The ammonia-free partial reduction of substituted pyridinium salts

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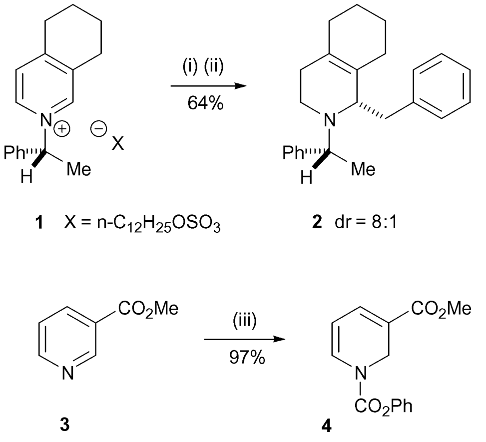
This paper reports a study into the partial reduction of *N*-alkylpyridinium salts together with subsequent elaboration of the intermediates thus produced. Activation of a pyridinium salt by placing an ester group at C-2, allows the addition of two electrons to give a synthetically versatile enolate intermediate which can be trapped with a variety of electrophiles. Furthermore, the presence of a 4-methoxy substituent on the pyridine nucleus enhances the stability of the enolate reaction products, and hydrolysis *in situ* gives stable dihydropyridone derivatives in good yields. These versatile compounds are prepared in just three steps from picolinic acid and can be derivatised at any position on the ring, including nitrogen when a *p*-methoxybenzyl group is used as the *N*-activating group on the pyridinium salt. This publication describes our exploration of the optimum reducing conditions, the most appropriate *N*-alkyl protecting group, as well as the best position on the ring for the methoxy group. Electrochemical techniques which mimic the synthetic reducing conditions are utilised and they give clear support for our proposed mechanism of reduction in which there is a stepwise addition of two electrons to the heterocycle, mediated by di-*tert*-butylbiphenyl (DBB). Moreover, there is a correlation between the viability of reduction of a given heterocycle under synthetic conditions and its electrochemical response; this offers the potential for use of electrochemistry in predicting the outcome of such reactions.

Introduction

The piperidine ring is one of the central motifs in natural product chemistry, and this heterocycle is present in a wide variety of compounds with biological activity. Many naturally-occurring piperidines are present in complex structures and represent challenging synthetic targets.[1] The use of pyridinium salts as precursors to piperidines is an attractive approach, because control of a reduction or addition process allows access to dihydropyridine, tetrahydropyridine or piperidine derivatives directly. A further advantage is the ready availability of various substituted pyridines *via* literature routes and the ease of activation of this heterocycle as a pyridinium salt. In this regard, there are two complementary methods of effecting the reductive transformation of pyridinium salts: (i) direct attack of a *nucleophile* onto the heterocycle,[2] or (ii) the use of a reducing agent which provides electrons and forms an anion capable of reacting with *electrophiles*.[3] The addition of organometallic reagents to pyridinium salts (especially acylpyridinium salts) is well documented in the literature. The choice of nucleophilic reagent is very important with respect to regiochemistry because hard reagents, such as organolithiums, favour attack at the 2-position[4] and softer reagents, such as organocuprates, attack at the 4-position.[5] A recent example showing the use of Grignard reagents adding to pyridinium salts in conjunction with stereochemical control by a chiral auxiliary is shown in Scheme 1.[6] When hydride reagents are used as nucleophiles, regiocontrol can be difficult to achieve and requires careful choice of both reagent and conditions in order to be synthetically useful: a pertinent recent example of the Fowler reduction by Ganem *et al.* is shown in Scheme 1 (**3** → **4**).[7] The use of dissolving metals in ammonia (such as the Birch reduction)



Scheme 1 *Reagents and conditions*: (i) $C_6H_5CH_2MgBr$; (ii) $NaBH_4$; (iii) $NaBH_4$, PhOCOCl, MeOH, −78 °C.

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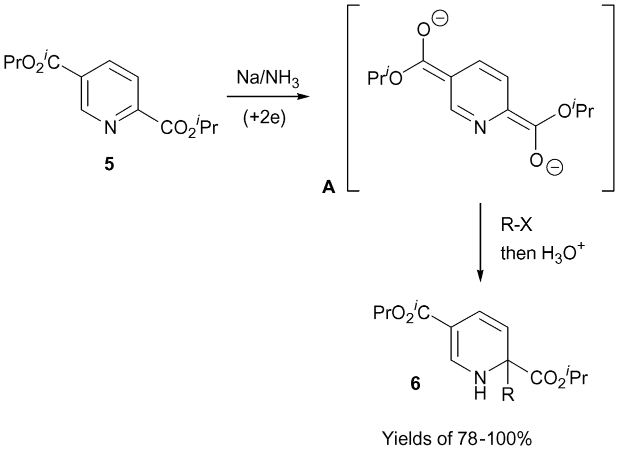
as a source of electrons to effect the reduction of pyridines has been known since 1925.[8] However, this reaction often gives multicomponent mixtures, limiting its synthetic utility. Modification of the procedure by the use of pyridinium salts in the Birch reduction has allowed regiocontrol of the reduction to be achieved, with the conditions favouring formation of a 1,4-dihydropyridine.[9]

Previously, we had shown that selective reduction of the pyridine nucleus using Birch conditions is made possible by positioning electron-withdrawing substituents on the heterocycle (Scheme 2).[10] This methodology was found to be a general one, compatible with a wide variety of electrophilic quenches which furnished the substituted dihydropyridines **6** in excellent yields. However, the approach suffers from a number of drawbacks. It was found that at least two electron-withdrawing groups were needed to properly activate the ring towards reduction and the relative positioning of these groups was critical for the success of this reduction (Scheme 2). In essence, the ability of the substituted pyridine to stabilise a dianionic intermediate (generated by the addition of two electrons) was crucial, thus restricting the placement of the groups (see **A**, Scheme 2). Also, further modification of the products generated by this reduction reaction was found to be limited, particularly with respect to the fixed carbon substituent pattern that the two electron-withdrawing groups imposed. Thus, an investigation into the development of a more versatile method of activating the pyridine nucleus was sought.

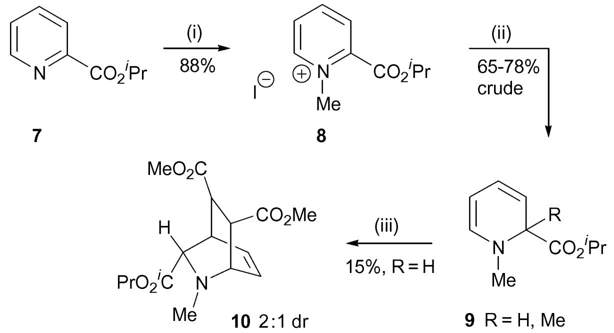


Scheme 2 Partial reduction of 2,5-disubstituted pyridines.

Results and discussion

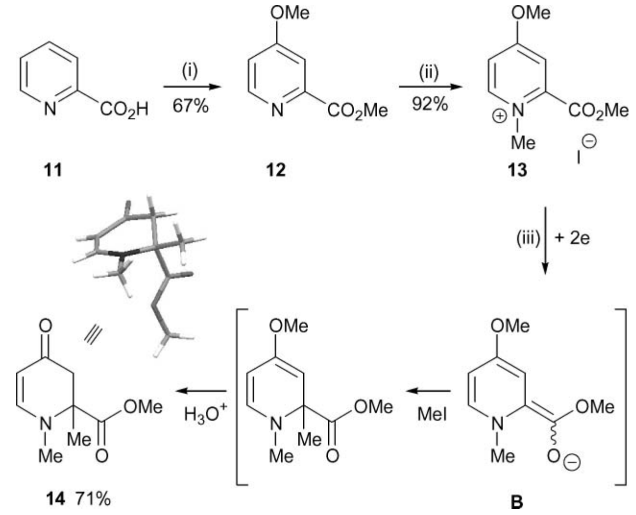
Establishing conditions for the ammonia-free Birch reduction of pyridinium salts

Pyridinium salts have already found limited use as substrates for the Birch reduction and shown potential for controlling the extent of reduction. Therefore, it was hypothesised that the further activation of pyridines (bearing *one* electron-withdrawing group) as pyridinium salts would negate the need for the second electron-withdrawing group as shown in Scheme 2.[11] In the reduction of a pyridinium salt, by the addition of two electrons, the use of an ester group at the C-2 position may allow for the generation of an anion stabilised as an enolate, giving an opportunity to alkylate the heterocyclic nucleus by quenching the reaction with an electrophile. In order to test this hypothesis, the synthesis of pyridinium salt **8** was accomplished by heating *iso*-propyl picolinate **7** in neat methyl iodide overnight (Scheme 3). These harsh conditions were necessary to overcome electronic deactivation by the ester group adjacent to the heterocyclic nitrogen. Subsequent reaction of pyridinium salt **8** under standard Birch reduction conditions (sodium, ammonia and tetrahydrofuran at −78 °C) followed by quenching of the reaction with an acid led to the formation of a crude product that was consistent with the desired dihydropyridine **9** (R = H) by ^{1}H NMR spectroscopy (Scheme 3). However, attempts at purification failed because the product was apparently unstable. The instability of the expected 1,2-dihydropyridine species **9** has been well documented in the literature; indeed, the addition of catalytic *p*-toluenesulfonic acid to a fresh sample of crude dihydropyridine in deuterated chloroform led to extremely rapid degradation. One potential route for decomposition of a putative dihydropyridine would be re-aromatisation *via* air oxidation. Therefore, the reduction of **8** was repeated, followed by quenching with methyl iodide as an electrophile. However, again the crude product of the reductive alkylation reaction **9** (R = Me) was found to be just as unstable to purification as the protonated species **9** (R = H), indicating an alternative pathway for product decomposition. One strategy for the isolation of unstable dihydropyridine intermediates is to convert them into a more stable derivative *in situ*.[12] Thus, the crude diene **9** (R = H) was subjected to a Diels–Alder reaction. Initial use of maleic anhydride as a dienophile to capture **9** offered no advantage as attempts at purification of the adduct failed, possibly because of facile retro-cycloaddition. Instead, the crude reaction mixture was treated with dimethyl fumarate in dichloromethane, which furnished the Diels–Alder adduct **10** as a mixture of isomers (stereochemistry not assigned). However, the disappointing yield of this reaction led to the conclusion that the intermediates generated here were again too unstable to be synthetically useful.



Scheme 3 *Reagents and conditions*: (i) MeI, Δ; (ii) Na, NH$_3$, THF, −78 °C then isoprene then NH$_4$Cl or MeI; (iii) dimethyl fumarate, CH$_2$Cl$_2$, Δ.

Therefore, an alternative approach was sought that would lead to the transformation (and thus stabilisation) of the 1,2-dihydropyridine species *in situ*. Initial ideas, such as hydrogenation, were rejected as this would greatly reduce the synthetic potential of the reduction product by removal of the double bonds. We were aware that Comins and co-workers had successfully developed the use of C-4 methoxy-substituted acyl pyridinium salts as versatile electrophiles.[13] The advantage of the placement of a methoxy group at C-4 was that it allowed a method of avoiding unstable 1,2-dihydropyridines after reduction: acid catalysed hydrolysis *in situ* liberated a stable dihydropyridone. Using this idea as a starting point, an efficient, one-step synthesis of methyl 4-methoxypicolinate **12** (Scheme 4) was achieved from picolinic acid **11** *via* a method originally reported by Sundberg and Jiang.[14] Compound **12** was then *N*-alkylated by use of the same procedure as previously described to give the *N*-methylpyridinium salt **13** in excellent yield.[11] It was reasoned that the use of traditional Birch reduction conditions – sodium and liquid ammonia – would be inappropriate and that an electron transfer agent such as di-*tert*-butylbiphenyl (DBB) or naphthalene in combination with an alkali metal could be used to facilitate reduction.[15] The reasoning behind this change was three-fold: firstly, the *in situ* acidic work-up required to hydrolyse the enol ether would clearly be incompatible with a liquid ammonia solvent; secondly, previous experience had shown that methyl esters are often prone to nucleophilic attack by amide anions formed during the Birch reduction; and finally, the use of ammonia-free conditions would allow the use of sensitive electrophiles, such as methyl chloroformate, as traps for the reduction.[15] Thus, pyridinium salt **13** was subjected to the ammonia-free reduction/hydrolysis strategy using sodium and naphthalene to achieve reduction and then methyl iodide as an electrophilic quench, followed by reaction with aqueous acid. The isolation of the desired dihydropyridone **14** in a yield of 71% validated the change in reaction conditions (Scheme 4); the dihydropyridone product **14** was completely stable at ambient temperature and its structure was proven by X-ray crystallography.† The success of this alkylation/hydrolysis protocol lends credence to the original hypothesis that the addition of two electrons generated an enolate anion **B**, which was successfully alkylated and then hydrolysed to a stable vinylogous amide derivative *in situ*.



Scheme 4 *Reagents and conditions*: (i) $SOCl_2$, NaBr, MeOH, Δ; (ii) MeI; (iii) Na, naphthalene, −78 °C then MeI, then H_3O^+.

Optimising the *N*-alkyl substituent in the pyridinium salt

The next issue to be addressed was the removal of the *N*-methyl group from **14** because deprotection was required to allow variation in the substituents on the nitrogen for future studies. Initial work focused on classical electrophilic demethylation conditions such as the use of methyl chloroformate and boron tribromide; however, only the starting material **14** was returned, indicating that the nitrogen lone pair was strongly conjugated into the enone system and thus unavailable for reaction. The use of both nucleophilic conditions, *e.g.* methionine in methanesulfonic acid, and oxidative conditions, *e.g.* chromium trioxide or Dess–Martin periodinane, either returned the starting material or led to decomposition.[16]

This failure to deprotect the nitrogen severely limited the scope of the reduction for its general use in organic synthesis and so it was decided to investigate other protecting groups on the heteroatom. The first area of investigation involved groups that could to be cleaved under acidic conditions to yield the *N*-H dihydropyridone. However, both an *N*-trialkylsilyl group and an *N*-boron trifluoride protected version of pyridinium salt **13**, when subjected to reduction, gave no identifiable products. The use of the corresponding *N*-oxide of **12** was also investigated but again reduction failed to give a single product. Attention was, therefore, returned to carbon-based protecting groups. One problem with attaching a range of groups on nitrogen was the poor reactivity of pyridine **12** towards electrophiles; for example, both benzyl and allyl bromides proved unreactive and did not achieve complete conversion. Attempted reaction of **12** with acylating agents only returned the starting material; this confirms literature reports of the relative instability of acylpyridinium species at room temperature and especially where *ortho* substitution on a pyridine provides steric hindrance.[13a] All this evidence demonstrated a lack of nucleophilicity of the substrate **12** towards alkyl halides and so a more reactive electrophile was chosen to effect alkylation. Alkyl triflates (trifluoromethanesufonates) are very reactive electrophiles, and so a test reaction using methyl triflate and **12** was conducted. The pyridinium salt **15** was formed easily at room temperature, and was then added immediately to a solution of sodium naphthalenide. After alkylation with methyl iodide and acidic hydrolysis, dihydropyridone **14** was isolated in 44% yield. Although this yield was less than for the corresponding reaction of iodide salt **13**, as a proof of concept the use of alkyl triflates for alkylating pyridine **12** had been demonstrated. It was decided to test if other alkyl groups could be introduced *via* the triflate route and were then tolerated by the reaction conditions. The 1-chloroethyl and homoallyl salts **16** and **17** were prepared (and isolated) from the respective triflates to examine the stability of more highly functionalised groups in the ammonia-free Birch reduction (Scheme 5). Both triflate salts underwent smooth reduction, with yields of the two dihydropyridones **18** and **19** being consistent with previous reductions of triflates – thus the compatibility of the ammonia-free reduction with both alkyl chlorides and isolated alkenes has been demonstrated. The drop in yield seen here would appear to indicate some form of counter-ion effect having a negative impact on the reduction; compare the reduction of **15** and **13**. Bearing in mind that the aim of further investigation was the ability to deprotect the nitrogen, the *N*-homoallyl dihydropyridone **19** was reacted

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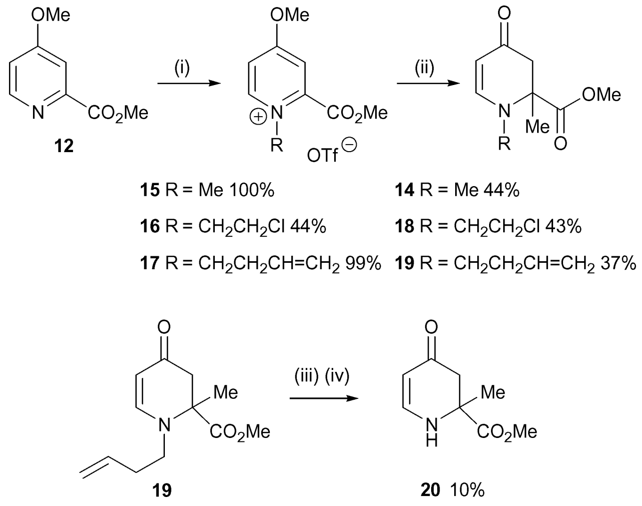
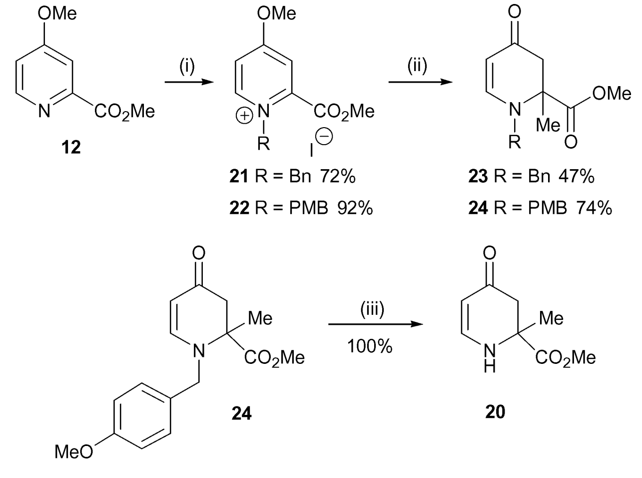
† *Crystal data* for **14**: $C_9H_{13}NO_3$, $M = 183.21$, monoclinic, $P2_1/n$, $a = 7.1187(2)$, $b = 12.4355(2)$, $c = 10.6250(3)$ Å, $\beta = 105.5450(8)°$, $V = 906.17(4)$ Å^3, $T = 150$ K, $Z = 4$, $\mu = 0.101$ mm^{-1}, reflections measured 12 098 (2169 unique), $R_{int} = 0.030$, $R = 0.0372$ (all data). CCDC reference number 294438. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517462g.



Scheme 5 *Reagents and conditions*: (i) R–OSO$_2$CF$_3$; (ii) Na, naphthalene, −78 °C then MeI, then H$_3$O$^+$; (iii) OsO$_4$, NaIO$_4$; (iv) Et$_3$N, Δ.

under Johnson–Lemieux oxidative cleavage conditions, followed by heating in triethylamine to trigger a β-elimination, liberating the *N*-H dihydropyridone **20** (Scheme 5). Although this sequence was successful in deprotecting the nitrogen and forming **20**, a poor yield of 10% was not encouraging for future use.

We have shown that reduction of a pyridinium iodide salt is superior to the corresponding triflate salt, and so a new series of iodides were sought to activate pyridine **12**; in this regard it was decided to evaluate both benzyl iodide and 4-methoxybenzyl (PMB) iodide as electrophiles. The increased leaving group aptitude of the iodide proved to be critical, as both the benzyl and PMB protected pyridinium salts **21** and **22** were isolated in good yields as easily handled micro-crystalline solids (Scheme 6). During the course of these studies a second reducing system of lithium and DBB was also tested on compound **13** and found to be superior to sodium and naphthalene in terms of isolated yield. Electrochemical data from experiments designed to mimic the ammonia-free reduction conditions showed that the reduction potential of DBB (−2.8 V) is more negative than that of naphthalene (−2.3 V), thus the radical anion is less stable and so LiDBB is a stronger reducing agent.[17] Treatment of **21** and **22** with lithium–DBB, using methyl iodide as the quench, furnished the dihydropyridone in both cases, and in particular the PMB protected dihydropyridone **24** was isolated in an encouraging yield of 74%, which is comparable to the analogous result obtained using methyl protected salt **13** (Scheme 6). It should be noted that yields suffered if too great an excess of lithium was used, which was attributed to reduction of the aromatic protecting group as well as the heterocycle. With this promising result in hand, deprotection of the dihydropyridone **24** was attempted next. Exposure of **24** to trifluoroacetic acid (TFA), followed by heating at reflux, led to the formation of the *N*-H dihydropyridone **20** in a quantitative yield (Scheme 6).

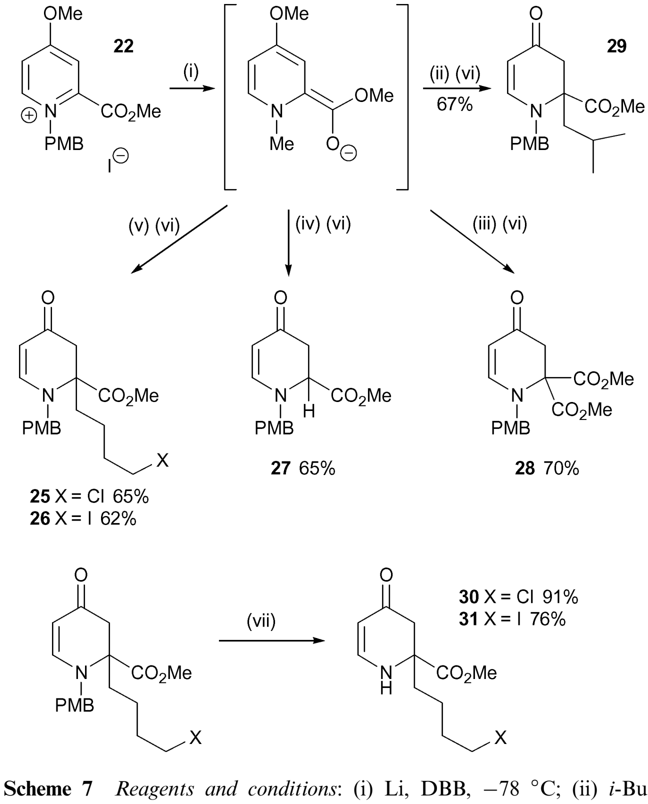


Scheme 6 *Reagents and conditions*: (i) BnI or PMBI; (ii) Li, DBB, −78 °C then MeI, then H$_3$O$^+$; (iii) TFA, Δ.

Thus far we have established optimal conditions for the activation and subsequent partial reduction of methoxypyridinium salts to highly functionalised and versatile dihydropyridone intermediates. We have demonstrated the efficiency of the ammonia-free Birch reduction conditions and have optimised these to the use of LiDBB. Also, we have identified the PMB group as the most appropriate *N*-protecting group in the activation of the methoxypyridine **12** as a pyridinium iodide salt.

Versatility of the methodology and elaboration of the dihydropyridones

With the basic elements of the synthetic approach established, we next investigated the utility of the intermediates obtained by this methodology. Thus, the PMB protected salt **22** was subjected to the ammonia-free Birch reduction, and the enolate quenched with a variety of electrophiles, including a proton source and carbon electrophiles comprising both alkyl and acyl species (Scheme 7).[11]

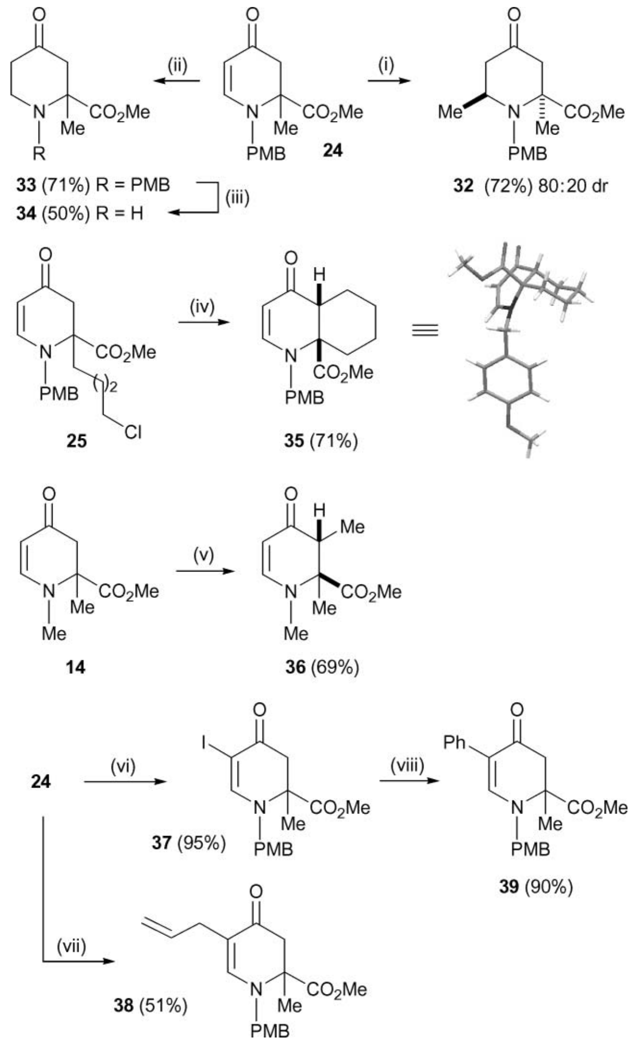


Scheme 7 *Reagents and conditions*: (i) Li, DBB, −78 °C; (ii) *i*-BuI; (iii) ClCO$_2$Me; (iv) NH$_4$Cl; (v) X(CH$_2$)$_4$I (X = Cl, I); (vi) H$_3$O$^+$; (vii) TFA, Δ.

Interesting points to note are that the yield of protonation was independent of the source of the acid used; saturated aqueous ammonium chloride solution, methanol or 2,6-di-*tert*-butylphenol all gave yields of around 65% of the dihydropyridone **27**. In addition, the use of a mixed halide electrophile showed complete selectivity for displacement of the better leaving group (**22** → **25**), as expected. Both halide-containing dihydropyridones **25** and **26** were deprotected to test if potentially sensitive functionality could survive the strongly acidic conditions. Pleasingly, both the *N*-H dihydropyridones **30** and **31** were isolated, with yields of 91% for the chloride and 76% for the iodide, with the lower value for the iodide perhaps revealing some sensitivity to the reaction conditions. The only class of electrophile that worked poorly under the partial reduction conditions was an aldehyde.[18] It is possible that during the acidic hydrolysis conditions (and as the reaction is warmed to room temperature) a retro-aldol reaction was occurring, leading to decomposition *in situ*.

These examples show the methodology to be a viable way of quickly accessing a synthetically useful template from a cheap and plentiful starting material, picolinic acid, in just three steps.

The potential for further modification and elaboration of these dihydropyridones, and their use in synthesis, can easily be predicted from substantial precedent for the reactivity of these systems in the literature. We have performed a range of derivatisation reactions on these templates, designed to show the flexibility that such platforms have for the introduction of groups *at any position* on the pyridone nucleus. The reactions detailed in Scheme 8 show that this is indeed possible. For example, functionalisation at C-6 was accomplished using an organo-cuprate in conjunction with Lewis acid activation of enone (**24** → **32**, 80 : 20 dr).[19] The relative stereochemistry of compound **32** (major isomer) was assigned by NOE experiments. Conjugate addition of hydride to **24** was also accomplished using L-selectride[20] and the PMB group then removed from tertiary amine product **33** using hydrogenolysis conditions to give **34** (surprisingly, we found that dihydropyridone **24** was itself inert to hydrogenolysis). Next, functionalisation at C-3 was examined by utilising the enolate derivative of pyridones **25** and **14**.[21] Intramolecular alkylation of **25** was accomplished by treatment with sodamide (this base alone was capable of enolising the dihydropyridone structure). Formation of the *cis*-azadecalin ring system **35** was confirmed by X-ray crystallographic analysis of this compound.‡ Moreover, intermolecular alkylation at C-3 was also readily accomplished when **14** was reacted with sodamide and then methyl iodide, to furnish **36** as a single diastereoisomer. We were unable to prove the relative stereochemistry of **36** beyond all doubt and it is assigned by analogy to **35**. Finally, the enamine-like character of these dihydropyridones was harnessed (and functionalisation at C-5 accomplished) by reaction of **24** with potent electrophiles.[22] For example, reaction with iodine gave vinyl iodide **37** in excellent yield, ready for derivatisation by radical reaction or transition metal coupling. Preliminary screens in this area showed that palladium coupling of **37** could be best accomplished with catalytic Pd/C under heterogeneous conditions in the presence of phenyl boronic acid to yield **39**.[23] Moreover, allyl iodide was also capable of reacting with the enamine **24** to yield the C-5 allyl compound **38** in reasonable yield (the site of initial allylation, and the ensuing [3,3] sigmatropic rearrangement that would follow from *N*- or *O*-allylation was not investigated).



Scheme 8 *Reagents and conditions*: (i) CuBr·SMe$_2$, THF; BF$_3$·OEt$_2$, −78 °C; MeMgBr, −10 °C; (ii) Li(*sec*-Bu)$_3$BH, THF, −78 °C; (iii) H$_2$, Pd/C, MeOH; (iv) NaNH$_2$, NH$_3$, −40 °C; (v) NaNH$_2$, NH$_3$, −78 °C, MeI; (vi) I$_2$, K$_2$CO$_3$, CH$_2$Cl$_2$, rt; (vii) allyl iodide, MeCN, Δ, 48 h; (viii) PhB(OH)$_2$, DME/H$_2$O, cat. Pd/C.

Thus, the varied reactivity pattern of dihydropyridones such as **24** has been explored and there is clearly plenty of scope to perform significant modification to the heterocyclic skeleton post-partial reduction.

Variation in the substitution pattern of activated pyridinium salts

Our next remit was to investigate variation in the position of the substituents around the pyridine ring of the starting substrate. Two criteria were applied in the choice of substrate to be reduced. Firstly, using our knowledge of the mechanism of reduction only certain substitution patterns (an ester at C-2 or C-4) were predicted to stabilise the anion generated upon addition of the electrons as an enolate. Moreover, positioning of the methoxy group *meta*

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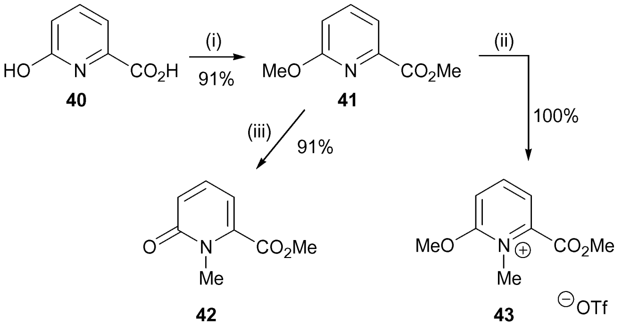
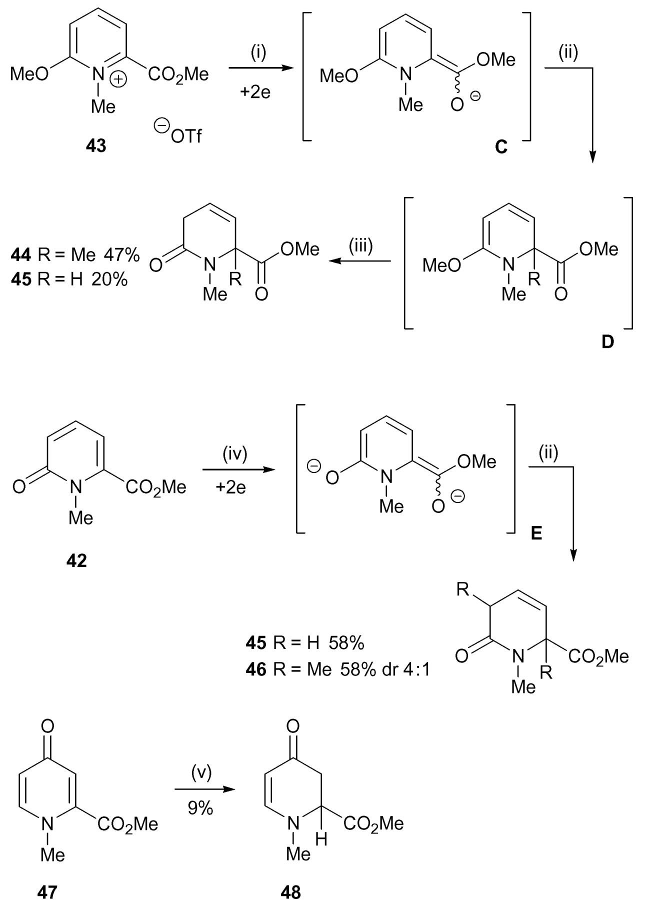
‡ *Crystal data* for **35**: $C_{19}H_{23}NO_4$, $M = 329.40$, monoclinic, $P2_1/c$, $a = 8.0683(2)$, $b = 10.3413(2)$, $c = 20.1216(4)$ Å, $\beta = 100.6130(9)°$, $V = 1650.16(6)$ Å^3, $T = 150$ K, $Z = 4$, $\mu = 0.093$ mm^{-1}, reflections measured 13 884 (3656 unique), $R_{int} = 0.030$, $R = 0.0397$ (all data). CCDC reference number 294439. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b517462g.

to the ester was deemed essential to allow stabilisation of the product from hydrolysis.[10c] Secondly, the starting material needed to be readily available to allow its use in synthesis, because multi-step routes to the pyridinium starting materials would not be attractive. Therefore, it was decided to investigate the properties of commercially available 6-hydroxypicolinic acid **40** to test if the position of the methoxy group was important during reduction. Esterification and etherification of **40** were achieved in a one-pot reaction by the addition of methyl iodide and silver carbonate to 6-hydroxypicolinic acid (Scheme 9).[24] The choice of base was crucial to the success of the reaction, with the use of potassium carbonate leading to methylation of the ring nitrogen instead of the hydroxy group, which then led to pyridone formation. Attempts to form the pyridinium salt of methyl 6-methoxypicolinate **41** using methyl iodide led exclusively to the synthesis of the *N*-methyl pyridone **42** as observed previously.[25] To prevent this side reaction from occurring, a non-nucleophilic counter-ion was used and attention was turned to the use of an alkyl triflate to alkylate **41**. Although previous work on the 4-methoxy salts **13** and **15** had shown the iodide derivatives to be superior to their triflate counterparts, the latter had worked in the ammonia-free Birch reduction and would allow the exploration of a new area of pyridinium salt chemistry. Consequently, treatment of pyridine **41** with methyl triflate led to the quantitative formation of pyridinium salt **43** (Scheme 9). Attempts to exchange the triflate counter-ion of **43** with iodide always led to the formation of **42**.



Scheme 9 *Reagents and conditions*: (i) MeI, Ag$_2$CO$_3$, CHCl$_3$, Δ; (ii) MeOTf; (iii) MeI, Δ.



Scheme 10 *Reagents and conditions*: (i) Na, naphthalene, THF, −78 °C; (ii) RX; (iii) then H$_3$O$^+$; (iv) LiDBB, THF, −78 °C; (v) LiDBB, THF, −78 °C, NH$_4$Cl$_{(aq)}$.

Following standard ammonia-free reductive alkylation procedures, using sodium–naphthalene as the source of electrons (to allow comparison with previous work on triflate salt **15**) and methyl iodide as the electrophile, reaction of **43** gave the 6-dihydropyridone **44** in a yield of 36% after acidic hydrolysis of the enol ether (Scheme 10). Protonation of the enolate (**C**) proved to be more problematic with a highest yield of **45** being 20% obtained using methanol as proton source. Evidence was accumulated which suggested another reaction pathway was operating during the reaction. Examination of the aqueous layer from the reaction work-up using ^{1}H NMR spectroscopic analysis showed the presence of peaks in the vinylic region which did not correspond to the dihydropyridone **44**. It was proposed that, during acidic hydrolysis, protonation of **D** could occur not only on the enol ether but also on the nitrogen. This pathway could lead to ring-opening and, after ester hydrolysis, to the formation of an amino acid; basification would generate the highly water soluble carboxylate form. The use of acetic anhydride, added during the work-up of the reaction, to trigger the cyclisation of the amino acid back to the desired dihydropyridone, increased the yield of the methylated product **44** to 47% (LiDBB conditions did not improve the yield), comparable with that obtained from the 4-methoxy derivative **14**. However, further studies showed that this yield was the maximum that could be obtained from this system and could not be optimised further despite much experimentation. In a move to simplify the reaction, and to negate the need for a strongly acidic work-up, the ammonia-free Birch reduction of pyridone **42** was examined. It was proposed that the addition of two electrons to **42** would lead to the formation of a bis-enolate **E**, opening up the potential for selective alkylation, and quenching with either a carbon electrophile or a proton leading to dihydropyridone formation. Thus, reduction of **42** was investigated under the ammonia-free Birch conditions using LiDBB. Protonation of the dianion **E** using saturated aqueous ammonium chloride was found to be substantially better than for the pyridinium salt **43**, with the dihydropyridone **45** now isolated in a respectable yield of 58%. Moreover, reductive alkylation of **42** led to the formation of the di-alkylated product **46**, again in 58% yield. However, it was found that it was not possible to control the selectivity of alkylation with variations in experimental conditions (equivalents of electrophile, *etc.*) all producing each of the possible isomers of mono- and di-alkylation in differing ratios. When the reaction was pushed through to the di-alkylated dihydropyridone **46**, a potentially useful diastereomeric ratio of 80 : 20 was obtained, although the diastereomers were inseparable and remain unassigned. Attempts to reproduce this methodology with the 4-pyridone **47** were unsuccessful,[26] with only trace amounts of the dihydropyridone **48** formed. Ultimately, the lack of enolate differentiation in reactivity of the bis-enolate **E** limited the flexibility and generality of this approach to synthetic applications.

Correlation of synthetic studies with electrochemical analysis

Introduction. In order better to understand the electron transfer processes that are taking place under synthetic reducing conditions we were interested in developing an electrochemical analysis that would replicate the conditions of lithium–DBB in THF at −78 °C and would allow us to measure the reduction potentials of a variety of aromatic heterocycles.[18,27] We aimed to determine if the formation of a radical anion or dianion from aromatic heterocycles was mechanistically reasonable. We also aimed to obtain data regarding the rate of electron transfer to these aromatic compounds in order to understand the role of the electron transfer agent (typically DBB) in the ammonia-free reduction.[28] In the shorter term, we aimed to use electrochemistry as a technique to enable us to predict not only the products of a reduction but also the relative rate at which various compounds will be reduced under such lithium/THF conditions; this knowledge will have useful applications in organic synthesis.

A sealed cell was used for cyclic voltammetry experiments, containing THF and the supporting electrolyte, tetra-*n*-butylammonium perchlorate (0.5 M). Silver wire was used as the quasi-reference electrode, the potential of which is open to some drift (±10 mV); however, in most cases the electrode was found to behave in a stable manner upon repetition of the electrochemistry experiments. The working electrode was, in general, a 1 mm radius platinum macroelectrode. When investigating DBB a 5 µm microdisc was used. All experiments were carried out under anhydrous and oxygen-free conditions at $T = 200$ K.

For each substrate, two parameters were investigated: the formal potential $E^{0'}$ and the diffusion coefficient D were determined. The formal potential is defined by eqn. (1), where E_p^{Red} and E_p^{Ox} are the cathodic and anodic peak potentials in an electrochemically reversible (or quasi-reversible) cyclic voltammogram.

$$E^{0'} = \frac{\left(E_p^{Red} + E_p^{Ox}\right)}{2} \qquad (1)$$

Here, $E^{0'}$ is the formal potential of the redox couple, a measure of the thermodynamic 'ease' of reduction of the substrate, F is the Faraday constant, n is the number of electrons transferred and A is the electrode area The diffusion coefficient D is a measure of the rate at which the molecule can diffuse through the solvent and is a function of several variables including the effective size of the species and the solvent viscosity. The coefficient D appears in eqn. (2) and can be inferred from the gradient of a plot of the peak current density, i_p, against the square root of the scan rate, v, for an electrochemically reversible process. C_{bulk} is the concentration of the bulk solution.

$$i_p = 0.4463 C_{bulk} \left(\frac{F^3}{RT}\right)^{1/2} v^{1/2} A D^{1/2} n^{3/2} \qquad (2)$$

Eqn. (1) and (2) were used to generate initial estimates for our parameters which were then established by simulation of the cyclic voltammograms using the commercially available DIGISIM™ software package; the value reported is the average result over all scan rates.

Cyclic voltammetry was undertaken on a selection of aromatic heterocyclic compounds to provide further insight into the mechanism of the partial reduction. The compounds examined and their voltammograms are shown in Fig. 1.[3a]

Each compound investigated (except **43**) gave a one-electron, quasi-reversible wave, as evidenced by the shift in peak potential with scan rate. The two parameters above were determined by fitting the experimental data to electrochemical models using DIGISIM™. Table 1 summarises the results.

The experimental error for the $E^{0'}$ values is ±0.05 V and can be attributed, in part, to the slight drift in the potential of the quasi-reference electrode. However, the electrode appeared to behave well during experiments and the reproducibility of results was good. DBB was included in the study to validate the conditions used for the electrochemical cell. Comparison of the data collected for DBB with that found in previous studies[17]**17** showed that the system employed was working satisfactorily.

The mechanism that we proposed for the partial reductions indicates that these substrates undergo a two-electron reduction to yield an enolate (*e.g.* **B**) that then reacts upon the addition of an electrophile (Scheme 4). This implies that the radical and anion derived from these heterocycles should both be less reducing than the DBB radical anion (*i.e.* have a less negative $E^{0'}$). Consequently, it was also expected that further electrochemical studies of the pyridinium salts should yield two-electron reduction waves representing the formation firstly of a radical and then of an enolate.

The cyclic voltammograms for three species (**13**, **21**, **22**) did indeed show two single-electron reduction waves, both of which were quasi-reversible. Table 2 gives the formal potentials for both electron transfers. As expected, the reduction potentials for the second electron transfer are less negative than that for the single electron reduction of DBB, confirming that it is reasonable to assume that an enolate such as **B** can be formed during synthetic reductions of the pyridinium salts by LiDBB.

The $E^{0'}$ values for both the first and second electron reductions gave a relative order for the thermodynamic ease of reduction of the pyridinium salts, with **21** being the easiest to reduce and **13**

Table 1 Electrochemical data determined by DIGISIM™

Compound	$10^6\ D/\mathrm{cm^2\ s^{-1}}$	$E^{0'}$/V *vs.* Ag
13	2.4	−0.63
21	3.1	−0.50
22	0.75	−0.58
43	—	−1.03
42	1.7	−1.66
DBB	3.5	−2.80

Table 2 First and second formal potentials

Compound	$E^{0'}$/V *vs.* Ag (1st e$^-$)	$E^{0'}$/V *vs.* Ag (2nd e$^-$)
13	−0.63	−1.49
21	−0.50	−1.29
22	−0.58	−1.38
DBB	−2.80	—

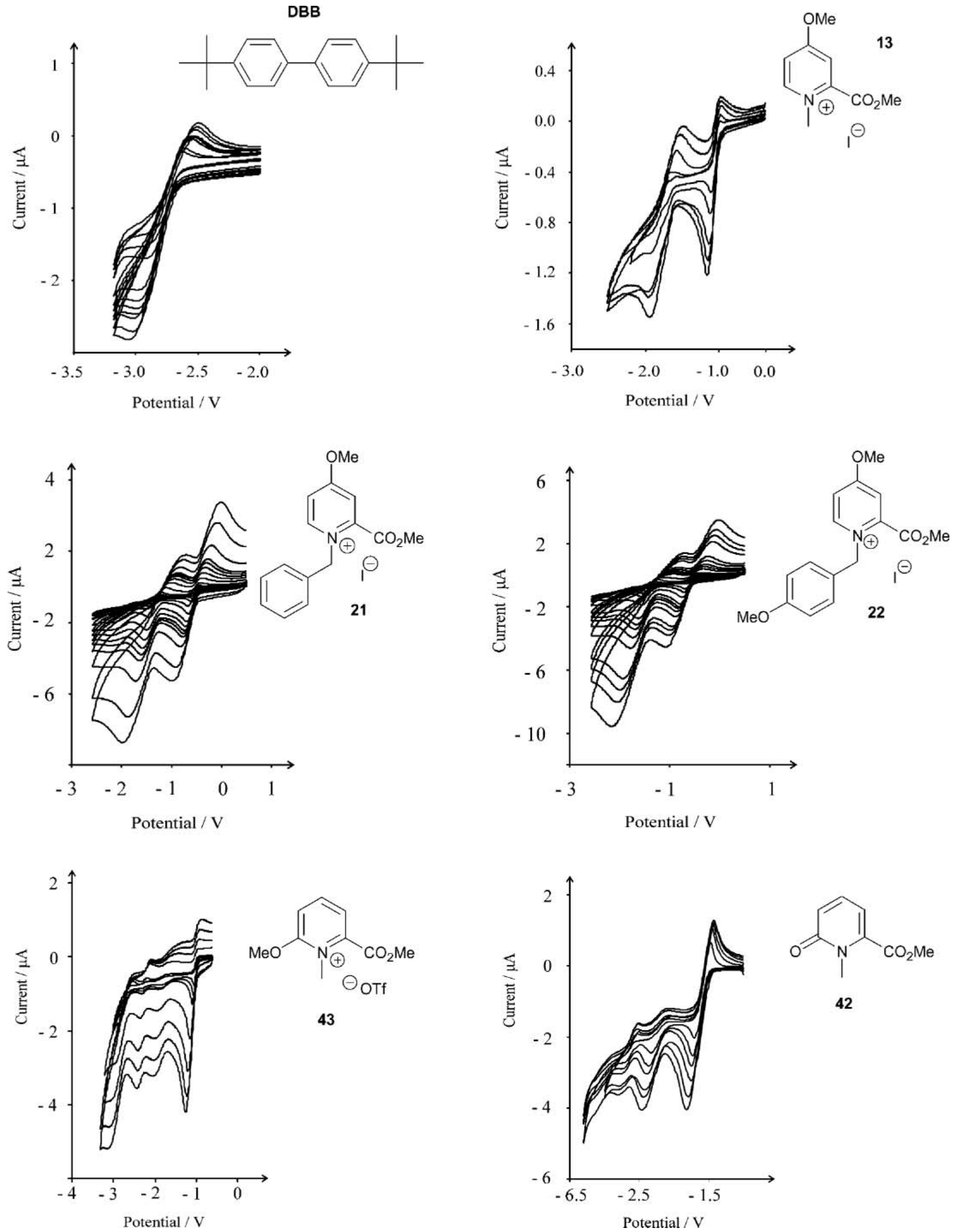


Fig. 1 Cyclic voltammograms of electron transfer agents, pyridinium salts and pyridones.

being the most difficult (**21** > **22** > **13**). However, the difference in half-wave potentials for the three compounds is relatively small and so an explanation for this order may be quite subtle.

Investigations then moved on to **42** and **43**, both of which have been shown to be relatively poor substrates for the ammonia-free partial reduction. The observation that pyridinium salt **43** does not give satisfactory yields under synthetic reducing conditions is particularly surprising given its similarity to substrate **13**, the 4-methoxy analogue. As outlined earlier, Scheme 10, the mechanism for the reduction of **43** is expected to be almost identical to that of compound **13**, forming anion **C** in solution. The pyridine **42** is clearly different from the pyridinium salts and should give a *dianion* **D** upon addition of two electrons.

As the synthetic results for both **42** and **43** indicate a two-electron reduction mechanism (albeit with poor yields), it was expected that a two-electron reduction wave would be observed electrochemically at potentials more positive than DBB, Table 3.

The results of the cyclic voltammetry in Table 3 are in line with these expectations. Note the absence of a back peak on the cyclic voltammogram for **43** which indicated that *both* electron transfers are irreversible. This indicated that both of the reduced species are involved in homogeneous reactions *in situ*. Two further, smaller,

Table 3 First and second formal potentials

Compound	$E^{0'}$/V *vs.* Ag (1st e^-)	$E^{0'}$/V *vs.* Ag (2nd e^-)
43	−1.03	−2.10
42	−1.66	−2.00
DBB	−2.80	—

reduction peaks can also be seen in the voltammogram, possibly from the products of reactions the reduced species underwent.

Compound **42** has a quasi-reversible first electron reduction but the second electron reduction is irreversible, again indicating reaction of the second reduced species *in situ*. For compounds **42** and **43** it is clear that neither give clean electrochemical responses when compared to their isomeric analogues (**13**, **22**). Moreover, both of them are significantly more difficult to reduce than the 4-methoxy analogues (compare **13**: $E^{0'} = -0.63, -1.49$ with **43**: $E^{0'} = -1.03, -2.10$ V). Not only does cyclic voltammetry show that **42** and **43** are relatively difficult to reduce but it also hints that the reduced species, once formed, are capable of undergoing reaction *in situ*. Thus, there is a clear correlation between the appearance of the voltammograms, and the cleanliness with which the compounds are reduced under synthetic conditions.

Conclusions

This paper describes our studies on the partial reduction of electron-deficient pyridinum salts. By judicious choice of pyridinium substitution pattern, and also the introduction of a *p*-methoxybenzyl group on the heterocyclic nitrogen, we were able to effect smooth partial reduction. Subsequent alkylation and hydrolysis, all *in situ*, furnished a range of dihydropyridones with the potential for the introduction of a variety of groups at the C-2 position. The rich functionality contained within the dihydropyridone ring systems affords highly versatile intermediates and it is worth noting that these valuable compounds are prepared from picolinic acid in just three steps. We have also described the electrochemical analysis of a range of pyridinium heterocycles utilising conditions that mimic those attained under synthetic conditions. This study has provided support for a proposed mechanism of reduction involving the addition of two electrons to form an enolate, all mediated by electron transfer from LiDBB. Pyridinium salts with various substitution patterns were examined both synthetically and electrochemically, and a correlation was found between the yields obtained during synthetic transformations and the appearance of the cyclic voltammogram. This could have significant ramifications for the future use of electrochemistry as a predictive technique for the outcome of partial reduction reactions.

Experimental

General experimental

All solvents were distilled before use. Tetrahydrofuran was freshly distilled from sodium-benzophenone ketyl radical whilst dichloromethane was freshly distilled from calcium hydride. All non-aqueous reactions were carried out under argon using oven-dried glassware.

Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on commercially available pre-coated plates (Merck silica Kieselgel 60F_{254}).

Proton and carbon NMR spectra were recorded on Bruker DPX 400 Fourier transform spectrometer using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants *J* are quoted in Hz and are not rationalised. Carbon NMR spectra were recorded with broad band proton decoupling and NMR assignments were made possible using Attached Proton Test (APT) and HMQC spectra where appropriate. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Positive ion chemical ionisation (CI) mass spectra and accurate mass data were recorded on a Micromass GCT instrument connected to an Agilent 6890 Series GC system.

Electrochemical instrumentation and procedure

The electrochemical measurements were made using a computer-controlled μ-Autolab system (EcoChemie, Utrecht, Netherlands) potentiostat. The electrochemical cell was an airtight three-electrode arrangement. The counter electrode was a large area bright platinum wire with a pseudo silver wire as the reference electrode. The working electrodes were either a 5 μm (radius) or a 1 mm (diameter) platinum disc electrode. The working electrode was polished on soft lapping pads (Kemet, UK) with 1.0 μm sized aqueous alumina slurry before rinsing in de-ionised water with a resistivity not less than 18 MΩcm from an Elgastat filter system (Vivendi, Bucks., UK). Before carrying out electrochemical experiments the working electrode's radius (for the microelectrode) was electrochemically calibrated. The working electrode and all components of the cell were rigorously dried before use. Tetra-*n*-butylammonium perchlorate (*ca.* 1.36 g), the supporting electrolyte, and the substrate (0.04 mmol) were dissolved in anhydrous THF (40 cm^3). The low temperature experiments were conducted in a dry ice–acetone bath (200 K). Before taking measurements the system was degassed thoroughly by bubbling impurity-free nitrogen gas (BOC Gases, UK) into the solution to remove any dissolved oxygen for at least 20 min.

General procedures

(A) Sodium–naphthalene. Sodium (5 equiv.) and naphthalene (5 equiv.) were added to THF (40 mL) at rt and sonicated for 4 h forming a dark green solution under an atmosphere of argon. The reaction was cooled to −78 °C and the pyridinium salt was added either as a solid or in a solution of THF (10 mL). The reaction was stirred for 1 h at −78 °C and then the electrophile (5 equiv.) was added dropwise. After a further one hour at −78 °C, saturated NH_4Cl solution (10 mL) was added and stirred for 15 min, followed by HCl (10 mL, 3 M) and the reaction was allowed to warm to rt over 16 h. The aqueous layer was washed with Et_2O (3 × 50 mL), basified with saturated Na_2CO_3 solution until the pH was >9 and extracted with CH_2Cl_2 (6 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*.

(B) Lithium–di-*tert*-butylbiphenyl (LiDBB). Sliced lithium wire (4 equiv.) and DBB (4 equiv.) were added to a Schlenk tube containing glass anti-bumping granules under an atmosphere of argon. The mixture was stirred vigorously for 2–4 h until the the lithium had been reduced to a fine powder. THF (30 mL) was added and the resultant deep blue-green solution was cooled to −78 °C and stirred for 30 min. The pyridinium salt (1 equiv.) was added as a solid and the reaction stirred for a further 15 min. 1,2-Dibromoethane (filtered through K_2CO_3 and $MgSO_4$) was added dropwise until the blue-green colour was quenched. The electrophile (4 equiv.) was added dropwise and the reaction stirred for 3 h before NH_4Cl (5 mL, saturated solution) was added, followed by stirring for a further 15 min. HCl (10 mL, 1 M) was added and the reaction was warmed to rt and stirred for 16 h. The reaction was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were washed with brine (50 mL, saturated solution), dried ($MgSO_4$) and concentrated *in vacuo*.

2-*iso*-Propoxycarbonyl-1-methyl-pyridinium iodide 8

A solution of pyridine **7** (2.35 g, 14.3 mmol) in methyl iodide (10 ml, 160 mmol) was heated at reflux for 16 h. Et_2O (30 ml) was added, and the resulting suspension filtered to give compound **8** (3.87 g, 88%) as a yellow solid which was washed with Et_2O (2 × 10 ml) and dried under vacuum. Mp 120–123 °C (Et_2O); ν_{max} (nujol)/cm^{-1}: 1735, 1621, 1457, 1283; δ_H (400 MHz, $CDCl_3$) 9.82 (1 H, d, *J* 6.0, CH), 8.86 (1 H, dd, *J* 7.9 and 7.9, CH), 8.53 (1 H, dd, *J* 7.9 and 1.2, CH), 8.44 (1 H, ddd, *J* 7.6, 6.4 and 1.2, CH), 5.34 [1 H, sp, *J* 6.3, $\mathrm{C}\mathit{H}(\mathrm{CH}_3)_2$], 4.74 (3 H, s, NCH_3), 1.43 [6 H, d, *J* 6.3, $\mathrm{CH}(\mathrm{C}\mathit{H}_3)_2$]; δ_C (100 MHz, $CDCl_3$) 158.6, 150.2, 147.3, 142.5, 131.4, 130.2, 73.9, 50.0, 21.8; HRMS (ESI) found 180.1023, $C_{10}H_{14}NO_2$ (M^+) requires 180.1025.

2-Methyl-2-aza-bicyclo[2.2.2]oct-7-ene-3,5,6-tricarboxylic acid 3-*iso*-propyl ester 5,6-dimethyl ester 10

A solution of dihydropyridine **9** (216 mg, 1.20 mmol) and dimethyl fumarate (203 mg, 1.41 mmol) in CH_2Cl_2 (10 ml) was heated at 55 °C for 3 h. The solvent was removed *in vacuo* and the crude residue purified by gradient flash column chromatography (SiO_2, petroleum ether to 5 : 95 acetone–petroleum ether) to produce the Diels–Alder adduct **10** (59 mg, 15%, 2 : 1 dr) as a yellow oil. ν_{max} (thin film)/cm^{-1}: 2982, 2933, 1732, 1436, 1374, 1200; δ_H (400 MHz, $CDCl_3$) (minor isomer): 6.73–6.69 (1 H, m, C5-H), 6.04 (1 H, t, *J* 7.3, C4-H), 5.01 [1 H, sp, *J* 6.4, $\mathrm{C}\mathit{H}(\mathrm{CH}_3)_2$], 4.01 (1 H, br. d, *J* 6.6, 6-H), 3.77 (3 H, s, CO_2CH_3), 3.74–3.64 (1 H, m, 7-H), 3.70 (3 H, s, CO_2CH_3), 3.53–3.48 (1 H, m, 3-H), 3.14 (1 H, d, *J* 1.4, 2-H), 2.89 (1 H, dd, *J* 5.2 and 1.7, 8-H), 2.50 (3 H, s, NCH_3), 1.24 (6 H, d, *J* 6.3, 2 × $\mathrm{CHC}\mathit{H}_3$); (major isomer) 6.52–6.48 (1 H, m, C5-H), 6.31 (1 H, t, *J* 7.1, C4-H), 4.98 [1 H, sp, *J* 6.3, $\mathrm{C}\mathit{H}(\mathrm{CH}_3)_2$], 3.80 (1 H, br. dd, app. *J* 6.0 and 2.2, 6-H), 3.78 (3 H, s, CO_2CH_3), 3.74–3.64 (1 H, m, 7-H), 3.68 (3 H, s, CO_2CH_3), 3.41–3.37 (1 H, m, 3-H), 3.09 (1 H, dd, *J* 6.0 and 2.9, 8-H), 2.86 (1 H, d, *J* 1.8, 2-H), 2.61 (3 H, s, NCH_3) 1.23 (3 H, d, *J* 6.4, $\mathrm{CHC}\mathit{H}_3$), 1.22 (3 H, d, *J* 6.4, $\mathrm{CHC}\mathit{H}_3$); δ_C (100 MHz, $CDCl_3$) (minor isomer): 173.7, 173.3, 172.3, 138.6, 127.9, 68.5, 65.4, 56.9, 52.5, 52.5, 46.0, 43.5, 41.7, 36.0, 22.0; (major isomer): 173.7, 173.3, 172.3, 135.3, 131.3, 68.6, 61.7, 56.5, 52.7, 52.5, 44.2, 41.2, 38.7, 35.9, 22.0; HRMS (ESI) found 326.1605, $C_{16}H_{24}NO_6$ (M + H^+) requires 326.1604.

4-Methoxy-2-methoxycarbonyl-1-methylpyridinium trifluoromethanesulfonate 15

Methyl trifluoromethanesulfonate (0.75 mL, 6.6 mmol) was added to a stirred solution of pyridine **12** (1.02 g, 6.13 mmol) in CH_2Cl_2 (5 mL) and stirred for 16 h at room temperature. The solution was concentrated *in vacuo* and the crude residue was purified *via* flash column chromatography (SiO_2, 5 : 95 MeOH–CH_2Cl_2) to furnish the pyridinium salt **15** (2.03 g, 100%) as a white solid. Mp 69–71 °C (CH_2Cl_2); ν_{max} (KBr)/cm^{-1}: 3078, 1637; δ_H (400 MHz, $CDCl_3$) 8.87 (1 H, d, *J* 7.2, CH), 7.84 (1 H, d, *J* 3.1, CH), 7.60 (1 H, dd, *J* 7.2 and 3.1, CH), 4.40 (3 H, s, NCH_3), 4.16 (3 H, s, OCH_3), 4.05 (3 H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 171.9, 159.8, 151.5, 143.5, 117.6, 114.5, 58.8, 54.8, 47.4; MS (ESI) 182 (M + H^+, 100%); HRMS (ESI) found 182.0826, $C_9H_{12}NO_3$ (M^+) requires 182.0817.

1-(2-Chloroethyl)-4-methoxy-2-methoxycarbonylpyridinium trifluoromethanesulfonate 16

A solution of pyridine **12** (820 mg, 4.90 mmol) and chloroethyl trifluoromethanesulfonate (1.03 g, 4.84 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 3 h. The solution was concentrated *in vacuo* and purified by gradient flash column chromatography (SiO_2, 1 : 9 acetone–CH_2Cl_2 to acetone) to isolate the product **16** (835 mg, 44%) as an oil which was thoroughly dried under high vacuum prior to further use. ν_{max} (KBr)/cm^{-1}: 1636; δ_H (400 MHz, $CDCl_3$) 9.00 (1 H, d, *J* 7.2, CH), 7.89 (1 H, d, *J* 3.4, CH), 7.68 (1 H, dd, *J* 7.3 and 3.2, CH), 5.23 (2 H, t, *J* 5.5, $\mathrm{ClCH_2C}\mathit{H}_2\mathrm{N}$), 4.22 (3 H, s, CH_3), 4.08 (3 H, s, CH_3), 4.04 (2 H, t, *J* 5.5, $\mathrm{ClC}\mathit{H}_2\mathrm{CH_2N}$); δ_C (100 MHz, $CDCl_3$) 172.5, 160.1, 151.7, 143.6, 118.1, 114.5, 59.1, 59.0, 55.1, 43.5; HRMS (ESI) found 230.0584, $C_{10}H_{13}NO_3Cl$ (M^+) requires 230.0584.

1-But-3-enyl-4-methoxy-2-methoxycarbonylpyridinium trifluoromethanesulfonate 17

Triflic anhydride (0.90 mL, 6.5 mmol) was added to a solution of homoallyl alcohol (0.43 mL, 5.0 mmol) and Hünig's base (0.95 mL, 5.5 mmol) in toluene (5 mL) at 0 °C. The mixture was stirred for 16 h at room temperature, and the resultant suspension was filtered to give a brown solution to which pyridine **12** (0.678 g, 4.06 mmol) was added. The mixture was stirred for 16 h and concentrated *in vacuo* to give the crude product as a brown oil which was taken up into CH_2Cl_2 (30 mL) and extracted with distilled H_2O (6 × 40 mL). The aqueous extracts were combined, concentrated *in vacuo* and thoroughly dried under high vacuum over phosphorus pentoxide to give pyridinium salt **17** (1.49 g, 99%) as an oil. ν_{max} (KBr)/cm^{-1}: 1743 and 1636; δ_H (400 MHz, $CDCl_3$) 8.95 (1 H, d, *J* 7.2, 6-H), 7.85 (1 H, d, *J* 3.0, 3-H), 7.65 (1 H, dd *J* 7.2 and 3.1, 5-H), 5.77 (1 H, ddt, *J* 17.0 10.0 and 7.0, $\mathrm{C}\mathit{H}{=}\mathrm{CH_2}$), 5.09 (1 H, dd, *J* 10.2 and 0.4, $\mathrm{CH{=}C}\mathit{H}_\mathrm{A}\mathrm{H_B}$), 5.00 (1 H, dd, *J* 17.2 and 0.8, $\mathrm{CH{=}CH_A}\mathit{H}_\mathrm{B}$), 4.87 (2 H, t, *J* 7.0, NCH_2), 4.19 (3 H, s, CH_3), 4.09 (3 H, s, CH_3), 2.66 (2 H, dt, *J* 7.0 and 7.0, $\mathrm{NCH_2C}\mathit{H}_2$); δ_C (100 MHz, $CDCl_3$) 171.9, 160.0, 151.0, 143.3, 131.9, 120.5, 117.8, 114.7, 58.9, 58.3, 55.0 and 35.7; HRMS (ESI) found 222.1131, $C_{12}H_{16}NO_3$ (M^+) requires 222.1130.

(2-*RS*)-1-(2-Chloroethyl)-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 18

Sodium (112 mg, 4.90 mmol), naphthalene (776 mg, 6.06 mmol) and pyridinium salt **16** (365 mg, 0.96 mmol) were subjected to general procedure A using methyl iodide (0.5 mL, 8.03 mmol) as the electrophile. The residue was purified by reverse-phase chromatography (0.5 M NaCl) to give the product **18** (95.1 mg, 43%) as a yellow oil. $\nu_{\max}$ (thin film)/cm^{-1}: 2956, 1737, 1640, 1585, 1436, 1373 and 1272; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.07 (1 H, d, *J* 7.8, NC*H*=CH), 5.05 (1 H, dd, *J* 7.8 and 1.1, NCH=C*H*), 3.78–3.60 (3 H, m, $\mathrm{CH_2Cl}$ and $\mathrm{NC}H_{\mathrm{A}}\mathrm{H_BCH_2Cl}$), 3.74 (3 H, s, $\mathrm{CO_2CH_3}$), 3.57–3.50 (1 H, m, $\mathrm{NCH_A}H_{\mathrm{B}}\mathrm{CH_2Cl}$), 2.89 (1 H, d, *J* 16.3, $\mathrm{C{=}OC}H_{\mathrm{A}}\mathrm{H_B}$), 2.61 (1 H, dd, *J* 16.3 and 1.1, $\mathrm{C{=}OCH_A}H_{\mathrm{B}}$) and 1.59 (3 H, s, $\mathrm{CH_3}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 190.3, 173.4, 154.8, 101.0, 65.7, 53.3, 52.8, 47.2, 43.4 and 23.0; HRMS (ESI) found 232.0743, $\mathrm{C_{10}H_{15}NO_3Cl}$ (M + H$^+$) requires 232.0740.

(2-*RS*)-1-But-3-enyl-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 19

Sodium (457 mg, 19.9 mmol), naphthalene (3.16 g, 24.7 mmol) and pyridinium salt **17** (1.60 g, 2.69 mmol) were subjected to general procedure A using methyl iodide (2.5 mL, 40 mmol) as the electrophile. The crude residue was purified by flash column chromatography ($\mathrm{Et_3N}$-doped $\mathrm{SiO_2}$, 75 : 24.5 : 1 EtOAc–petroleum ether–$\mathrm{Et_3N}$) to give the product **19** (0.359 g, 37%) as a brown oil. $\nu_{\max}$ (thin film)/cm^{-1}: 2954, 1735, 1641, 1585 and 1270; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.03 (1 H, d, *J* 7.7, NC*H*=CH), 5.80–5.70 (1 H, m, NCH=C*H*), 5.14–5.12 (1 H, m, $\mathrm{CH{=}C}H_{\mathrm{A}}\mathrm{H_B}$), 5.09 (1 H, s, $\mathrm{CH{=}CH_A}H_{\mathrm{B}}$), 4.98 (1 H, dd, *J* 7.8 and 0.8, NCH=C*H*), 3.71 (3 H, s, $\mathrm{CO_2CH_3}$), 3.39 (1 H, qn, *J* 7.4, $\mathrm{NC}H_{\mathrm{A}}\mathrm{H_B}$), 3.26 (1 H, qn, *J* 7.4, $\mathrm{NCH_A}H_{\mathrm{B}}$), 2.86 (1 H, dd, *J* 16.5 and 0.8, $\mathrm{C{=}OC}H_{\mathrm{A}}\mathrm{H_B}$), 2.55 (1 H, d, *J* 16.5, $\mathrm{C{=}OCH_A}H_{\mathrm{B}}$), 2.36 (2 H, q, *J* 7.4, $\mathrm{NCH_2C}H_2$), 1.56 (3 H, s, $\mathrm{CH_3}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 190.1, 173.5, 154.6, 134.1, 118.1, 99.5, 65.7, 53.1, 50.9, 47.1, 35.4, 22.6; HRMS (ESI) found 224.1284, $\mathrm{C_{12}H_{18}NO_3}$ (M + H$^+$) requires 224.1287.

1-Benzyl-4-methoxy-2-methoxycarbonylpyridinium iodide 21

Pyridine **12** (632 mg, 3.78 mmol) was added to benzyl iodide (5.00 g, 22.9 mmol) at 30 °C under an atmosphere of argon. The reaction was wrapped in foil and stirred for 48 h. THF (20 mL) was added to the reaction and the precipitate was isolated by filtration and washed with further portions of THF (2 × 10 mL). The resulting solid was dried under high vacuum to furnish the pyridinium salt **21** (1.04 g, 72%) as a yellow powder. Mp 105–106 °C (THF); $\nu_{\max}$ (KBr)/cm^{-1}: 3031, 1743, 1626, 1570, 1332; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 9.83 (1 H, d, *J* 7.2, NCH), 7.90 [1 H, d, *J* 3.0, $\mathrm{C(OCH_3)C}H$], 7.78 (1 H, dd, *J* 7.2 and 3.0, NCH=C*H*), 7.37–7.30 (5 H, m, Ph), 6.19 (2 H, s, $\mathrm{NCH_2}$), 4.25 (3 H, s, $\mathrm{OCH_3}$), 3.96 (3 H, s, $\mathrm{OCH_3}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 171.7, 159.9, 150.5, 143.8, 133.0, 129.5, 129.3, 128.5, 117.7, 114.9, 61.0, 59.8, 55.0; *m/z* (ESI) 258 (M$^+$, 100%); HRMS (ESI) found 258.1132, $\mathrm{C_{15}H_{16}NO_3}$ (M$^+$) requires 258.1130.

(2-*RS*)-1-Benzyl-2-methyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 23

Lithium (19 mg, 2.7 mmol), DBB (536 g, 2.02 mmol) and pyridinium salt **21** (188 mg, 0.49 mmol) were subjected to general procedure B using methyl iodide (0.13 mL, 2.02 mmol) as the electrophile. The reaction was stirred for 5 min before the addition of 1,2-dibromoethane and the crude residue was purified *via* flash column chromatography ($\mathrm{SiO_2}$, 500 mL 1 : 99 $\mathrm{Et_2O}$–petroleum ether followed by 1 : 9 acetone–$\mathrm{CH_2Cl_2}$) to furnish the dihydropyridone **23** (60 mg, 47%) as a yellow oil. $\nu_{\max}$ (film)/cm^{-1}: 2994, 2952, 1739, 1641, 1578, 1451, 1372, 1271, 1212; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.39–7.27 (5 H, m, Ph), 7.00 (1 H, d, *J* 7.8, NCH), 5.01 (1 H, d, *J* 7.8, NCH=C*H*), 4.55 (1 H, d, *J* 15.8, $\mathrm{NC}H_{\mathrm{A}}\mathrm{H_B}$), 4.42 (1 H, d, *J* 15.8, $\mathrm{NCH_A}H_{\mathrm{B}}$), 3.72 (3 H, s, $\mathrm{CO_2CH_3}$), 2.92 (1 H, d, *J* 16.4, $\mathrm{C{=}OC}H_{\mathrm{A}}\mathrm{H_B}$), 2.62 (1 H, d, *J* 16.4, $\mathrm{C{=}OCH_A}H_{\mathrm{B}}$), 1.50 (3 H, s, $\mathrm{CCH_3}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 190.1, 173.3, 154.7, 137.4, 129.0, 128.0, 127.4, 100.0, 65.8, 55.1, 53.0, 47.0, 22.7; *m/z* (ESI) 318 (M + MeCN + $\mathrm{NH_4}^+$, 52%), 260 (M + H$^+$, 100); HRMS (ESI) found 260.1282, $\mathrm{C_{15}H_{18}NO_3}$ (M + H$^+$) requires 260.1287.

(2-*RS*)-2-(4-Iodobutyl)-1-(4-methoxybenzyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 26

Lithium (30 mg, 4.3 mmol), DBB (1.07 g, 4.04 mmol) and pyridinium salt **22** (414 mg, 1.00 mmol) were subjected to general procedure B using 1,4-diiodobutane (0.55 mL, 4.17 mmol) as the electrophile. The crude residue was purified *via* flash column chromatography ($\mathrm{SiO_2}$, 500 mL 1 : 99 $\mathrm{Et_2O}$–petroleum ether followed by 1 : 9 acetone–$\mathrm{Et_2O}$) to furnish the dihydropyridone **26** (281 mg, 62%) as a yellow oil. $\nu_{\max}$ (thin film)/cm^{-1}: 2593, 1737, 1581, 1514, 1460, 1252, 732; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.23 (2 H, d, *J* 8.8, ArH), 6.96 (1 H, d, *J* 7.8, NCH), 6.91 (2 H, d, *J* 8.8, ArH), 4.97 (1 H, d, *J* 7.8, NCH=C*H*), 4.48 (1 H, d, *J* 14.8, $\mathrm{NC}H_{\mathrm{A}}\mathrm{H_B}$), 4.36 (1 H, d, *J* 14.8, $\mathrm{NCH_A}H_{\mathrm{B}}$), 3.81 (3 H, s, $\mathrm{OCH_3}$), 3.72 (3 H, s, $\mathrm{CO_2CH_3}$), 3.14–3.06 (2 H, m, $\mathrm{CH_2I}$), 2.87 (1 H, d, *J* 16.3, $\mathrm{C{=}OC}H_{\mathrm{A}}\mathrm{H_B}$), 2.70 (1 H, d, *J* 16.3, $\mathrm{C{=}OCH_A}H_{\mathrm{B}}$), 2.00–1.86 (2 H, m, $\mathrm{CH_2}$), 1.84–1.65 (2 H, m, $\mathrm{CH_2}$), 1.55–1.39 (2 H, m, $\mathrm{CH_2}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 190.2, 172.9, 159.5, 154.2, 129.5, 128.3, 114.4, 99.8, 68.8, 55.3, 53.7, 52.9, 43.5, 33.4, 33.1, 24.8, 5.8; HRMS (ESI) found 458.0830, $\mathrm{C_{19}H_{25}NO_4I}$ (M + H$^+$) requires 458.0828.

(2-*RS*)-2-(4-Chlorobutyl)-1-*H*-5,6-dihydropyridone-2-carboxylic acid methyl ester 30

Dihydropyridone **25** (26 mg, 0.07 mmol) in trifluoroacetic acid (5 mL) was heated at reflux for 16 h. The reaction was concentrated *in vacuo* and the residue was dissolved in $\mathrm{CH_2Cl_2}$ (5 mL). Potassium carbonate (46.9 mg, 0.34 mmol) was added and the reaction mixture stirred for 16 h before being filtered and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography ($\mathrm{SiO_2}$, 1 : 9 acetone–$\mathrm{Et_2O}$) to furnish the product **30** (16 mg, 91%) as a pale yellow oil. $\nu_{\max}$ (thin film)/cm^{-1}: 3237, 2955, 1738, 1579, 1439, 1238, 1019; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.19–7.14 (1 H, m, NCH), 5.59 (1 H, br. s, NH), 5.03 (1 H, dd, *J* 7.6 and 1.1, NCH=C*H*), 3.79 (3 H, s, $\mathrm{CO_2CH_3}$), 3.52 (2 H, t, *J* 6.4, $\mathrm{CH_2Cl}$), 2.88 (1 H, d, *J* 16.3, $\mathrm{C{=}OC}H_{\mathrm{A}}\mathrm{H_B}$), 2.61 (1 H, d, *J* 16.3, $\mathrm{C{=}OCH_A}H_{\mathrm{B}}$), 2.06–1.97 (1 H, m, C*H*H), 1.80–1.69 (3 H, m, C*H*H and $\mathrm{CH_2}$), 1.52–1.32 (2 H, m, $\mathrm{CH_2}$); δ_{C} (100 MHz, $\mathrm{CDCl_3}$) 190.5, 173.3, 149.0, 99.6, 63.2, 53.1, 44.3, 43.5, 35.1, 31.9, 21.0; HRMS (ESI) found 246.0890, $\mathrm{C_{11}H_{17}NO_3Cl}$ (M + H$^+$) requires 246.0897.

(2-*RS*)-1-*H*-2-(4-iodobutyl)-5,6-dihydropyridone-2-carboxylic acid methyl ester 31

Dihydropyridone **26** (358 mg, 0.78 mmol) was treated by the same method as reported for dihydropyridone **25** and furnished the product **31** (199 mg, 76%) as a yellow oil. $\nu_{\max}$ (thin film)/cm^{-1}: 3229, 2952, 1738, 1580, 1437, 1237, 731; δ_{H} (400 MHz, $\mathrm{CDCl_3}$) 7.20–7.15 (1 H, m, NCH), 5.72 (1 H, br. s, NH), 5.02 (1 H, dd, *J* 7.5 and 1.0, NCH=C*H*), 3.78 (3 H, s, $\mathrm{CO_2CH_3}$), 3.16 (2 H, t, *J* 6.8, CH_2I), 2.87 (1 H, d, *J* 16.3, C=OCH_AH$_B$), 2.60 (1 H, d, *J* 16.3, C=OCH$_A$$H_B$), 2.03–1.94 (1 H, m, C*H*H), 1.82–1.67 (3 H, m, C*H*H and CH_2), 1.46–1.27 (2 H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 190.6, 173.3, 149.4, 99.4, 63.2, 53.1, 43.5, 34.7, 32.6, 24.6, 6.0; HRMS (ESI) found 338.0253, $C_{11}H_{17}NO_3I$ (M + H$^+$) requires 338.0253.

(2-*RS*)-2-Methyl-1-(4-methoxybenzyl)-tetrahydropyridone-2-carboxylic acid methyl ester 33

L-Selectride (0.34 mL, 1 M in THF, 0.34 mmol) was added dropwise to a stirred solution of dihydropyridone **24** (50 mg, 0.17 mmol) in THF (3 mL) at −78 °C. The reaction was stirred for 1 h before the addition of MeOH (2 mL) and H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers where dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (SiO_2, 2 : 3 Et_2O-petroleum ether) to yield the tetrahydropyridone **33** (34 mg, 71%) as an oil. ν_{max} (thin film)/cm^{-1}: 2956, 2836, 1727, 1612, 1512, 1245; δ_H (400 MHz, $CDCl_3$) 7.28 (2 H, d, *J* 8.6, ArH), 6.88 (2 H, d, *J* 8.6, ArH), 4.11 (1 H, d, *J* 13.9, NCH_AH$_B$), 3.81 (3 H, s OCH_3), 3.74 (3 H, s, CO_2CH_3), 3.24 (1 H, d, *J* 13.9, NCH$_A$$H_B$), 2.92 (1 H, ddd, *J* 14.6, 6.4 and 3.6, NCH_AH$_B$CH$_2$), 2.72 (1 H, dd, *J* 14.7 and 1.8, C=OCH_AH$_B$), 2.58 (1 H, ddd, *J* 14.6, 9.9 and 4.8, NCH$_A$$H_BCH_2$), 2.43 (1 H, d, *J* 14.7, C=OCH$_A$$H_B$), 2.34 (2 H, m, NCH$_2CH_2$), 1.53 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 207.1, 172.7, 158.8, 131.5, 129.4, 113.8, 65.0, 55.3, 53.6, 51.7, 50.8, 46.2, 40.7, 23.6; HRMS (ESI) found 314.1363, $C_{16}H_{21}NO_4Na$ (M + Na$^+$) requires 314.1363.

(2-*RS*)-1-*H*-2-Methyltetrahydropyridone-2-carboxylic acid methyl ester 34

Palladium on carbon (5 mg, 20% loading) was added to a stirred solution of tetrahydropyridone **33** (30 mg, 0.10 mmol) in MeOH (5 mL) under an atmosphere of hydrogen. The reaction was stirred for 2 h before filtration through Celite®. The mixture was concentrated *in vacuo* and the crude residue was purified *via* flash column chromatography (SiO_2, 3 : 2 acetone–petroleum ether) to furnish the tetrahydropyridone **34** (9 mg, 50%) as an oil. ν_{max} (thin film)/cm^{-1}: 3426, 2981, 2852, 1715, 1645, 1455, 1439, 1365, 1228, 1145; δ_H (400 MHz, $CDCl_3$) 3.73 (3 H, s, CO_2CH_3), 3.22 (1 H, ddd, *J* 12.4, 6.7 and 3.4, NCH_AH$_B$CH$_2$), 2.92 (1 H, ddd, *J* 12.4, 10.7 and 4.2, NCH$_A$$H_BCH_2$), 2.81 (1 H, dd, *J* 14.7 and 1.9, C=OCH_AH$_B$), 2.45 (1 H, ddd, 14.8, 10.7 and 6.7, NCH$_2$CH_AH$_B$), 2.37–2.29 (2 H, m, C=OCH$_A$$H_B$ and NCH$_2$CH$_A$$H_B$), 2.01 (1 H, br. s, NH), 1.41 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 206.9, 175.3, 62.0, 52.4, 49.7, 41.9, 40.78, 26.5; HRMS (ESI) found 194.0790, $C_8H_{13}NO_3Na$ (M + Na$^+$) requires 194.0788.

1,2,3-Trimethyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 36

Iron(III) chloride (5 mg) was added to a solution of sodium (30.0 g, 1.3 mmol) in ammonia (*ca.* 30 mL) and stirred until the dark blue colour faded to leave a grey suspension. Dihydropyridone **14** (99.5 mg, 0.54 mmol) was added in THF (10 mL). The solution was stirred at −78 °C for 30 min before the addition of methyl iodide (0.16 mL, 2.6 mmol) after which the mixture was stirred for a further 1 h. Saturated NH_4Cl solution (10 mL) was added and the mixture warmed to room temperature to allow the evaporation of the ammonia, basified (pH > 9) with saturated Na_2CO_3 solution and extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by gradient flash column chromatography (basic Al_2O_3, CH_2Cl_2 to 5 : 95 acetone–CH_2Cl_2) to give the product **36** (70.9 mg, 69%) as an off-white solid. Mp 93–96 °C; ν_{max} (thin film)/cm^{-1}: 2980, 2953, 1738, 1644 and 1591; δ_H (400 MHz, $CDCl_3$) 6.95 (1 H, d, *J* 7.5, NC*H*=CH), 4.89 (1 H, d, *J* 7.5, NCH=C*H*), 3.74 (3 H, s, CO_2CH_3), 3.06 (3 H, s, NCH_3), 2.77 (1 H, q, *J* 7.3, C=OC*H*CH$_3$), 1.43 (3 H, s, CH_3) and 1.07 [3 H, d, *J* 7.3, C=OCHCH_3)]; δ_C (100 MHz, $CDCl_3$) 194.7, 173.6, 154.6, 97.8, 68.3, 53.0, 47.0, 39.4, 17.1 and 11.4; HRMS (ESI) found 198.1137, $C_{10}H_{16}NO_3$ (M + H$^+$) requires 198.1130.

(2-*RS*)-1-(Methoxybenzyl)-2-methyl-5-phenyl-5,6-dihydropyridone-2-carboxylic acid methyl ester 39

Phenylboronic acid (136 mg, 1.12 mmol) and Na_2CO_3 (151 mg, 1.42 mmol) were added to a stirred solution of dihydropyridone **37** (230 mg, 0.56 mmol) and palladium/carbon (69 mg, 10% loading) in 1,2-dimethoxyethane–H_2O (5 mL, 1 : 1) at room temperature. The reaction was stirred for 18 h and then filtered through Celite® before being diluted with brine (5 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers where dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified *via* flash column chromatography (SiO_2, 7 : 3 Et_2O–petroleum ether) to yield the dihydropyridone **39** (184 mg, 90%) as an oil. ν_{max} (thin film)/cm^{-1}: 2998, 2953, 1738, 1641, 1594, 1513, 1367, 1249; δ_H (400 MHz, $CDCl_3$) 7.36–7.33 (2 H, m, ArH), 7.30–7.25 (5 H, m, ArH), 7.16 (1 H, tt, *J* 7.3 and 1.6, NCH), 6.93 (2 H, d, *J* 8.8, ArH), 4.56 (1 H, d, *J* 15.4, NCH_AH$_B$), 4.46 (1 H, d, *J* 15.4, NCH$_A$$H_B$), 3.82 (3 H, s, OCH_3), 3.75 (3 H, s, CO_2CH_3), 3.09 (1 H, d, *J* 16.2, C=OCH_AH$_B$), 2.79 (1 H, d, *J* 16.2, C=OCH$_A$$H_B$), 1.59 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 187.3, 173.3, 159.4, 153.3, 135.6, 129.0, 128.9, 128.1, 127.8, 125.9, 114.4, 112.4, 66.0, 55.3, 54.3, 53.0, 47.6, 22.4; HRMS (ESI) found 366.1698, $C_{22}H_{24}NO_4$ (M + H$^+$) requires 366.1705.

6-Methoxypyridine-2-carboxylic acid methyl ester 41

A suspension of 6-hydroxypicolinic acid **40** (2.53 g, 18.2 mmol), silver carbonate (15.0 g, 54.6 mmol) and methyl iodide (9 mL) in chloroform (100 mL) was heated at reflux for 18 h in the dark. The reaction mixture was filtered through a silica pad and the filtrate was concentrated *in vacuo*. Purification of the residue *via* flash column chromatography (SiO_2, 5 : 95 EtOAc–petroleum ether) gave the product **41** (2.75 g, 91%) as colourless cubes, whose data were consistent with those reported in the literature.[29]

1-Methyl-6-oxo-1,6-dihydropyridine-2-carboxylic acid methyl ester 42

A solution of methoxypyridine **41** (4.00 g, 23.9 mmol) in methyl iodide (7.44 mL, 120 mmol) was heated in a sealed tube at 200 °C for 18 h. The methyl iodide was evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2, 1 : 1 EtOAc–petroleum ether) to give pyridone **42** (3.65 g, 21.8 mmol, 91%) as colourless cubes. The data were consistent with those reported in the literature.[24]

6-Methoxy-2-carboxylic acid methyl ester-*N*-methylpyridinium trifluoromethanesulfonate 43

A solution of pyridine **41** (1.89 g, 11.3 mmol) and methyl trifluoromethanesulfonate (1.47 mL, 13.0 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the resulting crude residue was purified *via* flash column chromatography (SiO_2, 3 : 97 MeOH–CH_2Cl_2) to furnish the pyridinium salt **43** (3.73 g, 100%) as colourless needles. Mp 54–55 °C ($CHCl_3$–Et_2O); Anal. calc. for $C_{10}H_{12}F_3NO_6S$: C, 36.26; H, 3.65; N, 4.23; S, 9.68. Found: C, 36.11; H, 3.60; N, 4.09; S, 9.60%; ν_{max} (KBr)/cm^{-1}: 1745, 1628, 1590, 1511, 1438, 1349, 1271 and 1031; δ_H (400 MHz, $CDCl_3$) 8.52 (1 H, dd, *J* 8.9, 7.9 Hz, 4-H), 7.92–7.97 (m, 2 H, 3-H and 5-H), 4.46 (s, 3 H, OCH_3), 4.23 (s, 3 H, NCH_3) and 4.08 (s, 3 H, OCH_3); δ_C (100 MHz, $CDCl_3$) 162.0, 160.2, 147.6, 140.8, 121.4, 115.2, 60.5, 54.5, 38.5; *m/z* (ESI) 182 (M^+, 100%); HRMS (CI) found 182.0819, $C_9H_{12}NO_3$ (M^+) requires 182.0817.

(2-*RS*)-1,2-Dimethyl-3,4-dihydropyridone-2-carboxylic acid methyl ester 44

Sodium (173 mg, 7.5 mmol), naphthalene (960 mg, 7.50 mmol) and pyridinium salt **43** (490 mg, 1.48 mmol) were subjected to general procedure A using methyl iodide (0.62 mL, 7.5 mmol) as the electrophile. Removal of the aqueous solvent *in vacuo* gave a pale yellow crude residue which was added to an acetic anhydride–pyridine solution (1 : 1, 1.5 mL). The reaction was stirred for 20 h and concentrated *in vacuo*. NaOH (1 M, 10 mL) was added and the reaction mixture extracted with CH_2Cl_2 (6 × 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified *via* flash column chromatography (SiO_2, 5 : 95 acetone–CH_2Cl_2) to furnish dihydropyridone **44** (128 mg, 47%) as a yellow solid. Mp 93–96 °C (acetone–petroleum ether); ν_{max} (KBr)/cm^{-1}: 1738 and 1651; δ_H (400 MHz, $CDCl_3$) 5.86 (1 H, ddd, *J* 10.1, 3.6 and 3.5, $CH_2CH{=}CH$), 5.61 (ddd, 1 H, *J* 10.1, 2.2 and 2.0, $CH_2CH{=}CH$), 3.72 (s, 3 H, CO_2CH_3), 3.00–3.04 (m, 2 H, CH_2), 2.92 (s, 3 H, NCH_3) and 1.62 (s, 3 H, CH_3); δ_C (100 MHz, $CDCl_3$) 172.0, 167.7, 126.3, 123.9, 66.4, 53.0, 31.4, 30.3 and 23.9; *m/z* (CI) 184 (M + H$^+$, 100%), 124 (M − CO_2Me, 65%); HRMS (CI) found 184.0975, $C_9H_{14}NO_3$ (M + H$^+$) requires 184.0974.

(2-*RS*)-1-Methyl-3,4-dihydropyridone-2-carboxylic acid methyl ester 45

Sodium (115 mg, 5.0 mmol), naphthalene (641 mg, 5.0 mmol) and pyridinium salt **43** (336 mg, 1.02 mmol) were subjected to general procedure A using methanol (2 mL) as the electrophile. The crude residue was purified *via* flash column chromatography (SiO_2, 5 : 95 acetone–CH_2Cl_2) to furnish dihydropyridone **45** (34 mg, 20%) as a pale yellow oil. Anal. calc. for $C_8H_{11}NO_3$: C, 54.60; H, 6.45; N, 7.82. Found: C, 54.49; H, 6.43; N, 7.81%; ν_{max} (thin film)/cm^{-1}: 2955, 1746 and 1652; δ_H (400 MHz, $CDCl_3$) 5.94 (1 H, dddd, *J* 9.9, 4.1, 3.0 and 1.5, $CH_2CH{=}CH$), 5.82 (1 H, dddd, *J* 9.9, 4.8, 2.3 and 1.5, $CH_2CH{=}CH$), 4.58 (1 H, dddd, *J* 4.8, 3.5, 3.5 and 1.5, 2-H), 3.78 (3 H, s, CO_2CH_3), 3.01–3.05 (2 H, m, CH_2) and 2.98 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 169.7, 167.7, 126.4, 119.6, 63.8, 52.8, 33.7, 32.0; *m/z* (CI) 170 (M + H$^+$, 100%); HRMS (CI) found 170.0822, $C_8H_{12}NO_3$ (M + H$^+$) required 170.0817.

(2-*RS*)-1-Methyl-3,4-dihydropyridone-2-carboxylic acid methyl ester 45

Pyridone **42** (167 mg, 1.00 mmol) was reduced using the general procedure B. After addition of the 1,2-dibromoethane, saturated NH_4Cl solution (5 mL) was added. On work-up and purification by column chromatography (SiO_2, acetone–CH_2Cl_2, 20 : 80) dihydropyridone **45** (98 mg, 0.58 mmol, 58%) was obtained as colourless needles. Spectroscopic data were consistent with those reported earlier.

1,2,5-Trimethyl-3,4-dihydropyridone-2-carboxylic acid methyl ester 46

Lithium (28 mg, 4.0 mmol), DBB (1.05 g, 3.95 mmol) and pyridone **42** (175 mg, 1.05 mmol) were subjected to general procedure B using methyl iodide (0.36 mL, 5.8 mmol) as the electrophile. The crude residue was purified by flash column chromatography (SiO_2, 70 : 30 Et_2O–petroleum ether to Et_2O) to yield dihydropyridone **46** (121 mg, 58%, 4 : 1 dr) as a pale yellow oil. The diastereoisomers were inseparable and the data are quoted for the mixture. ν_{max} (thin film)/cm^{-1}: 2955, 1741, 1650; δ_H (400 MHz, $CDCl_3$) 5.80 (1 H, m, 4-H), 5.56 (1 H, d, *J* 10, 3-H), 3.74 (3 H, s, OCH_3), 2.93–3.03 (1 H, m, $CHCH_3$), 2.89 (3 H, m, NCH_3), 1.62 (3 H, m, C2–CH_3), 1.33 (3 H, d, *J* 7.4, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) 172.2, 171.5, 130.2 + 130.0, 125.0 + 124.9, 66.5 + 66.3, 53.0 + 53.0, 35.7 + 35.2, 30.6 + 30.5, 24.3 + 24.0, 19.4 + 19.1; MS (CI) 198 (M + H$^+$, 100%), 138 (M − CO_2Me, 38%); HRMS (CI) found 198.1130, $C_{10}H_{16}NO_3$ (M + H$^+$) requires 198.1123.

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