, reactivity and grafting on a Merrifield resin

Christiane Vitry, Jean-Luc Vasse, Georges Dupas, Vincent Levacher,* Guy Quéguiner and Jean Bourguignon

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

Received 20 November 2000; accepted 8 February 2001

Abstract—The synthesis of new chiral nicotinamide adenine dinucleotide hydrogenated models derived from quinoline is described. Using a biomimetic approach, the out-of-plane positioning of the amide carbonyl was obtained by involving the chiral auxiliary in a lactam structure. It is shown that electron-donating groups on the benzene ring of the quinoline structure are necessary to obtain high chemical yields during the reduction of methyl benzoylformate. An interesting variation of the enantioselectivity as a function of magnesium ion concentration has been observed. Under the best conditions, methyl mandelate was obtained in up to 95% ee (*R*). To facilitate the recycling of these models, grafting of reagent **4** on a Merrifield resin has been developed. The resulting polymer-supported reagent **4** was tested in the asymmetric reduction of methyl benzoylformate.

1. Introduction

For several decades now, nicotinamide adenine dinucleotide hydrogenated (NADH) models have been the focus of considerable interest. These biomimetic models were first studied to throw light on the biochemical behaviour of the coenzyme. Later models were also used for synthetic purposes in chemoselective reactions. A further step concerned the elaboration of chiral models, which could be used in asymmetric reductions.[1] Our group is involved in these directions.

A family of efficient chiral reagents[2] has been designed on the basis of the following consideration. Two structural key features of the coenzyme seem to play a crucial role in the stereochemical outcome of hydride transfer. The amide carbonyl of the 1,4-dihydronicotinamide part would be *cis* with respect to the hydrogen atoms at C_4.[3] Moreover, this amide carbonyl would be out of the plane of the dihydropyridine structure and *syn*-oriented with respect to the transferred hydrogen.[4] We synthesised chiral models bearing an aminoalcohol as chiral auxiliary where the amide function is involved in a cyclic structure to mimic these conformational features of the coenzyme (Fig. 1).[5]

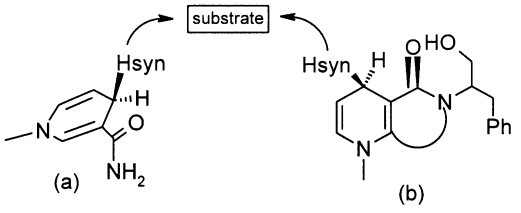
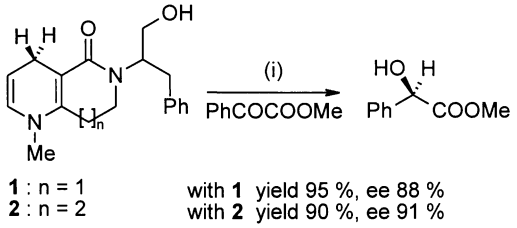


Figure 1. (a) Conformational analysis of the amide group in the coenzyme; (b) biomimetic approach in the design of new chiral NADH models.

Following this biomimetic approach, it emerged that model **1** in the naphthyridine series[5] and model **2** in the pyrido[3,2-c]azepin series[6] afforded the best results in terms of enantioselectivity during the reduction of methyl benzoylformate (Scheme 1).

However, NADH models are subjected to pernicious side reactions essentially caused by the effect of trace water on



Scheme 1. (i) (1) $Mg(ClO_4)_2/CH_3CN$/rt, (2) H_2O.

Keywords: biomimetic NADH model; asymmetric reduction; grafting; Merrifield resins.

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

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00166-1

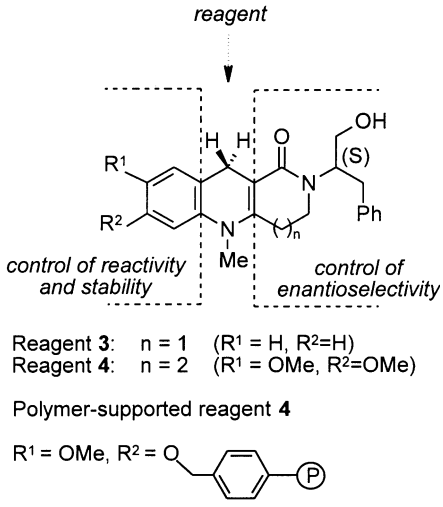


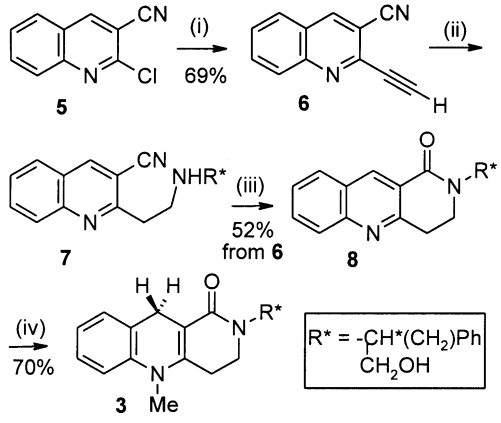
Figure 2. Design of a new class of chiral NADH models.

the fragile 5,6 double bond.[7] To tackle this problem, our group has developed a new generation of models where this bond is protected by annelation with an aromatic ring.[8] We wish to report in the present paper the synthesis of annelated reagents **3** and **4** which are expected to combine good stability and high degree of stereoselectivity. With intend to facilitate the recycling of these models, we developed the grafting of reagent **4** on a Merrifield resin (Fig. 2).

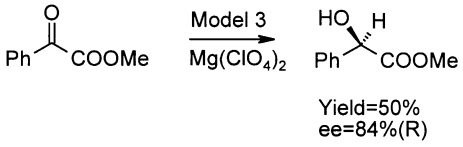
2. Result and discussion

2.1. Preparation of reagent 3: asymmetric reduction of methyl benzoylformate

Reagent **3** was synthesised using a route similar to that employed for the synthesis of model **1**.[5] Cross-coupling of quinoline **5** with trimethylsilylacetylene catalysed by $Pd_2(PPh_3)_2$ and subsequent cleavage of the trimethylsilyl group afforded the ethynyl derivative **6** in 69% yield. Addition of (*S*)-phenylalaninol followed by reduction of the enamine intermediate gave amine **7**, which on treatment with $EtOH/H_2O$ at reflux undergoes cyclization to produce



Scheme 2. (i) (1) Trimethylsilylacetylene/CuI/NEt_3/$PdCl_2(PPh_3)_2$, (2) OH^-; (ii) (1) (*S*)-phenylalaninol, (2) $NaBH_4$; (iii) $EtOH/H_2O$ (95:5); (iv) (1) MeI, (2) $Na_2S_2O_4$.



Scheme 3. Asymmetric reduction of methyl benzoylformate with model **3**.

lactam **8** in an overall yield of 52%. The later was finally converted into the desired target model **3** in two steps with an overall yield of 70% (Scheme 2).

Reduction of methylbenzoylformate with model **3** gave the (*R*)-methyl mandelate with 84% ee and only 50% chemical yield (instead of 88 and 95%, respectively, with model **1** under the same conditions). As can be seen, annelation of model **1** does not disturb the degree of enantioselectivity of the hydride equivalent transfer. However, the chemical yield was very much lowered. Loss of reactivity may be ascribed to the lack of electron donating groups on the annelated benzene ring, which would favour the hydride equivalent departure (Scheme 3).

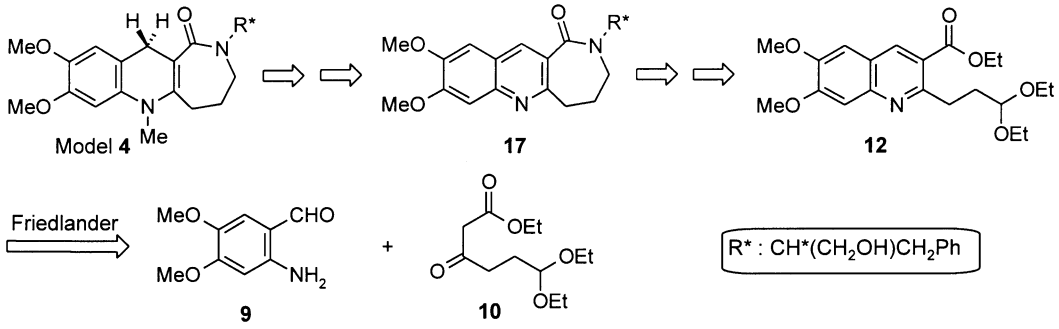
One may expect that increasing the electron donating effect of the benzene ring would improve the reducing properties of the model. To pursue this idea, the synthesis of a similar model with a benzene ring bearing methoxy groups was conceptualised using the same synthetic strategy. Unfortunately, this approach failed at the addition reaction step of the amino alcohol to the ethynyl derivative **6**. In view of this failure, we turned our interest to the preparation of model **4** designed so as to maintain the structural features defined for the chiral auxiliary and to exhibit greater reactivity owing to the presence of methoxy groups on the annelated benzene.

2.2. Preparation of reagent 4: asymmetric reduction of methylbenzoylformate

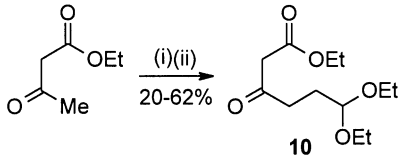
Our retrosynthetic analysis is based on a Friedlander type condensation[9] of 2-amino-4,5-dimethoxybenzaldehyde **9**[10] with an appropriate β-ketoester **10**. The crux of this reaction scheme is the realisation of β-ketoester **10**. Lactam **17** can be accessed from ketal **12** by reductive amination of the corresponding deprotected aldehyde followed by cyclization of the amino ester intermediate (Scheme 4).

Among the numerous methods available[11] for the synthesis of β-ketoester derivatives, our choice was the De Milo synthesis[11e] relying upon condensation of the dianion of ethyl acetoacetate with the iodoketal **11** (Scheme 5). Attempts to use the more available bromo derivative in this condensation were unsuccessful leading in all cases to the starting materials. This probably is due to the decreased leaving ability of the bromine atom.[12] Despite our efforts to get high and reproducible yields of the β-ketoester **10**, we were only able to realise modest yields, 20–62% range under the conditions described in Scheme 5. It was found that the reproducibility of this reaction was highly dependent on the quality of HMPA.

Thereafter, we also explored the Friedlander condensation with the isolated amine **9** in the presence of Na_2CO_3 in ethanol which afforded the desired quinoline in only 40%



Scheme 4. Retrosynthetic analysis of model 4.

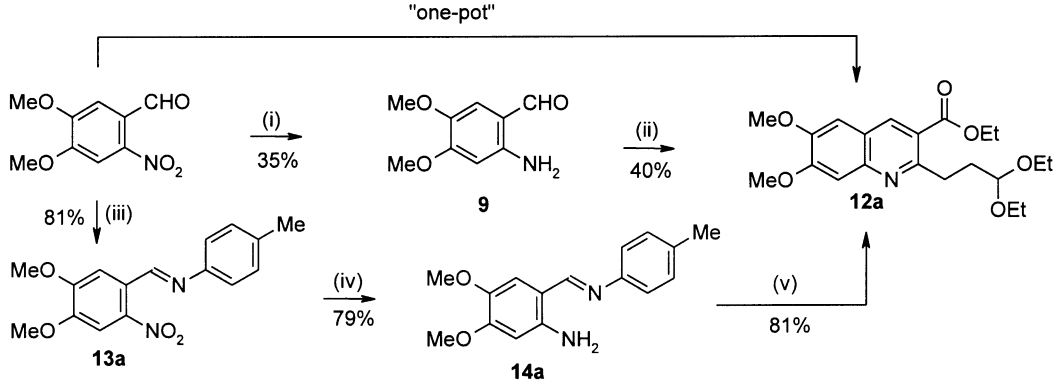


Scheme 5. (i) (1) NaH (1 equiv.)/*n*-BuLi, (2) HMPA; (ii) $ICH_2CH(OEt)_2$ (**11**).

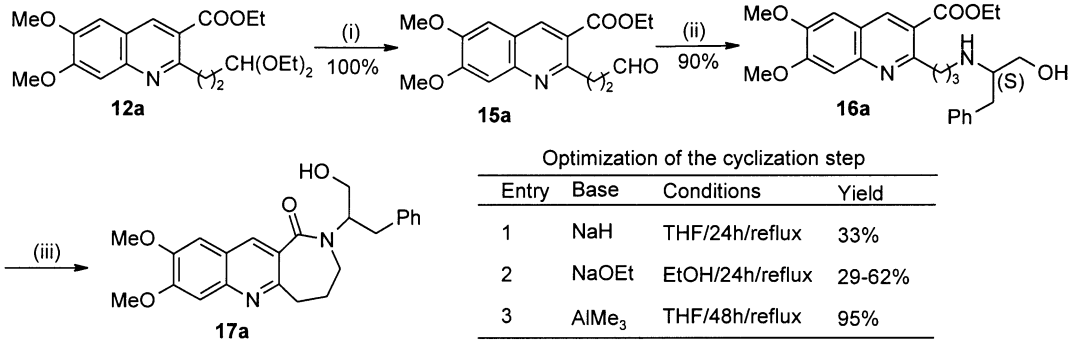
yield. The amine **9** was previously obtained with a modest yield (35%) by reduction of the corresponding nitro derivative with sodium dithionite.[10] Attempt to use a one pot procedure from the nitroaldehyde did not improve the overall yield of this sequence. The poor stability of *ortho*-aminobenzaldehydes owing to the occurrence of autocondensation reactions[13] prompted us to test the Borsche modification.[14] In a first step, the nitroaldehyde was converted into a nitroimine **13a** (81%) and subsequently reduced by Na_2S[15] to furnish imine **14a** (79%). The stable amino imine **14a** (79%) was condensed with β-ketoester **10** to produce the required quinoline **12a** in high yield (81%) (Scheme 6).

The last part of the synthesis concerns the construction of the lactam moiety (Scheme 7). The chemoselective deprotection of the ketal was realised with formic acid[16] followed by reductive amination.[17] The resulting crude amine **16a** was utilised in the lactamization step without further purification. When cyclization was carried out under basic conditions, lactam **17a** was obtained in poor yields (entries 1 and 2). Alternatively, the use of a large excess of Me_3Al[18] promoted the formation of the corresponding aluminium amide which was subsequently cyclized to give lactam **17a** in greater than 95% yield (entry 3).

The remaining steps for the transformation of **17a** to the target reagent **4** are shown in Scheme 8. Although, quaternization of quinoline **8** proceeded smoothly with methyl iodide in acetonitrile, under the same conditions, quinoline



Scheme 6. (i) $Na_2S_2O_4/Na_2CO_3$; (ii) Na_2CO_3/**10**/EtOH–H_2O (1:1); (iii) *p*-toluidine/EtOH/reflux; (iv) Na_2S/EtOH; (v) **10**/piperidine/EtOH/reflux.



Optimization of the cyclization step

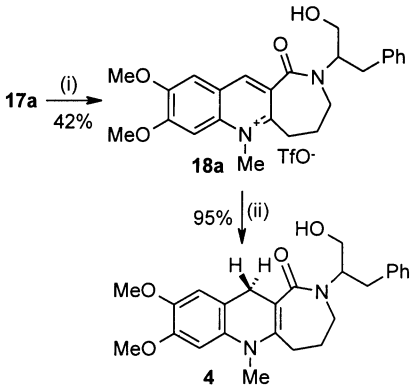
Entry	Base	Conditions	Yield
1	NaH	THF/24h/reflux	33%
2	NaOEt	EtOH/24h/reflux	29-62%
3	$AlMe_3$	THF/48h/reflux	95%

Scheme 7. (i) HCOOH/rt/2 h; (ii) (1) (*S*)-pheynylalaninol/EtOH, (2) $NaBH_4$/rt; (iii) see Table 1.

Table 1. Asymmetric reduction of methyl benzoylformate with model **4**

Entry	$[Mg^{2+}]$	Conversion %[a]	ee%[b]
1	0	0	–
2	0.25	67	92 (*R*)
3	0.5	100	95 (*R*)
4	0.75	100	89 (*R*)
5	1	100	86 (*R*)
6	2	100	73 (*R*)
7	3	100	66 (*R*)
8	4	100	60 (*R*)

[a] Calculated from ^{1}H NMR spectrum.
[b] Determined by HPLC with a Daicel Chiralcel OD column.



Scheme 8. (i) $MeOTf/CH_2Cl_2/rt/1$ h; (ii) $Na_2S_2O_4/Na_2CO_3/CHCl_3/H_2O$.

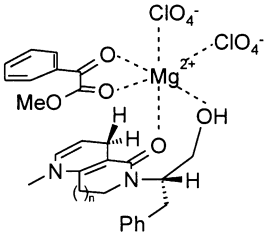


Figure 3. Proposed ternary complex (model/Mg^{2+}/substrate) of models bearing aminoalcohol as chiral auxiliary.

17a afforded quinolinium **18a** along with tarry material. Various attempts to isolate **18a** from the crude product were unsuccessful. The reaction of **17a** with other methylating agents was examined. Similarly, after two weeks in refluxing acetonitrile in the presense of methyl *p*-toluenesulfonate as methylating agent, the ^{1}H NMR spectrum of the crude product revealed the presence of quinolinium salt **18a** which was then isolated after flash chromatography in 25% yield together with some tarry material. However, we were able to improve both the reaction time and the yield using the strong methylating agent methyl trifluoromethanesulfonate, which afforded quinolinium **18a** in 42% yield after 1 h at room temperature. The quantitative and regioselective reduction of **18a** was realised by sequential addition of a large excess of sodium dithionite and sodium carbonate leading to model **4** in almost quantitative yield (Scheme 8).

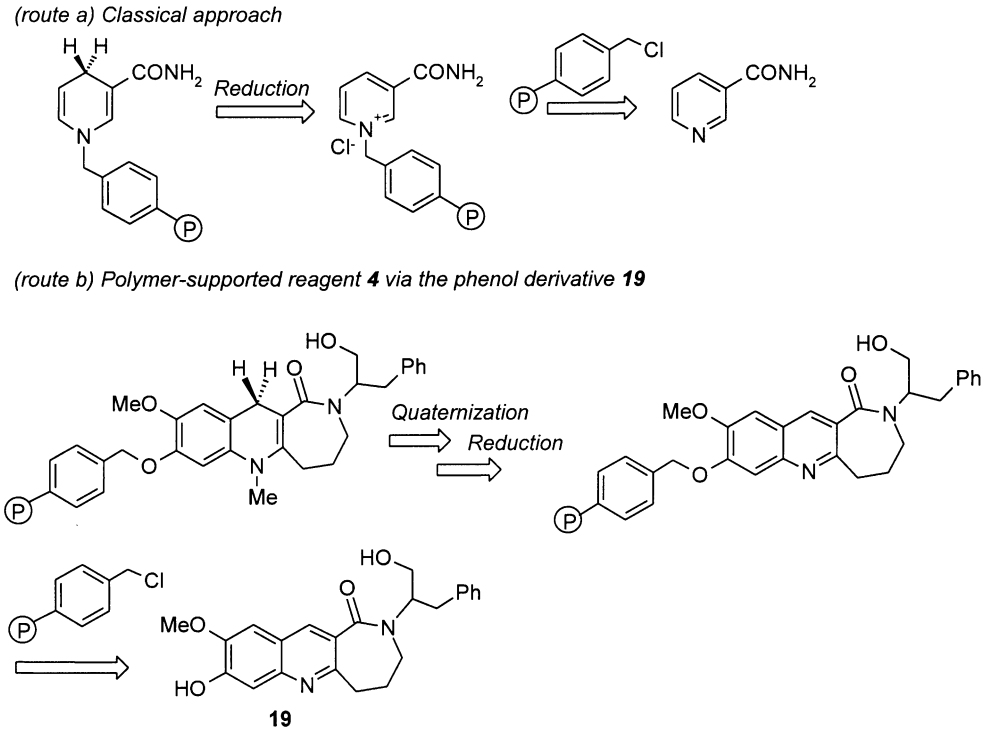
Furthermore, we studied the potential of model **4** as an asymmetric reducing agent. Reduction with NADH models are generally performed in the presence of magnesium ions, which play a fundamental role in the hydride equivalent transfer.[1] A ternary complex would be established between the model, Mg^{2+} ions and the substrate (generally methyl benzoylformate). Previously, we have suggested the ternary complex depicted in Fig. 3 to account for the enantioselection observed during reduction of methyl benzoylformate. In this complex, Mg^{2+} ions would be highly coordinated with the amide and alcohol functions of the model and with the ketone and ester functions of the substrate to give rise to (*R*)-methyl mandelate.[5]

With respect to model **4**, the presence of methoxy groups on the annelated benzene ring offer additional sites for chelation, which can compete with the amide and alcohol functions in coordination with Mg^{2+}. Consequently, it was of interest to test model **4** in the presence of various amounts of Mg^{2+} ions, the results are summarized in Table 1. The best degree of stereoselectivity (entry 3) is as high as that obtained with model **2**. As expected, addition of two electron-donating groups improved the reactivity of the model. The best enantioselectivity was observed at 0.5 equiv. of magnesium ions (entry 3) and decreased to 60% ee with 4 equiv. of magnesium ions (entry 8). There has been very little mentioned in literature on variation of the enantioselectivity as a function of magnesium ion concentration.[19] The phenomenon was not observed with model **2** and strongly suggests an important contribution of the methoxy groups in the stereochemical outcome of the reduction at high Mg^{2+} concentration. This phenomenon may be ascribed to a competitive complexation of Mg^{2+} with the methoxy groups leading to a poor enantioselective ternary complex at higher Mg^{2+} concentration. Interestingly, the quinolinium salt **18a** formed during the reaction could be recovered in good yield. After reduction with sodium dithionite, the recycled model **4** exhibited the same performance in terms of reactivity and stereoselectivity during the reduction of methyl benzoylformate.

The high stability of model **4** makes this reagent a good candidate to develop the preparation of polymer-supported NADH model with intent to facilitate their recycle. In a first approach, we have focused on the grafting of these stable NADH models on insoluble Merrifield resins.

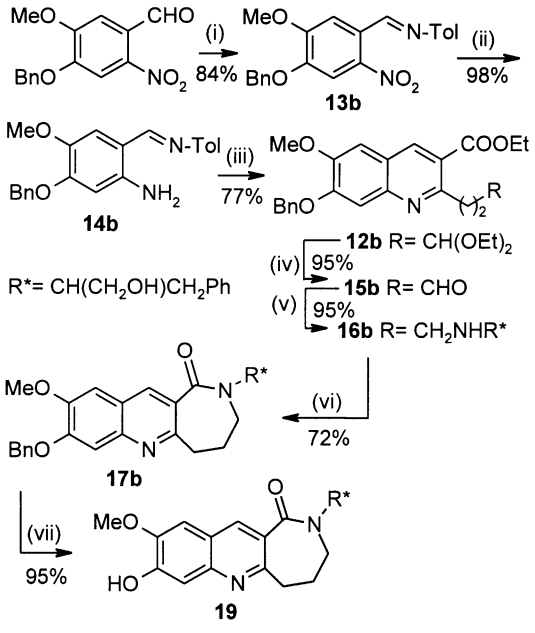
2.3. Preparation of polymer-supported reagent 4

Polymer-supported NADH models have been previously reported by our laboratory[20] and others.[21] The methodologies described in the literature are mostly based on quaternization of the pyridine nitrogen using chloromethylated polystyrenes (Scheme 9, route a). Due to steric hindrance at the nitrogen in compound **17a**, significant decrease effect in reactivity towards the quaternization step was observed. The poor reactivity of **17a** led us to develop a new route to attach reagent **4** on a Merrifield resin. Given that phenol derivatives have been shown to react readily with chloromethylated polystyrenes,[22] an alternative strategy would therefore consist in reacting the phenolic compound **19** with Merrifield resins prior to quaternization and reduction steps (Scheme 9, route b).



Scheme 9.

Consequently, we undertook the synthesis of **19** following the same reaction sequence as that employed for the preparation of compound **17a** (Scheme 10). The imine **13b** was obtained in 84% yield by reacting the corresponding *ortho*-nitrobenzaldehyde with *p*-toluidine. The phenol function, having been protected as its benzyl ether, is expected to be stable in the reaction sequence delineated. Reduction of **13b** was accomplished in 98% yield. Friedlander condensation of the resulting amine **14b** with β-ketoester **10** occurred smoothly under mild conditions leading to the quinoline **12b** in 77% yield, which was subsequently treated with formic acid to generate the aldehyde **15b** in almost quantitative yield. Reductive amination of **15b** with (*S*)-phenylalaninol afforded **16b** in 95% overall yield. Cyclization of **16b** afforded the desired lactam **17b** in 72% yield. Hydrogenolytic cleavage of the *O*-benzyl moiety furnished **19** in 95% yield.

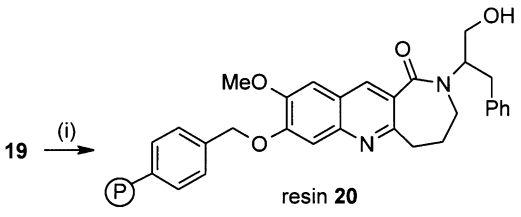


Scheme 10. (i) *p*-toluidine/EtOH/reflux; (ii) Na_2S/EtOH; (iii) **10**/piperidine/EtOH/reflux; (iv) HCOOH/rt/2 h; (v) (1) (*S*)-pheynylalaninol/EtOH, (2) $NaBH_4$/rt; (vi) NaOEt/EtOH/reflux/24 h; (vii) H_2/Pd–C/MeOH/24 h/rt.

Compound **19** was reacted with Merrifield resin (1% DVB, f_o=2–2.5 mmol) in DMF for 4 days at room temperature mediated by K_2CO_3 to yield the functionalised resin **20** with a loading of 0.74 mmol of compound **19**/g (estimated by elementary analysis) (Scheme 11).

To obtain further structural elucidation, a ^{13}C gel-phase NMR spectrum of the resin **20** was determined. The spectrum was compared to that of compound **17b**, which clearly indicated that the grafting was successful at the phenol function (Fig. 4).

The functionalised resin **20** was then treated with methyl trifluoromethanesulfonate in CH_2Cl_2 for 8 h at room temperature. Although the ^{13}C gel-phase NMR experiments



Scheme 11. (i) Merrifield resin (1% DVB; 2–2.5 mmol of chloromethyl groups/g of resin)/DMF/K_2CO_3/4 days.

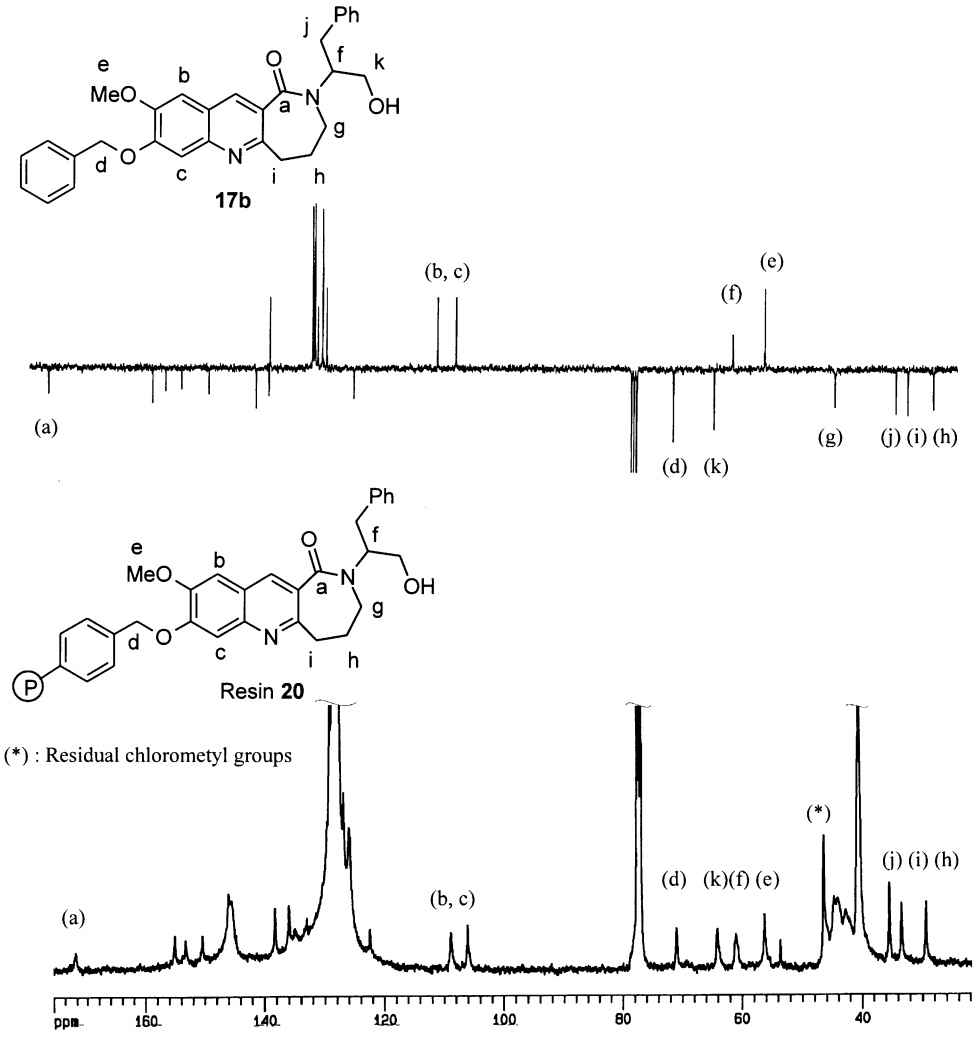
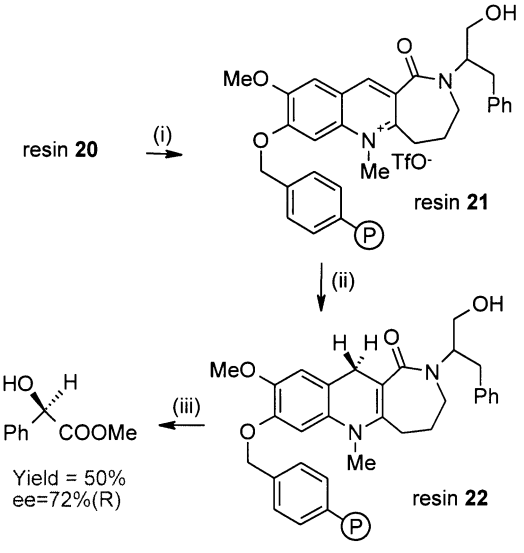


Figure 4. ^{13}C gel-phase NMR spectra of resin **20** in comparison with ^{13}C NMR spectra of **17b** in $CDCl_3$.

with the resulting resin **21** gave poor quality spectra, nonetheless some useful information were clearly distinctive. It was observed that the carbonyl lactam chemical shift in resin **21** (166.5 ppm) is much more shielded than that of resin **20** (172 ppm). Given that the same shielding is observed in compound **18a** (166.7 ppm) during the quaternization of compound **17a** (171.6 ppm), it can then be concluded that under those conditions, quaternization proceeded with resin **20**. Supporting evidence for quaternization may be deduced from the ^{19}F gel-phase NMR spectrum of resin **21** which features a single signal at −78.5 ppm corresponding to quinolinium triflate anion. We then went to examine the reduction step by reacting resin **21** with *N*-benzyl-1,4-dihydronicotinamide according to a literature procedure.[21] Having obtained resin **22**, asymmetric reduction of methyl benzoylformate was carried out in the presence of $Mg(ClO_4)_2$ in a mixture of acetonitrile–benzene (1:2). Under the conditions specified in Scheme 12, methyl mandelate was obtained in 50% yield and 72% ee (*R*). Resin **22** afforded modest results in terms of chemical yield and stereoselectivity in comparison with those obtained with reagent **4** in homogenous conditions. The low chemical yield obtained suggests either that the reduction of polymer-supported quinolinium salt **18a** was incomplete or that a large number of functional groups are



Scheme 12. (i) $TfOMe/CH_2Cl_2$/rt/8 h; (ii) *N*-benzyl-1,4-dihydronicotinamide/C_6H_6/CH_3CN (2:1)/rt/48 h; (iii) Methyl benzoylformate/C_6H_6/CH_3CN (2:1)/rt/48 h.

inaccessible to methyl benzoylformate. Accordingly, these primary results might be improved by the use of a spacer between the polymeric matrix and the reagent to increase the accessibility of the model (Scheme 12).

3. Conclusion

The rational design of new NADH models based on a biomimetic approach led us to prepare reagents **3** and **4**, both of which showed high degree of enantioselectivity in the course of the reduction of methyl benzoylformate. The presence of methoxy groups in reagent **4** improved the reactivity of these annelated models and is probably responsible for the high dependence of the stereoselectivity on magnesium ion concentration. The second aspect of this work aimed to obtain polymer-supported NADH models. In this respect, the good stability of annelated models and the possibility to recover the corresponding quinolinium salt, makes this class of reagents of particular interest. To this end, the grafting of model **4** to a Merrifield resin was successfully achieved by an original approach from phenol derivative **19**. The resulting resin **22** was involved with modest success in the reduction of methyl mandelate.

4. Experimental

4.1. General

The infrared spectra were recorded on a Beckmann IR 4250 spectrometer. The ^{1}H 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 chromatographies were performed with silica 60 (70–230 mesh from Merck) and monitored by thin layer chromatography (TLC) with silica plates (Merck, Kieselgel 60 F_{254}). The following compounds were prepared by literature methods: 4-benzyloxy-3-methoxybenzaldehyde,[23] 4,5-dimethoxy-2-nitrobenzaldehyde.[24]

4.1.1. 2-Chloroquinoline-3-carbonitrile (5). Quinoline-3-carbonitrile (3.0 g, 19 mmol) was dissolved in dichloromethane (20 mL). A solution of *m*-chloroperbenzoic acid (3.6 g, 21 mmol) in dichloromethane (35 mL) was then added dropwise. The mixture was stirred for 30 min at 40°C and a solution of *m*-chloroperbenzoic acid (1.95 g, 11 mmol) in dichloromethane (20 mL) was then added. Stirring was maintained 24 h at 40°C. After cooling at room temperature, water (50 mL) was added, the aqueous phase was basified with sodium carbonate, then extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), the solvent was evaporated leading to the crude *N*-oxide which was used without further purification. A sample of the *N*-oxide was recrystallized from ethanol to afford a brown solid. Mp 106°C. IR (KBr) 2235 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.77 (d, J=8.5 Hz, 1H); 8.62 (d, J=1.3 Hz, 1H); 8.07 (s, 1H); 7.99–7.76 (m, 3H). Anal. calcd for $C_{10}H_6N_2O$: C, 70.58; H, 3.52; N, 16.45. Found: C, 70.2; H, 3.5; N, 16.3. To the above crude *N*-oxide (1 g) was introduced freshly distilled phosphorus oxychloride (5 mL). The mixture was heated to reflux for 12 h, and the excess of reagent was removed under vacuum. Ice was cautiously added and the resulting solution was neutralized with potassium carbonate. The resulting precipitate was filtered, dried and purified by sublimation at 90°C under 1 Torr. The overall yield for the two steps was 55%. White solid. Mp 160°C (lit.[25]). IR (KBr): 2231 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H); 8.10 (d, J=8.4 Hz, 1H); 7.99–7.68 (m, 3H). Anal. calcd for $C_{10}H_5ClN_2$: C, 63.68; H, 2.65; N, 14.85. Found: C, 63.7; H, 2.6; N, 14.8.

4.1.2. 2-Ethynylquinoline-3-carbonitrile (6). Cuprous iodide (0.16 g, 0.84 mmol) was dissolved in triethylamine (4 mL) at 40°C in a flask flushed with argon. Trimethylsilylacetylene (0.17 mL, 1.2 mmol) was added at room temperature. The mixture was stirred for 10 min and bis(triphenylphosphine)palladium (II) chloride (0.3 g, 0.42 mmol) was added. After 10 min at room temperature, 2-chloroquinoline-3-carbonitrile freshly purified by sublimation (1.7 g, 9 mmol), triethylamine (10 mL) and trimethylsilylacetylene (1.7 mL, 12 mmol) were added. The mixture was stirred at 100°C for 12 h. After cooling, volatile products were eliminated under reduced pressure. The residue was extracted with Et_2O (4×30 mL). The ethereal extract was concentrated under reduced pressure. The resulting dark residue was dissolved in THF (50 mL) and a solution of 0.1 M aqueous NaOH (45 mL) was added. After 2 h stirring, evaporation of THF formed a precipitate, which was filtrated. The aqueous phase was extracted with Et_2O (3×30 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, giving a residue, which was combined with the above precipitate. After purification by chromatography on silica gel (eluent: CH_2Cl_2/EtOH, 95:5), compound **6** was obtained in 69% yield from **5**. White solid. Mp 202°C. IR (KBr) 2231 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H); 8.19 (d, J=8.5 Hz, 1H); 7.99–7.90 (m, 2H); 7.74 (t, J=7.1 Hz, 1H); 3.60 (s, 1H). Anal. calcd for $C_{12}H_6N_2$: C, 80.88; H, 3.39; N, 15.72. Found: C, 80.7; H, 3.3; N, 15.6.

4.1.3. 2-[(*S*)-2-Benzyl-1-hydroxyethyl]-1-oxo-1,2,3,4-tetrahydrobenzo[1,3-b]naphthyridine (8). A solution of compound **6** (1.8 g, 10 mmol) and (*S*)-phenylalaninol (1.66 g, 11 mmol) in THF (35 mL) was heated to reflux for 24 h. After evaporation of the solvent, the residue was dissolved in methanol (50 mL) and treated with sodium cyanoborohydride (1.3 g, 20 mmol) and zinc chloride (1.4 g, 10 mmol). After stirring at room temperature for 1 h, sodium cyanoborohydride (0.65 g, 10 mmol) and zinc chloride (0.7 g, 5 mmol) were added. The resulting solution was stirred for a further 1 h at this temperature. After addition of sodium hydroxide (50 mL, 0.1 M aqueous solution), the aqueous phase was extracted with dichloromethane (3×30 mL). The organic phase was dried ($MgSO_4$) and evaporated to afford compound **7** as oil, which was used in the next step without further purification. Compound **7**. ^{1}H NMR ($CDCl_3$) δ 8.47 (s, 1H); 8.05–7.40 (m, 4H); 7.23–7.02 (m, 5H); 3.81–3.62 (m, 2H); 3.55–3.00 (m, 7H); 2.88–2.70 (m, 2H). The oily residue was refluxed for 48 h in a 95:5 mixture of ethanol/water (20 mL). After evaporation of ethanol, the obtained solid was purified by chromatography

on silica gel (eluent: CH_2Cl_2/EtOH, 95:5). Overall yield from **6**: 52%. Yellow solid. Mp 157°C. IR (KBr): 1630 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H); 8.02–7.45 (m, 4H); 7.29–7.10 (m, 5H); 4.95–4.80 (m, 1H); 4.01–3.90 (m, 2H); 3.65–3.53 (m, 2H); 3.20–3.00 (m, 4H). Anal. calcd for $C_{21}H_{20}N_2O_2$: C, 72.32; H, 6.42; N, 9.92. Found: C, 72.2; H, 6.4; N, 10.0.

4.1.4. 5-Methyl-2-[(*S*)-2-benzyl-1-hydroxyethyl]-1-oxo-1,2,3,4,5,10-hexahydrobenzo[1,6-b]naphthyridine (3). A solution of compound **8** (1.32 g, 4 mmol) in acetonitrile (5 mL) and methyl iodide (5 mL, 80 mmol) was refluxed for 12 h. After evaporation of the solvent, Et_2O was added. The resulting suspension was stirred for 2 h. The precipitate was filtered, washed with Et_2O and dried ($MgSO_4$) affording the quinolinium salt. ^1H NMR (DMSO-d_6) δ 9.59 (s, 1H); 8.59 (d, J=9.0 Hz, 2H); 8.30 (t, J=7.1 Hz, 1H); 8.02 (t, J=7.1 Hz, 1H); 7.28–7.20 (m, 5H); 5.00–4.90 (m, 1H); 4.42 (s, 3H); 3.72–3.40 (m, 6H); 2.97–2.92 (m, 2H). The crude salt (0.330 g, 0.7 mmol) was dissolved in a solution of degassed ethanol (4 mL) and water (10 mL). Sodium dithionite (0.685 g, 4 mmol) and sodium carbonate (0.295 g, 2.8 mmol) were then added and the mixture stirred under argon for 45 min. Addition of the same amounts of sodium dithionite and sodium carbonate were repeated twice at 30 min intervals. Finally, the aqueous phase was extracted with dichloromethane (3×10 mL). After evaporation, the oily residue was kept in the dark. Due to instability reagent **3** was not further purified. Yield 70%. ^1H NMR ($CDCl_3$) δ 7.22 (m, 7H); 6.98 (d, 1H); 6.87 (d,1H); 4.26 (m, 1H); 3.92–3.72 (m, 4H); 3.36–3.02 (m, 2H); 3.12 (s, 3H); 2.32 (t, 3H).

4.1.5. 3,4-Dimethoxy-6-aminobenzaldehyde (9). In a solution of 3,4-dimethoxy-6-nitrobenzaldehyde[10] (0.422 g, 2 mmol) in methanol (25 mL) was introduced a solution of sodium carbonate (0.424 g, 4 mmol) and sodium dithionite (0.696 g, 4 mmol) in water (15 mL). After 30 min, a solution of sodium dithionite (0.0696 g, 4 mmol) in water (10 mL) was added. The solution became orange. After 1 h at room temperature, the solution was extracted with dichloromethane (3×20 mL). The organic phases were dried and concentrated under reduced pressure. The product was not further purified. Orange oil. Yield 35%. ^1H NMR ($CDCl_3$) δ 9.63 (s, 1H); 6.62 (s, 1H); 6.09 (brs, 3H); 3.83 (s, 3H), 3.80 (s, 3H).

4.1.6. Ethyl-6,6-diethoxy-3-oxohexanoic acid (10). In a flask, flushed with argon and cooled at 0°C, was introduced sodium hydride (0.850 g, 21 mmol, 60% dispersion in oil) in anhydrous THF (100 mL). Ethyl acetoacetate (2.7 mL, 21 mmol) was added dropwise, followed by a solution of *n*-BuLi in hexane (2.5 M, 8.5 mL, 21 mmol). Stirring was maintained for 15 min and hexamethylphosphoramide (11.1 mL, 63 mmol) was then added. After 20 min, 1,1-diethoxy-2-iodoethane **11** (5.185 g, 21 mmol) was added. The mixture was stirred at room temperature for 12 h and an aqueous saturated solution of ammonium chloride (20 mL) was slowly added. After evaporation of THF, the residue was taken into water, then extracted with ethyl acetate (4×100 mL). The combined organic phases were washed with water and a saturated solution of sodium chloride. After drying and evaporation to dryness, the remaining oil was distilled (Kugelrohr). The fraction of $bp_{0.5}$=120°C was finally purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 95:5) leading to 2.82 g of **10** (yellow oil). Yield 69%. IR: 1745, 1716 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.47 (t, J=5.3 Hz, 1H); 4.17 (q, J=7.1 Hz, 2H); 3.69–3.37 (m, 6H); 2.61 (t, J=7.1 Hz, 2H); 1.90 (dt, J=7.1 and 5.3 Hz, 2H); 1.25 (t, J=7.1 Hz, 3H); 1.16 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 203.1; 167.9; 102.5; 62.4; 62.0; 50.0; 38.5; 28.3; 15.9; 14.75. Anal. calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.3; H, 8.6.

4.1.7. 1,1-Diethoxy-2-iodoethane (11). To a solution of 1,1-diethoxy-2-bromoethane (20 g, 100 mmol) in acetone (200 mL) was added sodium iodide (30.4 g, 200 mmol). The solution was stirred at room temperature for 5 days. The resulting precipitate was filtrated and washed with acetone (100 mL). Acetone was evaporated and the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 95:5) leading to 22.4 g of **11** (colourless oil). Yield 91%. IR: 2975, 2879, 1122, 1056, 1005 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.55 (t, J=5.5 Hz, 1H); 3.70–3.42 (m, 4H); 3.14 (d, J=5.5 Hz, 2H); 1.17 (t, J=7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 101.46; 61.93; 14.97; 5.44. Anal. calcd for $C_6H_{13}IO_2$: C, 29.53; H, 5.37. Found: C, 29.71; H, 5.24.

4.1.8. 6-(*p*-Tolylaminomethylidene)-3,4-dimethoxynitrobenzene (13a). In a flask were introduced 3,4-dimethoxy-6-nitrobenzaldehyde (8.44 g, 40 mmol), *p*-toluidine (4.98 g, 40 mmol) and ethanol (250 mL). The mixture was refluxed for 2 h under stirring. After cooling at 0°C, compound **13a** was isolated by filtration and dried under vacuum. Yield 9.75 g (81%). Yellow solid. Mp 147°C (lit.[26] 131°C). IR (KBr): 1567; 1519; 1329; 1286 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.04 (s, 1H); 7.78 (s, 1H); 7.62 (s, 1H); 7.22 (s, 4H); 4.08 (s, 3H); 4.01 (s, 3H); 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 155.2; 153.1; 150.4; 148.6; 142.5; 136.7; 129.8; 126.0; 121.1; 109.85; 107.3; 56.6; 56.5; 21.0. Anal. calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.8; H, 5.4; N, 9.5.

4.1.9. 6-(*p*-Tolylaminomethylidene)-3-benzyloxy-4-methoxynitrobenzene (13b). Compound **13b** was prepared in the same manner as compound **13a**, from 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde (5.74 g, 20 mmol) and *p*-toluidine (2.14 g, 20 mmol) in ethanol (300 mL). Yield 6.32 g (84%). Yellow solid. Mp 147°C (ethanol). IR (KBr): 1570; 1517; 1327; 1283 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.04 (s, 1H); 7.79 (s, 1H); 7.69 (s, 1H); 7.47–7.39 (m, 5H); 7.23 (s, 4H); 5.26 (s, 2H); 4.08 (s, 3H); 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 155.25; 153.62; 149.4; 148.6; 142.2; 136.7; 135.25; 129.8; 128.8; 128.4; 127.5; 126.2; 121.15; 110.1; 109.15; 71.3; 56.6; 21.0. Anal. calcd for $C_{22}H_{20}N_2O_4$: C, 70.18; H, 5.35; N, 7.44. Found: C, 70.2; H, 5.4; N, 7.4.

4.1.10. 6-(*p*-Tolylaminomethylidene)-3,4-dimethoxyaniline (14a). A solution of compound **13a** (6 g, 20 mmol) in ethanol (200 mL) was heated to reflux. To the hot solution, sodium sulfide nonahydrate (10.57 g, 44 mmol) was added. After a few minutes, a vigorous reaction occurred and the heating was maintained for 10 min. After cooling at 0°C for 4 h, the precipitate was filtered. The remaining solution was

concentrated under reduced pressure. Water (100 mL) was added to the residue and a new crop of precipitate was obtained. Yield 79%. Mp 123°C (ethanol) (lit.[26] 115°C). IR (KBr): 3346; 1626; 1557; 1507; 1272 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H); 7.14 (m, 4H); 6.81 (s, 1H); 6.43 (brs, 2H); 6.24 (s, 1H); 3.90 (s, 3H); 3.85 (s, 3H); 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 161.05; 152.7; 149.5; 144.9; 140.5; 134.7; 129.6; 120.6; 116.2; 109.8; 99.0; 56.55; 55.7; 20.8. Anal. calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.1; H, 6.7; N, 10.4.

4.1.11. 6-(*p*-Tolylaminomethylidene)-3-benzyloxy-4-methoxyaniline (14b). Compound **14b** was prepared in the same manner as compound **14a**, from compound **13b** (3.76 g, 10 mmol) and sodium sulfide nonahydrate (5.28 g, 22 mmol) in ethanol (250 mL). Yield 98%. Mp 141°C (ethanol). IR (KBr): 3428; 1623; 1598; 1547; 1507 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H); 7.46–7.33 (m, 5H); 7.22–7.08 (m, 4H); 6.86 (s, 1H); 6.37 (brs, 2H); 6.26 (s, 1H); 5.19 (s, 2H); 3.87 (s, 3H); 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 161.1; 152.1; 149.5; 144.6; 141.0; 136.5; 134.7; 129.6; 128.5; 127.9; 127.1; 120.7; 117.3; 110.2; 100.95; 70.42; 57.0; 20.9. Anal. calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.0; H, 6.4; N, 8.03.

4.1.12. Ethyl-2,2-(3,3-diethoxypropyl)-6,7-dimethoxyquinoline-3-carboxylate (12a). To a solution of compound **14a** (5.94 g, 20 mmol) and compound **10** (4.92 g, 20 mmol) in ethanol (200 mL) was added a few drops of piperidine. The resulting solution was refluxed for 24 h. After cooling and evaporation of the solvent, the residue was purified by chromatography on neutral alumina (eluent: petroleum ether/ethyl acetate, 90:10) affording 6.30 g (81%) of compound **12a**. White powder. Mp 88°C (cyclohexane). IR (KBr): 1717 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.57 (s, 1H); 7.38 (s, 1H); 7.08 (s, 1H); 4.69 (t, J=7.1 Hz, 1H); 4.43 (q, J=7.1 Hz, 2H); 4.06 (s, 3H); 4.02 (s, 3H); 3.78–3.32 (m, 6H); 2.20–2.09 (m, 2H); 1.45 (t, J=7.1 Hz, 3H); 1.21 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.8; 159.25; 154.1; 149.7; 146.1; 138.0; 121.8; 121.05; 107.4; 105.4; 102.7; 61.15; 60.8; 56.2; 56.0; 33.3; 32.9; 15.3; 14.3. Anal. calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.6; H, 7.5; N, 3.5.

4.1.13. Ethyl-2,2-(3,3-diethoxypropyl)-6-methoxy-7-benzyloxyquinoline-3-carboxylate (12b). Compound **12b** was prepared in the same manner as compound **12a**, from **14b** (3.46 g, 10 mmol), **10** (2.71 g, 11 mmol) and a few drops of piperidine in ethanol (200 mL). Chromatography on neutral alumina (eluent: petroleum ether/ethyl acetate, 75:25) afforded 3.6 g (77%) of compound **12b**. Beige powder. Mp 93°C (cyclohexane). IR (KBr): 1714 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.56 (s, 1H); 7.52–7.29 (m, 6H); 7.10 (s, 1H); 5.31 (s, 2H); 4.67 (t, J=7.1 Hz, 1H); 4.42 (q, J=7.1 Hz, 2H); 4.00 (s, 3H); 3.78–3.33 (m, 6H); 2.18–2.08 (m, 2H); 1.44 (t, J=7.1 Hz, 3H); 1.20 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.85; 159.20; 153.3; 150.1; 146.0; 138.0; 135.95; 128.65; 128.15; 127.45; 121.9; 121.2; 108.8; 105.6; 102.8; 70.75; 61.2; 60.9; 56.1; 33.3; 32.9; 15.35; 14.3. Anal. calcd for $C_{27}H_{33}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.2; H, 7.1; N, 3.2.

4.1.14. Ethyl-2-(2-formylethyl)-6,7-dimethoxyquinoline-3-carboxylate (15a). A solution of **12a** (5.87 g, 15 mmol) in formic acid (100 mL) was stirred 2 h at room temperature. The mixture was evaporated to dryness and dichloromethane (50 mL) and water (50 mL) were added to the resulting residue. The aqueous phase was neutralized with sodium hydrogenocarbonate. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2×50 mL). The combined organic phases were dried and concentrated leading to crude **15a**, which was not further purified. Yield 100%. Yellow solid. Mp 98°C. IR (KBr): 1712 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.97 (t, J=1.5 Hz, 1H); 8.61 (s, 1H); 7.31 (s, 1H); 7.08 (s, 1H); 4.42 (q, J=7.1 Hz, 2H); 4.05 (s, 3H); 4.01 (s, 3H); 3.69 (t, J=7.1 Hz, 2H); 2.97 (td, J=7.1 and 1.5 Hz, 2H); 1.44 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 202.1; 166.4; 157.1; 154.3; 149.9; 145.85; 138.2; 121.1; 107.3; 105.4; 61.2; 56.2; 56.0; 41.5; 30.3; 14.3. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.1; H, 6.0; N, 4.4.

4.1.15. Ethyl-2-(2-formylethyl)-6-methoxy-7-benzyloxyquinoline-3-carboxylate (15b). Compound **15b** was prepared in the same manner as compound **15a**, from **12b** (4.67 g, 10 mmol) and formic acid (150 mL). Yield 95%. Yellow solid. ^1H NMR ($CDCl_3$) δ 9.97 (t, J=1.5 Hz, 1H); 8.61 (s, 1H); 7.53–7.34 (m, 6H); 7.10 (s, 1H); 5.29 (s, 2H); 4.42 (q, J=7.1 Hz, 2H); 4.00 (s, 3H); 3.69 (t, J=7.1 Hz, 2H); 2.96 (td, J=7.1 and 1.5 Hz, 2H); 1.44 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 198.4; 166.3; 157.1; 153.7; 150.35; 145.5; 138.4; 135.8; 128.65; 128.2; 127.5; 121.3; 121.2; 108.4; 105.7; 70.85; 61.25; 56.1; 41.3; 30.4; 14.3.

4.1.16. Ethyl 2-{[*N*((*S*)-1-hydroxy-3-phenyl)prop-2-yl]-3-aminopropyl}-6,7-dimethoxyquinoline-3-carboxylate (16a). A solution of aldehyde **15a** (3.17 g, 10 mmol) and (*S*)-phenylalaninol (1.51 g, 10 mmol) in ethanol (75 mL) was stirred at room temperature for 45 min. After cooling at 0°C, sodium borohydride (0.416 g, 10 mmol) was added. The solution was then stirred at room temperature for a further 45 min. A mixture of water (50 mL) and dichloromethane (50 mL) was then added, and the aqueous phase was neutralized by adding 1N aqueous HCl. After phase separation, the aqueous phase was extracted with dichloromethane (2×50 mL). The combined organic phases were dried, evaporated to dryness leading to 4.75 g of crude compound **16a**, which was used in the next step without further purification. IR (KBr): 1719 cm^{-1}. ^1H NMR ($CDCl_3$ 200 MHz) δ 8.53 (s, 1H); 7.55 (s, 1H); 7.17 (m, 5H); 7.02 (s, 1H); 4.40 (q, J=7.1 Hz, 2H); 4.01 (s, 6H); 3.80 (dd, J=12.5 and 5.2 Hz, 1H); 3.39 (m, 2H); 3.12 (m, 3H); 2.45 (m, 2H); 1.44 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.6; 159.6; 154.4; 149.85; 146.0; 138.6; 138.3; 129.1; 128.45; 126.25; 121.5; 121.2; 107.15; 105.4; 62.0; 61.2; 60.1; 56.3; 56.1; 46.0; 38.0; 34.8; 30.2; 14.3.

4.1.17. Ethyl 2-{[*N*((*S*)-1-hydroxy-3-phenyl)prop-2-yl]-3-aminopropyl}-6-methoxy-7-benzyloxyquinoline-3-carboxylate (16b). Compound **16b** was prepared in the same manner as compound **16a**, from **15b** (393 mg, 1 mmol), (*S*)-phenylalaninol (151 mg, 1 mmol) and sodium borohydride (38 mg, 1 mmol). The crude product (528 mg) was used in the next step without further purification. IR (KBr): 1716 cm^{-1}. ^1H NMR ($CDCl_3$ 200 MHz) δ 8.59 (s, 1H); 7.52–7.09 (m, 12H); 5.30 (s, 2H); 4.40 (q, J=7.1 Hz, 2H);

4.00 (s, 3H); 3.81–3.29 (m, 5H); 3.00–2.50 (m, 6H); 1.95 (m, 2H); 1.43 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.6; 159.4; 153.5; 150.2; 145.85; 138.6; 138.3; 135.8; 129.1; 128.6; 128.4; 128.1; 127.4; 126.2; 121.5; 121.2; 108.5; 105.6; 70.7; 61.4; 60.1; 56.05; 45.8; 37.9; 34.6; 30.0; 14.3.

4.1.18. -[(*S*)-1-Hydroxy-3-phenylprop-2-yl]-2,3,4,5-tetrahydro-8,9-dimethoxyazepino[4,3-b]quinolin-1-one (17a). In a flask flushed with nitrogen, was introduced compound **16a** (2.26 g, 5 mmol) dissolved in anhydrous THF (25 mL). After cooling at 0°C, a solution of trimethylaluminium in heptane (2 M, 25 mL, 50 mmol) was added and the mixture was refluxed for 48 h. After cooling, water was added dropwise, the resulting precipitate was filtered and washed with a mixture of dichloromethane and water (1:1). The combined organic phases were dried and concentrated under vacuum. The residue was purified by flash chromatography (neutral alumina/eluent: dichloromethane/ethanol, 95:5) leading to 1.83 g of compound **17a**. Yield 95%. Yellow solid. IR (KBr): 1622 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.28 (s, 1H); 7.36 (s, 1H); 7.29 (m, 5H); 7.08 (s, 1H); 4.69 (m, 1H); 4.03 (s, 3H); 4.01 (s, 3H); 3.91 (d, J=5.9 Hz, 2H); 3.36 (brs, 1H); 3.23–2.86 (m, 3H); 2.00 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.6; 154.8; 153.7; 149.8; 145.5; 137.95; 136.0; 128.9; 128.6; 128.05; 126.7; 122.2; 107.1; 105.55; 64.05; 61.1; 56.2; 56.1; 44.8; 35.1; 33.05; 29.1. Anal. calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.9; H, 6.4; N, 6.7.

4.1.19. 2-[(*S*)-1-Hydroxy-3-phenylprop-2-yl]-2,3,4,5-tetrahydro-8-benzyloxy-9-methoxyazepino[4,3-b]quinolin-1-one (17b). To a solution of **16b** (1.06 g, 2 mmol) in EtOH (50 mL) was added portion wise sodium (138 mg, 6 mmol). The solution was stirred at reflux for 24 h. After cooling, the solution was neutralised (pH=6–7) with a solution of 10% aqueous HCl. After addition of water (50 mL) and CH_2Cl_2 (50 mL), the organic layer was dried ($MgSO_4$). The aqueous phase was extracted twice with CH_2Cl_2 (2×25 mL). The combined organic phases were dried and the solvent evaporated under vacuum. The residue was chromatographed (neutral alumina/eluent: dichloromethane/ethanol, 95:5) affording 695 mg (72%) of lactam **17b** as a beige solid. Mp 93°C. IR (KBr): 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H); 7.50–7.27 (m, 11H); 7.07 (s, 1H); 5.29 (s, 2H); 4.72 (m, 1H); 3.99 (s, 3H); 3.89 (m, 2H); 3.13–3.05 (m, 4H); 2.83 (t, J=7.1 Hz, 2H); 1.98 (q, J=7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 171.6; 154.8; 152.7; 150.05; 145.6; 137.95; 135.9; 135.7; 128.9; 128.6; 128.5; 128.05; 127.3; 126.6; 122.2; 108.7; 105.8; 70.6; 63.8; 60.75; 56.1; 44.55; 35.1; 33.05; 29.1. Anal. calcd for $C_{30}H_{30}N_2O_4$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.5; H, 6.3; N, 5.75.

4.1.20. 2-[(*S*)-1-Hydroxy-3-phenylprop-2-yl]-2,3,4,5-tetrahydro-8-hydroxy-9-methoxyazepino[4,3-b]quinolin-1-one (19). To a solution of **17b** (804 mg, 1.7 mmol) in methanol (50 mL) was added 10% Pd/C (400 mg). The solution was stirred for 24 h at room temperature under a hydrogen atmosphere. The catalyst was filtered through a plug of cotton and washed with methanol. Evaporation of the solvent afforded 621 mg (95%) of **19** as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H); 7.27 (m, 5H); 7.14 (s, 1H); 6.78 (s, 1H); 4.82 (m, 1H); 3.92 (m, 2H); 3.81 (s, 3H); 3.37 (m, 2H); 3.11 (m, 2H); 2.64 (m, 2H); 1.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.6; 154.45; 152.4; 149.0; 144.28; 137.8; 136.4; 128.8; 128.6; 127.2; 126.7; 121.5; 107.8; 105.4; 64.0; 55.6; 35.1; 32.0; 29.65; 20.2.

4.1.21. 2-[(*S*)-1-Hydroxy-3-phenylprop-2-yl]-2,3,4,5-tetrahydro-8,9-dimethoxy-6-methyl-1-oxo-azepino[4,3-b]-quinolinium trifluoromethanesulfonate (18a). Compound **17a** (0.406 g, 1 mmol) and freshly distilled acetonitrile (5 mL) were introduced in a flask flushed with argon. Methyl trifluoromethanesulfonate (0.136 mL, 1.2 mmol) was added dropwise via a syringe and the mixture was stirred for 1 h at room temperature. After evaporation of acetonitrile under reduced pressure, the residue was purified by chromatography on neutral alumina (eluent: ethyl acetate/ethanol, 90:10) affording 0.251 g (42%) of compound **18a**. Yellow solid. IR (KBr): 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H); 7.54 (s, 1H); 7.35 (s, 1H); 7.24 (m, 5H); 4.81 (m, 1H); 4.49 (s, 3H); 4.19 (s, 3H); 4.05 (s, 3H); 3.79 (m, 2H); 3.25–2.92 (m, 7H); 2.15 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 166.7; 158.14; 154.3; 151.5; 142.5; 138.45; 137.6; 130.3; 128.8; 128.5; 126.7; 124.4; 123.6; 117.3; 107.7; 99.0; 62.3; 59.8; 57.6; 56.8; 42.4; 40.4; 34.9; 28.7; 28.4. Anal. calcd for: $C_{26}H_{29}F_3N_2O_7S$: C, 54.73; H, 5.12; N, 4.91. Found: C, 54.9; H, 5.1; N, 5.0.

4.1.22. 2-[(*S*)-1-Hydroxy-3-phenylprop-2-yl]-2,3,4,5,6,11-hexahydro-8,9-dimethoxy-6-methylazepino[4,3-b]quinolin-1-one (4). Compound **18a** (0.571 g, 10 mmol), degassed water (18 mL) and degassed chloroform (2 mL) were introduced in a flask flushed with argon, in the dark. The following procedure was repeated once: sodium dithionite (0.870 g, 5 mmol) and sodium carbonate (0.318 g, 3 mmol) were added. After 90 min, a solution of sodium dithionite (1.740 g, 10 mmol) and sodium carbonate (0.318 g, 3 mmol) in degassed water (18 mL) was added. The reaction mixture was stirred for 14 h. After phase separation, the aqueous layer was extracted with chloroform (3×50 mL). The combined organic layers were dried and concentrated to dryness to give **4** (0.422 g). Yield 95%. Yellow solid, which was not further purified before use in the reduction of a substrate. ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H); 6.60 (s, 1H); 6.40 (s, 1H); 4.51 (m, 1H); 4.12 (brs, 1H); 3.87 (s, 3H); 3.84 (s, 3H); 3.53 (s, 2H); 3.21–2.93 (m, 7H); 2.16 (m, 2H); 1.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 175.5; 147.4; 146.5; 144.5; 138.5; 135.8; 129.0; 128.5; 126.5; 116.1; 111.8; 102.05; 98.9; 64.9; 61.1; 56.3; 45.05; 35.3; 34.5; 30.4; 27.7; 24.7.

4.1.23. Polymer-supported compound 19 (resin 20). To a solution of compound **19** (350 mg, 0.9 mmol) and potassium carbonate (494 mg, 0.9 mmol) in dry DMF (10 mL) was added the chloromethylated polystyrene (300 mg, 2–2.5 mmol of chloromethyl groups/g of resin, 0.6–0.75 mmol of chloromethylated groups). The suspension was stirred at room temperature for 4 days under N_2. The resin was removed by filtration and washed successively with water/THF (1:1, 3×50 mL), CH_2Cl_2 (3×50 mL), methanol (3×50 mL) and CH_2Cl_2 (3×50 mL). Resin **20** was dried at room temperature under vacuum for at least 12 h. Weight gain: 110 mg corresponding to 0.75 mmol of compound **19**/g of resin (%N=2.07 corresponding to 0.74 mmol of compound 19/g of resin). ^{13}C gel-phase NMR (75 MHz, $CDCl_3$) δ 172.0; 155.1; 153.2; 150.4;

138.2; 137.1; 122.4; 108.8; 106.0; 70.95; 64.0; 61.0; 56.2; 35.4; 33.4; 29.4.

4.1.24. Polymer-supported quinolinium 18 (resin 21). To a suspension of resin **20** (350 mg, 0.75 mmol of compound **19**/g of resin, 0.26 mmol of **19**) in CH_2Cl_2 (10 mL) was added methyl trifluoromethanesulfonate (95 μL, 2 mequiv.). The resin was stirred at room temperature for 4 h. The polymer was filtrated and washed successively with water/THF (1:1, 3×50 mL), CH_2Cl_2 (3×50 mL), methanol (3×50 mL) and CH_2Cl_2 (3×50 mL). Resin **21** (371 mg) was dried at room temperature under vacuum for at least 12 h. ^{13}C gel-phase NMR (75 MHz, $CDCl_3$) δ 166.5 ppm. ^{19}F gel-phase NMR (188 MHz, $CDCl_3$) δ −78.5 ppm. Anal. found %N=1.71 corresponding to 0.61 mmol of quinolinium **18**/g of resin.

4.1.25. Polymer-supported model 4 (resin 22). To a solution of benzene (4 mL) and acetonitrile (2 mL), flushed with N_2, was added resin **21** (1 g, 0.61 mmol of quinolinium **18**/g of resin, 0.61 mmol) and *N*-benzyl-1,4-dihydronicotinamide (261 mg, 1.2 mmol). The suspension was stirred at room temperature for 48 h in the dark. The polymer was removed by filtration and washed successively with water/THF (1:1, 3×50 mL), CH_2Cl_2 (3×50 mL), methanol (3×50 mL) and CH_2Cl_2 (3×50 mL). Resin **22** (1 g) was dried at room temperature under vacuum for at least 12 h. Anal. found %N=1.80 corresponding to 0.65 mmol of model **4**/g of resin.

4.1.26. Reduction of methyl benzoylformate with resin 22. In a flask, flushed with argon, were introduced resin **22** (1 g, 0.65 mmol of model **4**/g of resin, 0.65 mmol), acetonitrile (3 mL), methyl benzoylformate (92 μL, 0.65 mmol) and magnesium perchlorate (145 mg, 0.65 mmol). The solution was stirred at room temperature for 24 h in the dark. The resin was removed by filtration and successively washed with acetonitrile (3×10 mL), water/THF (1:1) (2×10 mL). Organic solvents were evaporated and the resulting aqueous phase was extracted twice with CH_2Cl_2 (10 mL). After drying ($MgSO_4$) and evaporation of the solvent, the residue was chromatographed on silica gel (eluent: Et_2O/cyclohexane, 2:1). Yield 50%. Enantiomeric excesses were determined by HPLC analysis using a Chiracel OD column (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]. Enantiomeric excess: 72% (*R*).

4.1.27. Typical procedure for the reduction of methyl benzoylformate with the free models 3 and 4. In a flask, flushed with argon, were introduced model **4** (0.422 g, 1 mmol), acetonitrile (3 mL), methyl benzoylformate (142 mL, 1 mmol) and magnesium perchlorate (110 mg, 0.5 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 purified and analysed as described above. Yield 67–100%. Enantiomeric excess: 95% (*R*).

References

1. (a) Inouye, Y.; Oda, J.; Baba, N. In *Reductions with Chiral Dihydropyridine Reagents in Asymmetric Synthesis*, Morrison, J. D., Ed.; Academic: New York, 1983; vol. 2, pp 92–124. (b) Ohno, A.; Ushida, S. Mechanistic Models of Asymmetric Reductions. In *Lecture Notes in Bio-Organic Chemistry*, Baulieu, E., Jaenicke, L., Massey, V., Williams, R. J. P., Winnacker, E. L., Zerner, B., Eds.; Springer Verlag: Berlin, 1986; pp 1–105. (c) Burgess, V. A.; Davies, S. G.; Skerj, R. T. *Tetrahedron: Asymmetry* **1991**, *2*, 299–328.
2. See for example: (a) Dupas, G.; Levacher, V.; Bourguignon, J.; Queguiner, G. *Heterocycles* **1994**, *39*, 405–429. (b) Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Trends Heterocycl. Chem.* **1995**, *4*, 293–302.
3. Li, H.; Goldstein, B. *J. Med. Chem.* **1992**, *35*, 3560–3567.
4. (a) Ecklund, H.; Samama, J. P.; Jones, T. A. *Biochemistry* **1984**, *23*, 5982. (b) Skarzynski, T.; Moody, P. C. E.; Wonacott, A. J. *J. Mol. Biol.* **1987**, *193*, 171.
5. Combret, Y.; Torché, J. J.; Plé, N.; Duflos, J.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Tetrahedron* **1991**, *47*, 9369–9382.
6. Bédat, J.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Chem. Lett.* **1996**, 359–360.
7. (a) Johnson, C. C.; Gardner, J. L.; Snelter, C. H.; Metzler, D. E. *Biochemistry* **1963**, *2*, 689. (b) Youn Kim, C. S.; Chaykin, S. *Biochemistry* **1968**, *7*, 2339. (c) Van Eikeren, P.; Kenny, P.; Tokmakian, R. *J. Am. Chem. Soc.* **1979**, *101*, 7406.
8. (a) Cazin, J.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Tetrahedron Lett.* **1986**, *27*, 2375–2378. (b) Levacher, V.; Boussad, N.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Tetrahedron* **1992**, *48*, 831–840. (c) Charpentier, P.; Lobrégat, V.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron Lett.* **1998**, *39*, 4013–4016.
9. Cheng, C. C.; Yan, S. J. In *The Friedlander synthesis of quinolines organic reactions*, Wiley: New York, 1982; vol. 28, pp 37–202.
10. (a) Rao, K. V.; Kuo, H. S. *J. Heterocycl. Chem.* **1979**, *16*, 1241. (b) Shafiee, A.; Parang, K.; Khazan, M.; Ghasemian, F. *J. Heterocycl. Chem.* **1992**, *29*, 1859.
11. (a) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087–2090. (b) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087. (c) Ohta, S.; Shimabayashi, A.; Hayakawa, S.; Sumino, N.; Okamoto, M. *Synthesis* **1985**, 45–48. (d) Langlois, M.; Yang, D.; Soulier, J. L.; Florac, C. *Synth. Commun.* **1992**, *22*, 3115–3127. (e) Lee, C. J.; De Milo, A. B.; Waters, R. M. *Synth. Commun.* **1996**, *26*, 153–160.
12. (a) Hampton, K. G.; Flannery, R. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2308. (b) Hampton, K. G.; Flannery, R. E. *J. Org. Chem.* **1972**, *37*, 2806–2810.
13. (a) Friedländer, P.; Henriques, S. *Chem. Ber.* **1882**, *15*, 2572. (b) McGeachin, S. G. *Can. J. Chem.* **1966**, *44*, 2323. (c) Abert, A.; Yamamoto, H. *J. Chem. Soc. B* **1966**, 956–963.
14. (a) Borsche, W.; Ried, W. *Liebigs Ann. Chem.* **1943**, *554*, 269. (b) Borsche, W.; Barthenheier, J. *Liebigs Ann. Chem.* **1941**, *548*, 50.
15. Porter, H. K. The Zinin reduction of nitroarenes. *Org. React.* **1973**, *20*, 455–481.
16. Gorgues, A. *Bull. Soc. Chim. Fr.* **1974**, 529–530.

17. Saavedra, J. E. *J. Org. Chem.* **1985**, *50*, 2271–2273.
18. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171–4174.
19. (a) Makino, T.; Numozawa, T.; Baba, N.; Oda, J.; Inouye, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 7–10. (b) Leroy, C.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3309–3318.
20. (a) Losset, D.; Dupas, G.; Bourguignon, J.; Quéguiner, G. *Polym. Bull.* **1989**, 649–654. (b) Dupas, G.; Decormeille, A.; Bourguignon, J.; Quéguiner, G. *Tetrahedron* **1989**, *45*, 2579–2590.
21. Obika, S.; Nishiyama, T.; Tatematsu, S.; Nishimoto, M.; Miyashita, K.; Imanishi, T. *Heterocycles* **1998**, *49*, 261–267 (and references therein).
22. (a) Levacher, V.; Moberg, C. *J. Org. Chem.* **1995**, *60*, 1755–1762. (b) Levacher, V.; Moberg, C. *React. Polym.* **1995**, *24*, 183–193. (c) Levacher, V.; Adolfsson, H.; Moberg, C. *Acta Chem. Scand.* **1996**, *50*, 454–457.
23. Castellan, A.; Grelier, S.; Kessab, L.; Nourmamode, A.; Hannachi, Y. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1131–1138.
24. Kumar, S.; Wachtel, E. J.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 3821–3827.
25. Nandeeshaiah, S. K.; Sarvottam, Y. *Indian J. Chem., Sect. B* **1994**, *33*, 375.
26. Rilliet, A. *Helv. Chim. Acta* **1922**, *5*, 547–552.