# Use of dissolving metals in the partial reduction of pyridines: formation of 2-alkyl-1,2-dihydropyridines

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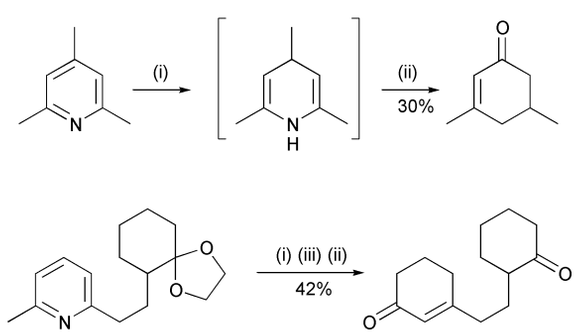
The partial reduction of a series of electron deficient pyridines to give both 1,2- and 2,5-dihydropyridines is described. The factors that lead to formation of such dihydropyridines are discussed and it was found that, generally, the presence of two activating groups on the pyridine nucleus is optimal. A series of 2-alkyl-1,2-dihydropyridines was prepared using either Birch or sodium naphthalenide reducing conditions and some preliminary derivatisation chemistry has been examined. The identity of three relevant nitrogen containing heterocycles was proven by X-ray crystallography.

## Introduction

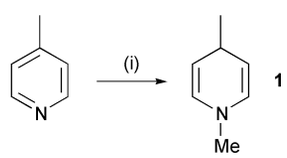
During the past five years we have reported the results of a study into the partial reduction reactions of various aromatic heterocycles.[1] This work was driven by the belief that such chemistry would prove to be a viable and versatile method of forming biologically active natural products. While early work concentrated on the reduction of both pyrroles[2] and furans,[3] we had the longer term goal of studying the partial reduction of pyridines and applying this methodology in synthesis. Recently, we reported the preliminary results of a study into the use of sodium–ammonia to reduce the pyridine nucleus and we now wish to describe our efforts in full.[4]

Initial reports, from the beginning of the twentieth century, describe the reduction of pyridine using metal–ammonia conditions.[5] In most cases, however, the resulting dihydropyridines were not isolated but instead hydrolysed to the corresponding 1,5-diketone. Similar reductions were carried out by Shaw,[5] Birch[6] and Danishefsky,[7] with subsequent hydrolysis conditions resulting in the isolation of the aldol condensation products from the initially formed 1,5-diketones (Scheme 1).




**Scheme 1** *Reagents:* i. Na, $NH_3$, EtOH; ii. $H_3O^+$; iii (aq.) NaOH.

More recent investigations into the metal–ammonia reduction of pyridines worked towards isolation of the dihydropyridine intermediates discussed earlier. Although the synthesis of dihydropyridine systems had been achieved decades earlier, the first reported isolation of dihydropyridine compounds from the partial reduction of pyridine was by Birch in 1975.[8] Reduction of 4-methylpyridine with lithium–ammonia (with one equivalent of ethanol present) followed by addition of an electrophile, enabled dihydropyridine adduct **1** to be isolated (Scheme 2). Olah and Hunadi noted that some of the dihydropyridines made *via* this procedure were particularly sensitive to oxygen and unstable above 0 °C, although storage at freezer temperature under an atmosphere of argon was possible.[9]




**Scheme 2** *Reagents:* i. Li, $NH_3$, EtOH (1 eq.), then MeX.

Many research groups have reported the partial reduction of pyridines and pyridinium salts using a plethora of reducing agents and placing the results obtained under Birch conditions into the context of other related reductions is a complex task. Generally, however, it can be seen that the hydride promoted reduction of electron deficient pyridines usually gives 1,4-dihydropyridines[10] while reduction of acyl pyridinium salts tends to produce 1,2-dihydropyridine compounds.[11] In light of this, the general regiochemical outcome and opportunity for reductive alkylation procedures expected for the Birch reduction make this approach unique and potentially useful.

## Results and discussion

With the literature precedent in mind, we thought it odd that the three acid derivatives of pyridine (picolinic, nicotinic and isonicotinic) had not been successfully reduced under Birch's conditions. A brief consideration of the likely structure of the dihydropyridine products suggested to us that they may be unstable with respect to autooxidation (or even decarboxylation) and rearomatisation probably occurs. So, in an attempt to circumvent this pitfall, we examined reductive alkylation reactions of the three esters **2**, **3** and **4**, Scheme 3. Unfortunately, all attempts to isolate dihydropyridine products from **2** and **3** were unsuccessful with complex multicomponent mixtures being formed. However, we were able to accomplish the reductive alkylation of **4** and trap the enolate intermediate with three

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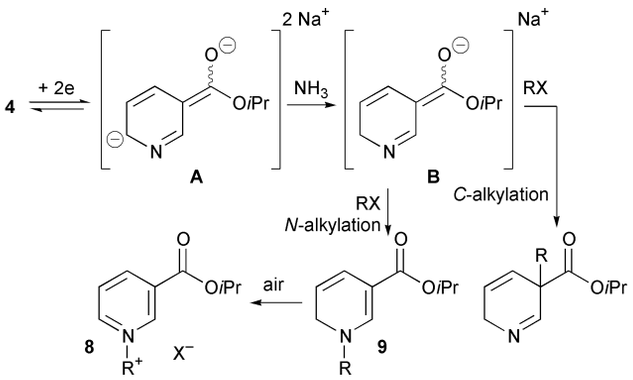
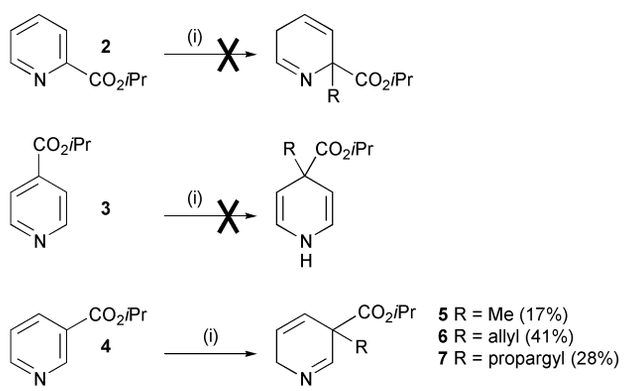



**Fig. 1**




**Scheme 3** *Reagents:* i. Na, $NH_3$, then RX.

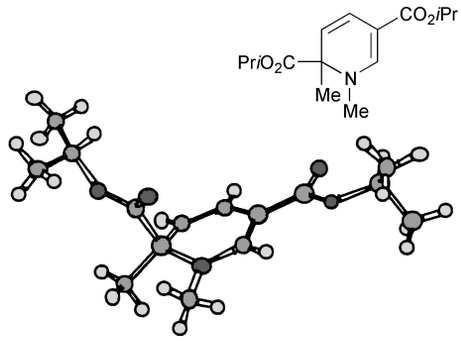
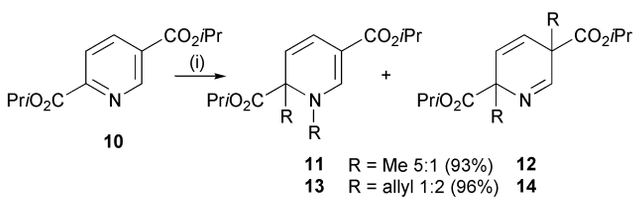


**Fig. 2** X-Ray structure of **11**

propargyl bromide as evidenced by the higher yields with these two electrophiles. We suspect that this bias may be related to the hard/soft characteristics of the electrophile.

In an attempt to overcome the issue of enolate regioselectivity we prepared pyridine diester **10** in one step from the commercially available diacid, (*i*PrOH, $H_2SO_4$, 65%, Scheme 4).




**Scheme 4** *Reagents:* i. Na, $NH_3$, then RX.

different electrophiles. The structure of these compounds was evident from NMR data and, for example, compound **5** displayed $^1$H NMR $\delta$ 7.81 (1H, br s, *H*C=N): the IR of **5**, **6**, and **7** also showed absorptions at 1674–1676 cm$^{-1}$, which is typical for an imine stretch.

Despite this success, the yields of **5**, **6**, and **7** were not particularly good and varied with the electrophile chosen to quench the reaction. While the reaction mixture, isolated after work-up, was quite clean and contained mostly the desired product, the mass recovery from such a work up was low. In one case we managed to track down some of the missing mass by evaporation of the aqueous extracts and observation ($^1$H NMR spectroscopy) of pyridinium salt **8** (R = Me, Fig. 1). This was a key observation as it allowed us to postulate a mechanism and, more importantly, identify one major problem in the reductive pathway. We propose that pyridine **4** accepts, at least in part, two electrons to form a reactive dianion **A** which is capable of deprotonating ammonia to furnish enolate **B**, Fig. 1. The presence of such a reactive species is necessary to rationalise the fact that reduction proceeds without a conventional proton source being added (*e.g. tert*-butyl alcohol) and that ammonia (p$K_a$ ~34) must be deprotonated: we would not expect simple radical anions to be basic enough to do this.[12] The problem arises when we attempt to alkylate **B**, which can either react at the alpha position (as extended enolates do) on carbon or on the nitrogen atom (presumably *via* reaction with the orthogonal lone pair). We suggest that the product from alkylation on nitrogen **9** is unstable with respect to autooxidation and so is transformed to a pyridinium salt **8** on work-up (1,6-dihydropyridines of type **9** are not common in the literature[13]). A control experiment was performed when compound **4** was dissolved in ammonia, at −78 °C and then quenched with methyl iodide. No reaction ensued and starting material was recovered quantitatively, so proving that the pyridinium salt **8** did indeed originate from a reductive process and was not merely formed by way of unreacted pyridine **4**.

It was noticed that the ratio of *C* to *N* alkylated products seems to be biased more towards *C*-alkylation with allyl- and

We reasoned that the presence of another ester group at C-2 would perturb the reaction of an enolate corresponding to **B** and so bias alkylation of an extended enolate at the alpha position. In the event, this proved not to be the case and reductive methylation with sodium in ammonia gave two dimethylated compounds **11** and **12** in a ratio of 5 : 1 and 93% yield. We were able to separate the major compound from this reaction and the structure of the conjugated diene **11** was confirmed by X-ray crystallography, Fig. 2. In a separate experiment, reaction with sodium–ammonia, followed by quenching with allyl bromide gave two diallylated compounds **13** and **14** in a ratio of 1 : 2 (96%). In this instance we could purify the imine isomer **14** completely and confirmed that it had the structure shown: $^1$H NMR spectroscopy showed $\delta$ 7.99 (dd, 1H, *J* 2.5, 0.7, *H*C=N) and IR spectroscopy showed an imine stretch at 1679 cm$^{-1}$.

These results dovetail nicely with the mechanism proposed earlier in Fig. 1. We believe that pyridine **10** is now sufficiently electron deficient to sustain a dianion **C** in liquid ammonia and this dianion reacts twice with an external electrophile, Fig. 3. One would predict that dianion **C** should react firstly at C-2 to furnish enolate **D** (which is analogous to enolate **B**, Fig. 1). It appears that the neopentyl-like nature of the enolate nitrogen is insufficient to discourage subsequent alkylation of **D** on the nitrogen atom (to form **11** and **13**); this is accompanied by some reaction at the carbon (alpha) site to furnish **12** and **14**. It is noteworthy that allyl bromide again gives more *C*-alkylation than methyl iodide, continuing the trend seen in Scheme 3. In essence, compounds **12** and **14** are analogues of the putative intermediate **9** shown in Fig. 1 although, in this case, we can isolate them because the site of autooxidation is blocked.

If one quenches the dianion **C** directly with excess ammonium chloride then only pyridine **10** is recovered, suggesting that under these conditions any dihydropyridine intermediate formed is unstable and undergoes rapid autooxidation.[14]

Construction of the mechanistic model described above allowed us to propose that dianion **C** could conceivably be alkylated once (at C-2) and then protonated. We reasoned that the site of protonation (*i.e.* carbon *versus* nitrogen) would be

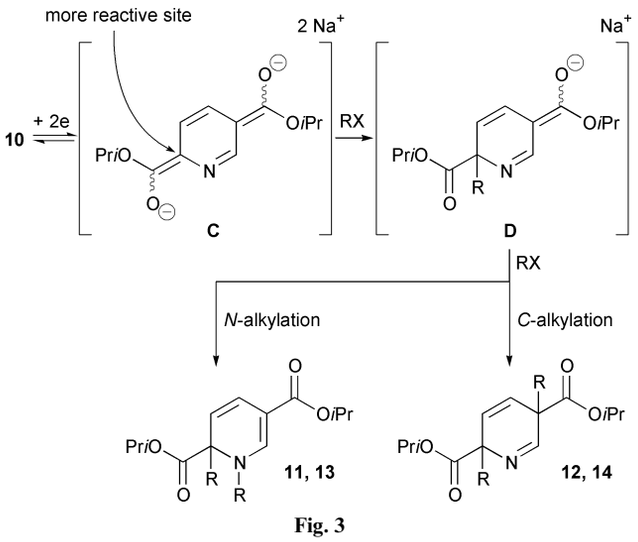
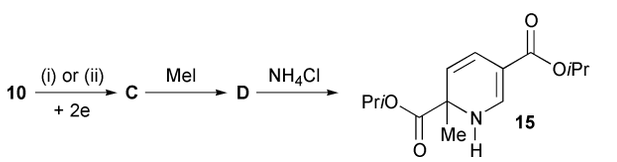



**Fig. 3**

unimportant as the products could tautomerise to the more thermodynamically stable compound *i.e.* that derived from protonation on nitrogen. This proved to be the case when compound **10** was reduced with sodium in ammonia and the dianion **C** quenched firstly with methyl iodide and secondly with aqueous ammonium chloride, Scheme 5. The time lag




**Scheme 5** *Reagents:* i. Na, $NH_3$, −78 °C (99%); ii. Na, naphthalene. THF, −78 °C (86%).

between addition of methyl iodide and ammonium chloride (8 seconds) was crucial to the success of this reaction. Too short an interval and the dianion **C** protonates twice (and we observe pyridine **10**): too long an interval and the dianion doubly alkylates to furnish **11** and **12**.

Use of other metals in the Birch reduction was briefly explored and, surprisingly, lithium metal gave a much less clean reaction when compared to sodium. In contrast, the reduction of **10** with calcium in ammonia, quenching firstly with methyl iodide and then ammonium chloride formed **15** in good yield (83%). Perhaps a more useful alternative to Birch reduction conditions was found when the ammonia solvent was replaced with THF and sodium–naphthalene was used as a source of electrons. This, recently developed, alternative to the Birch reduction has proven to be a practicable set of conditions for the partial reduction of heterocycles.[15] Under such conditions, naphthalene is used as an electron shuttle to transfer electrons from the metal to the heterocycle. ‡

Not surprisingly, when enolate **D** was generated under these 'ammonia free' conditions it behaved slightly differently to that generated in ammonia and the time lag between addition of the two electrophiles (1 minute) had to be re-optimised.

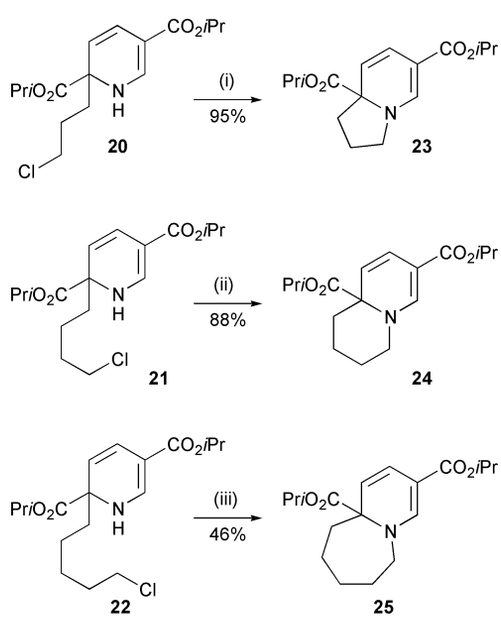
We then extended the methodology to encompass a range of electrophiles under both Birch and ammonia free conditions. In each case, we were able to achieve reductive (mono) alkylation in good to excellent yield, although an optimal time lag had to be sought for each electrophile under the two different sets of conditions, Table 1.

It should be mentioned at this point that the monoalkylated dihydropyridines **16–22** must be treated with care lest they rearomatise and that compound **19** is particularly sensitive. In each case studied, exposure to air causes loss of the R-group at C-2 and re-formation of pyridine **10** (this is a variable process and takes between 2–24 hours to become apparent by $^1$H NMR spectroscopy); this process can be prevented by storage in the freezer under an inert atmosphere. We suspect that this decomposition pathway is radical in nature.[16]

‡ It is important that the reaction is placed in a sonicator (typically for 1 h at RT) during formation of the sodium naphthalenide, as this process accelerates the dissolution of sodium metal.

### Derivatisation reactions of 2-alkyl-1,2-dihydropyridines

If this methodology is to prove useful in organic synthesis then it is imperative that we are able to manipulate the dihydropyridines thus formed. Initial studies concentrated on constructing another ring between the nitrogen and C-2 positions as related bicyclo-ring systems are present in a variety of interesting natural products. Although conceptually, it would seem that reaction of dianion **D** with 1,3-diiodopropane should give rise to a bicyclo 6,5-ring system directly, in practice, quenching the Birch reduction of **10** with this electrophile did not give rise to high yields of the desired product. Instead, we found it advantageous to reduce **10** and quench with a series of chloroiodoalkanes (Table 1, entries 7–12) and then perform cyclisation reactions on the derived 2-chloroalkyl-1,2-dihydropyridines, Scheme 6.



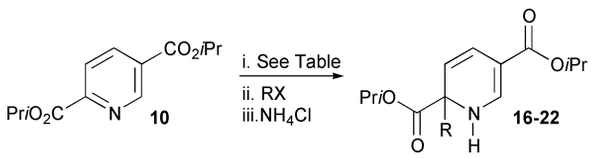

**Scheme 6** *Reagents:* i. DBU, $CH_2Cl_2$, Δ; ii. DBU, acetone, Δ; iii. KHMDS, 18-c-6, THF, Δ.

Preliminary experiments showed that both DBU in $CH_2Cl_2$ or acetone or a stronger base (sodium hydride or KHMDS) in THF effected a 5-*exo-tet* cyclisation[17] of **20** to the corresponding 6,5-bicyclo compound **23**. More challenging cyclisations were then performed on **21** and **22** in order to prepare bicyclo 6,6- and 6,7-ring systems respectively. As expected, the six membered ring formed rather easily and gave compound **24** in 88% yield with DBU in acetone but cyclisation of **22**, thus making a seven membered ring, was not as straightforward even though a variety of different conditions were screened. Eventually, we discovered that KHMDS in THF with 18-crown-6 additive gave the highest yield of **25** (46%).

Spectroscopic analysis confirmed the disappearance of a 3320 $cm^{-1}$ (N–H) peak in the IR spectrum of **23**, **24** and **25** and X-ray crystallography also confirmed the 6,5-bicyclic structure of **23** as shown below, Fig. 4.

It was also found that the dihydropyridine nitrogen could be protected as a Boc derivative under conditions that do not involve the use of a strong base, Scheme 7.[18] It is noteworthy

**Table 1**




| Entry | RX | R | Conditions | Yield (%) | Compound |
|---|---|---|---|---|---|
| 1 | EtI | Et | Na, $NH_3$ | 98 | **16** |
| 2 | EtI | Et | Na, naphthalene | 78 | **16** |
| 3 | *i*Bu | *i*Bu | Na, $NH_3$ | 93 | **17** |
| 4 | Epibromohydrin | [a] | Na, $NH_3$ | 90 | **18** |
| 5 | Epibromohydrin | [a] | Na, naphthalene | 84 | **18** |
| 6 | Allyl-Br | Allyl | Na, $NH_3$ | 99 | **19** |
| 7 | $I(CH_2)_3Cl$ | $(CH_2)_3Cl$ | Na, $NH_3$ | 96 | **20** |
| 8 | $I(CH_2)_3Cl$ | $(CH_2)_3Cl$ | Na, naphthalene | 96 | **20** |
| 9 | $I(CH_2)_4Cl$ | $(CH_2)_4Cl$ | Na, $NH_3$ | 100 | **21** |
| 10 | $I(CH_2)_4Cl$ | $(CH_2)_4Cl$ | Na, naphthalene | 91 | **21** |
| 11 | $I(CH_2)_5Cl$ | $(CH_2)_5Cl$ | Na, $NH_3$ | 97 | **22** |
| 12 | $I(CH_2)_5Cl$ | $(CH_2)_5Cl$ | Na, naphthalene | 94 | **22** |

[a] Formed as a mixture of diastereoisomers.

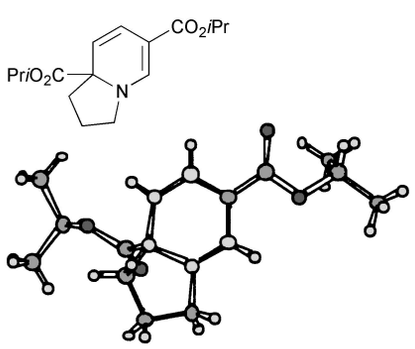



**Fig. 4** X-Ray structure of **23**.

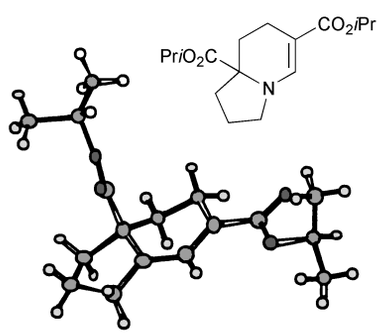
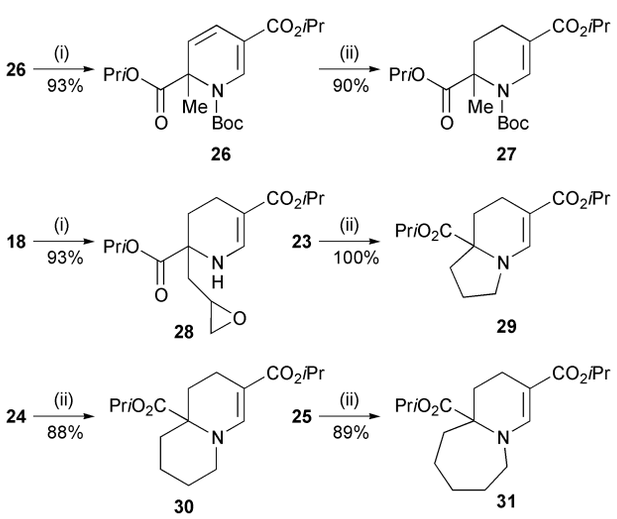



**Fig. 5** X-Ray structure of **29**.




**Scheme 7** *Reagents:* i. $(Boc)_2O$, $Et_3N$, DMAP, MeCN; ii. Pd/C, $H_2$.

that the product from this reaction **26** is much more air stable than the parent compound **15**, making handling and derivatisation easier.

Next, we examined catalytic hydrogenation of the diene unit under heterogeneous conditions and discovered that the C-3,4 alkene was more reactive than that at C-5,6, irrespective of the group on the nitrogen, Scheme 7. Given the extended conjugation present in the latter alkene, this difference in reactivity was not unexpected but it may, however, lead the way to further regioselective transformations of these compounds. The regioselective nature of the hydrogenation was indicated by examination of the NMR spectra of **27**–**31** which showed the presence of one alkene-hydrogen in the $^1H$ NMR spectrum, but of two alkene carbons in the $^{13}C$ NMR spectrum. The identity of compound **29** was further confirmed *via* X-ray crystallography, Fig. 5.

## Conclusions

To conclude, we have examined the partial reduction of a series of electron-deficient pyridines and have shown that alkylated dihydropyridines can be produced in moderate to excellent yields depending upon the substitution pattern of the pyridine; the presence of an alkyl group at either C-2 (**15**–**22**) or C-3 (**5**–**7**) was deemed to be essential to prevent subsequent autooxidation and rearomatisation. A range of different alkyl groups may be introduced onto the dihydropyridine skeleton using either the Birch reduction or alternative conditions that do not require ammonia solvent and which use naphthalene as an electron shuttle. Finally, these partial reduction procedures enabled us to produce precursors to a range of bicyclo-compounds *via* reductive alkylation with chloroiodoalkanes and these were subsequently cyclised under basic conditions to provide a short route to nitrogen containing 6,5- and 6,6- and 6,7-bicycles ready for further elaboration.

## Experimental

### General details

All reactions were carried out under an atmosphere of dry nitrogen. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian Inova 300 at 300 MHz, a Varian Inova 400 at 400 MHz or a Bruker Unity 500 (500 MHz). $^{13}C$ nuclear magnetic resonance spectra were recorded on Varian Inova 300 (75 MHz), Varian Inova 400 (100 MHz) and Bruker Unity 500 (125 MHz) instruments. Coupling constants (*J*) are quoted in Hz; sp indicates a septet. Infrared spectra (IR) were recorded on an ATI Mattson Genesis FTIR as evaporated films. Mass spectra were recorded on a Kratos Concept or a Micromass Trio 2000. Chemical ionisation (CI) was performed using $NH_3$. Microanalysis was obtained from the microanalytical section of the University of Manchester's Chemistry Department. Melting points were obtained on a Kofler heated stage microscope and are uncorrected. Thin layer chromatography (TLC) was carried out using Polygram $G/UV_{254}$ pre-coated plastic plates. Flash column chromatography was carried out using the solvent systems indicated and Silica Gel 60 (230–400 mesh). All solvents and reagents requiring purification were done so using standard laboratory techniques according to methods published in Purification of Laboratory Chemicals.[19] Tetrahydrofuran (THF) was dried and distilled from sodium metal using benzophenone as indicator, under an atmosphere of nitrogen. Dichloromethane (DCM) was distilled over calcium hydride. Petroleum ether (boiling range 40–60 °C) was distilled prior to use. Ammonia was distilled from sodium metal and ferric chloride.

### (*RS*)-3-Methyl-3,6-dihydropyridine-3-carboxylic acid isopropyl ester 5

A solution of freshly distilled ammonia (75 mL), THF (20 mL) and sodium (275 mg, 12.0 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine ester **4** (416 mg, 2.52 mmol) and bis(methoxyethyl)amine (2 mL, 13.5 mmol) in THF (10 mL) was followed by stirring for a further 40 minutes. Rapid addition of MeI (7.00 mL, 112 mmol) [reaction colour changed to yellow] was followed by continued stirring at −78 °C for 4 hours before addition of saturated ammonium chloride solution (3 mL). The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (1.28 g). Gradient column chromatography on silica eluting with 95 : 5 hexanes–EtOAc followed by 90 : 10 hexanes–EtOAc isolated **5** as a colourless oil (75.9 mg, 0.42 mmol, 17%). $\delta_H$ 7.81 (s, br, 1H), 5.90 (d, br, 1H, *J* 9.9), 5.82 (dd, br, 1H, *J* 9.9, *J* 1.8), 5.01 (sp, 1H, *J* 6.3), 4.15 (s, br, 2H), 1.38 (s, 3H), 1.23 (d, br, 6H, *J* 6.3); $\delta_C$ 171.55, 161.10, 125.44, 124.96, 68.79, 49.13, 43.92, 23.50, 21.52, 21.48; *m*/*z* 182 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{10}H_{15}O_2N$ ($+H^+$) requires 182.1181, found 182.1179 (1.1 ppm); IR (film)/$cm^{-1}$ 3441 (w), 2980 (s, C–H), 2926 (s, C–H), 2852 (m, C–H), 1727 (s, (C=O)O*i*Pr), 1674 (s, C=N), 1241 (s), 1104 (s), 912 (s), 733 (s).

### (*RS*)-3-Allyl-3,6-dihydropyridine-3-carboxylic acid isopropyl ester 6

A solution of freshly distilled ammonia (100 mL), THF (20 mL) and sodium (180 mg, 5.41 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine ester **4** (249 mg, 1.51 mmol) and bis(methoxyethyl)amine (1 mL, 6.77 mmol) in THF (20 mL) was followed by stirring for a further 1 hour. Isoprene (10 drops) was added until the blue colouration dissipated and a dark yellow solution resulted. Rapid addition of allyl bromide (1.90 mL, 22.0 mmol) [reaction colour changed to light yellow] was followed by continued stirring at −78 °C for 1 hour before addition of saturated ammonium chloride solution (3 mL). The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (554 mg). Flash column chromatography on silica eluting with 90 : 10 hexanes–EtOAc isolated **6** as a yellow liquid (127 mg, 0.61 mmol, 41%). $\delta_H$ 7.74 (dd, 1H, *J* 2.8, *J* 1.8), 5.87 (ddd, 1H, *J* 10.6, *J* 2.8, *J* 0.8), 5.71 (ddd, 1H, *J* 10.6, *J* 2.4, *J* 1.8), 5.64–5.56 (m, 1H), 5.09–5.01 (m, 2H), 4.93 (sp, 1H, *J* 6.2), 4.10–4.03 (m, 2H), 2.43 (dt, 2H, *J* 7.4, *J* 1.0), 1.15 (d, 6H, *J* 6.2); $\delta_C$ 170.53, 160.26, 131.58, 126.04, 123.67, 119.21, 68.87, 49.44, 47.42, 41.47, 21.54, 21.52; *m*/*z* 208 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{12}H_{17}NO_2$ ($+H^+$) requires 208.1337, found 208.1330 (3.4 ppm); IR (film)/$cm^{-1}$ 2980 (m, C–H), 1727 (s, (C=O)O*i*Pr), 1675 (m, N=C), 1642 (m), 1235 (m), 1106 (m).

### (*RS*)-3-Prop-2-ynyl-3,6-dihydropyridine-3-carboxylic acid isopropyl ester 7

A solution of freshly distilled ammonia (100 mL), THF (20 mL) and sodium (124 mg, 5.41 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine ester **4** (255 mg, 1.54 mmol) and bis(methoxyethyl)amine (1 mL, 6.77 mmol) in THF (20 mL) was followed by stirring for a further 1 hour. Isoprene (10 drops) was added until the blue colouration dissipated and a light yellow solution resulted. Rapid addition of propargyl bromide (800 μL, 8.98 mmol) [reaction colour changed to dark yellow] was followed by continued stirring at −78 °C for 1 hour before addition of saturated ammonium chloride solution (3 mL). The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a brown oil (764 mg). Gradient column chromatography on silica eluting with 90 : 10 hexanes–EtOAc followed by 60 : 40 hexanes–EtOAc isolated the title compound **7** as a colourless oil (89.4 mg, 0.44 mmol, 28%). $\delta_H$ 7.90 (s, 1H), 6.06 (d, 1H, *J* 10.2), 5.84 (dd, 1H, *J* 10.2, *J* 2.2), 5.05 (sp, 1H, *J* 6.5), 4.28–4.15 (m, 2H), 2.70 (ABX, 1H, *J* 16.9, *J* 2.7), 2.63 (ABX, 1H, *J* 16.9, *J* 2.7), 2.04 (t, 1H, *J* 2.7), 1.26 (d, 3H, *J* 6.5), 1.25 (d, 3H, *J* 6.5); $\delta_C$ 169.62, 158.86, 127.29, 123.04, 78.52, 71.48, 69.49, 49.75, 28.20, 27.03, 21.56 (2); *m*/*z* 206 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{12}H_{15}NO_2$ ($+H^+$) requires 206.1181, found 206.1181 (0 ppm); IR (film)/$cm^{-1}$ 3291 (w), 2981 (w, C–H), 1727 (s, (C=O)O*i*Pr), 1676 (w, N=C), 1237 (m), 1106 (m).

### Pyridine-2,5-dicarboxylic acid diisopropyl ester 10

To pyridine-2,5-dicarboxylic acid (8.01 g, 47.9 mmol) in isopropyl alcohol (IPA) (150 mL) was added concentrated $H_2SO_4$ (10 mL) and the reaction was heated at reflux for 16 hours. The reaction mixture was concentrated *in vacuo* before water (40 mL) was added. Organic components were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give a dark yellow oil. Flash column chromatography on silica eluting with 80 : 20 hexanes–$Et_2O$ isolated **10** as a white solid (7.81 g, 31.1 mmol, 65%). $\delta_H$ 9.32 (d, 1H, *J* 2.5), 8.41 (dd, 1H, *J* 8.3, *J* 2.5), 8.17 (d, 1H, *J* 8.3), 5.37 + 5.31 (2 × sp, 2H, *J* 6.5), 1.45 + 1.41 (2 × d, 12H, *J* 6.5); $\delta_C$ 164.00, 163.94, 151.34, 150.79, 138.00, 128.93, 124.41, 70.06, 69.64, 21.80 (2), 21.78 (2); *m*/*z* 252 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{13}H_{17}NO_4$ ($+H^+$) requires 252.1236, found 252.1236 (0 ppm); IR (film)/$cm^{-1}$ 2982 (m, C–H), 1721 (s, (C=O)O*i*Pr), 1292 (s), 1277 (s), 1144 (m), 1102 (s), 1023 (m), 745 (m). Elemental Analysis calculated for $C_{13}H_{17}NO_4$: C 62.12, H 6.82, N 5.60. Found C 62.25, H 6.61, N 5.66%; mp 68–69 °C.

### (*RS*)-1,2-Dimethyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 11/12

A solution of freshly distilled ammonia (100 mL), THF (10 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (117 mg, 5.09 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of **10** (314 mg, 1.25 mmol) in THF (15 mL) was followed by stirring for a further 20 minutes. A first portion of MeI (0.80 mL, 12.9 mmol) was added [reaction colour changed to orange] and the reaction was stirred for 1 hour [reaction colour lightened to light orange] before addition of a second portion of MeI (0.80 mL, 12.9 mmol). The reaction was stirred for 1 hour [by which time the solution had turned colourless] before addition of saturated ammonium chloride solution (5 mL). The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow liquid (873 mg). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated a mixture of regioisomers [5 : 1 **11** : **12**] as a pale yellow oil (326 mg, 1.16 mmol, 93%). Recrystallisation with acetone–hexanes allowed enhancement of the isomeric mixture such that the major isomer **11** could be partially characterised. $\delta_H$ 7.30–7.28 (m, br, 1H), 6.42 (d, 1H, *J* 9.9), 5.04 + 5.02 (2 × sp, 2H, *J* 6.3), 4.88 (d, 1H, *J* 9.9), 3.01 (s, 3H), 1.60 (s, 3H), 1.23 (d, 12H, *J* 6.3); $\delta_C$ 171.24, 165.77, 147.93, 122.58, 114.28, 96.84, 69.07, 66.04, 64.82, 39.41, 24.50, 22.16 (2), 21.62 (2); *m*/*z* 282 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{15}H_{23}NO_4$ ($+H^+$) requires 282.1705, found 282.1700 (1.8 ppm); IR (film)/$cm^{-1}$ 2980 (w, C–H), 1729 (s, (C=O)O*i*Pr), 1673 (s), 1571 (m), 1248 (m), 1094 (s).

Peaks for the minor isomer **12** could clearly be seen in the pre-recrystallised $^1H$ NMR. Although **12** is a novel compound, assignment was not possible.

### (*RS,RS*) and (*SR,RS*)-2,5-Diallyl-2,5-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 13/14

A solution of freshly distilled ammonia (75 mL), THF (20 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (189 mg, 5.09 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (378 mg, 1.50 mmol) in THF (15 mL) was followed by stirring for a further 20 minutes. Addition of isoprene until the reaction turned dark red was followed by rapid addition of allyl bromide (2.50 mL, 28.9 mmol) [reaction colour changed to orange]. Stirring at −78 °C was continued for 2 hours [reaction colour changed to dark yellow] before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (50 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow liquid (1.88 g). Flash column chromatography on silica eluting with 97.5 : 2.5 hexanes–acetone isolated a mixture of isomers [1 : 2 **13** : **14**] as a pale yellow oil (481 mg, 1.44 mmol, 96%). Attempted crystallisation with a number of solvent systems failed to isolate either regioisomer cleanly. A small amount of the major isomer **14** could be obtained as a pale yellow oil by repeated column chromatography and partial characterization was possible. $\delta_H$ 7.99 (dd, 1H, *J* 2.5, *J* 0.7), 6.03 (dd, 1H, *J* 10.7, *J* 0.7), 5.92 (dd, 1H, *J* 10.7, *J* 2.5), 5.73–5.54 (m, 2H), 5.17–4.98 (m, 6H), 2.83–2.51 (m, 4H), 1.29–1.23 (m, 12H); *m*/*z* 334 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{19}H_{27}NO_4$ ($+H^+$) requires 334.2018, found 334.2017 (0.6 ppm); IR (film)/$cm^{-1}$ 2981 (s, C–H), 1729 (s, (C=O)O*i*Pr), 1679 (w, C=N), 1237 (s), 1105 (s), 917 (m).

### (*RS*)-2-Methyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 15

A solution of freshly distilled ammonia (100 mL), THF (10 mL) and sodium (322 mg, 14.0 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (803 mg, 3.19 mmol) in THF (15 mL) was followed by stirring for a further 25 minutes. Addition of isoprene (0.5 mL) was followed by rapid addition of MeI (0.70 mL, 11.2 mmol) [reaction colour changed to light red] to the rapidly stirring solution. Stirring at −78 °C was continued for 8 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a pale yellow oil (966 mg). Gradient column chromatography on silica eluting with 95 : 5 hexanes–acetone followed by 90 : 10 hexanes–acetone isolated the title compound **15** as a pale yellow oil (843 mg, 3.15 mmol, 99%). $\delta_H$ 7.42 (dd, 1H, *J* 6.2, *J* 1.7), 6.45 (dd, 1H, *J* 9.9, *J* 1.7), 5.26 (d, br, 2H, *J* 9.9), 5.05 (sp, 2H, *J* 6.3), 1.41 (s, 3H), 1.27 + 1.24 (2 × d, 12H, *J* 6.3); $\delta_C$ 173.13, 165.90, 141.75, 121.99, 113.28, 97.39, 69.20, 65.99, 58.80, 28.72, 21.82 (2), 21.42 (2); *m*/*z* 268 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{14}H_{21}NO_4$ ($+H^+$) requires 268.1549, found 268.1552 (1.1 ppm); IR (film)/$cm^{-1}$ 3315 (w, br, N–H), 2980 (m, C–H), 1732 (s, (C=O)O*i*Pr), 1686 (m), 1668 (m), 1638 (m), 1252 (m), 1100 (s).

### (*RS*)-2-Methyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 15

A solution of freshly distilled ammonia (50 mL), THF (10 mL) and calcium (125 mg, 3.1 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (188 mg, 0.75 mmol) in THF (15 mL) was followed by stirring for a further 30 minutes. Addition of isoprene (0.5 mL) was followed by rapid addition of MeI (0.15 mL, 2.4 mmol) [reaction colour changed to light red] to the rapidly stirring solution. Stirring at −78 °C was continued for 8 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a pale yellow oil (210 mg). Gradient column chromatography on silica eluting with 93 : 7 hexanes–acetone isolated the title compound **15** as a pale yellow oil (166 mg, 0.62 mmol, 83%).

### (*RS*)-2-Methyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 15

A solution of naphthalene (935 mg, 7.25 mmol), sodium (180 mg, 7.85 mmol) and THF (30 mL) was sonicated at room temperature for 45 minutes, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (357 mg, 1.42 mmol) was added in THF (15 mL) and stirring was continued for a further 25 minutes. Rapid addition of MeI (270 μL, 4.34 mmol) to the rapidly stirring solution caused no noticeable colour change and stirring was continued for 1 minute before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a light yellow solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column), 95 : 5 hexanes–acetone and 90 : 10

hexanes–acetone isolated **15** as a pale yellow oil (326 mg, 1.22 mmol, 86%).

### (*RS*)-2-Ethyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 16

A solution of freshly distilled ammonia (100 mL), THF (10 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (102 mg, 4.44 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (349 mg, 1.39 mmol) in THF (15 mL) was followed by stirring for a further 30 minutes. Addition of isoprene (0.5 mL) [reaction colour changed to brown–red] was followed by rapid addition of EtI (310 μL, 3.88 mmol) [reaction colour changed to dark orange] to the rapidly stirring solution. Stirring at −78 °C was continued for 8 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow liquid (1.41 g). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated **16** as a pale yellow oil (384 mg, 1.37 mmol, 98%). $\delta_H$ 7.46 (dd, 1H, *J* 7.0, *J* 1.7), 6.51 (dd, 1H, *J* 10.1, *J* 1.7), 5.19 (d, br, 1H, *J* 10.1), 5.18 (s, br, 1H), 5.06 + 5.05 (2 × sp, 2H, *J* 6.3), 1.54–1.84 (m, 2H), 1.27 + 1.24 (2 × d, 12H, *J* 6.3), 0.88 (t, 3H, *J* 7.4); $\delta_C$ 172.78, 165.90, 141.77, 122.87, 112.23, 97.85, 69.33, 66.13, 62.80, 34.34, 22.07 (2), 21.63 (2), 6.93; *m*/*z* 282 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{15}H_{23}NO_4$ ($+H^+$) requires 282.1705, found 282.1704 (0.4 ppm); IR (film)/$cm^{-1}$ 3332 (w, br, N–H), 2978 (m, C–H), 1733 (s, (C=O)O*i*Pr), 1685 (s), 1667 (s), 1640 (s), 1243 (s), 1100 (s).

### (*RS*)-2-Ethyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 16

A solution of naphthalene (999 mg, 7.76 mmol), sodium (162 mg, 7.02 mmol) and THF (50 mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (355 mg, 1.41 mmol) was added in THF (20 mL) and stirring was continued for a further 30 minutes. Rapid addition of EtI (400 μL, 5.00 mmol) to the rapidly stirring solution caused no noticeable colour change and stirring was continued for 20 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a light orange solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column) and 95 : 5 hexanes–acetone isolated **16** as a pale yellow oil (312 mg, 1.11 mmol, 78%).

### (*RS*)-2-Isobutyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 17

A solution of freshly distilled ammonia (50 mL), THF (10 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (121 mg, 5.26 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (295 mg, 1.17 mmol) in THF (15 mL) was followed by stirring for a further 40 minutes. *i*BuI (1.40 mL, 12.2 mmol) [reaction colour changed to brown] was added to the rapidly stirring solution and stirring at −78 °C was continued for 30 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (506 mg). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated **17** as a colourless oil (337 mg, 1.09 mmol, 93%). $\delta_H$ 7.44 (dd, 1H, *J* 6.4, *J* 1.6), 6.45 (dd, 1H, *J* 10.3, *J* 1.6), 5.22 (s, br, 1H), 5.18 (d, 1H, *J* 10.3), 5.05 + 5.04 (2 × sp, 2H, *J* 6.3), 1.84 (sp, 1H, *J* 6.5), 1.77–1.67 (m, 1H), 1.54–1.44 (m, 1H), 1.27 + 1.26 (2 × d, 6H, *J* 6.3), 1.23 (d, 6H, *J* 6.3), 0.94 + 0.89 (2 × d, 6H, *J* 6.5); $\delta_C$ 173.13, 165.90, 141.54, 122.28, 113.38, 97.71, 69.38, 66.14, 62.39, 49.52, 24.22, 23.62, 23.58, 22.06 (2), 21.57 (2); *m*/*z* 310 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{17}H_{27}NO_4$ ($+H^+$) requires 310.2018, found 310.2020 (0.6 ppm); IR (film)/$cm^{-1}$ 3320 (w, br, N–H), 2979 (m, C–H), 1732 (m, (C=O)O*i*Pr), 1665 (m), 1638 (m), 1236 (s), 1100 (s).

### (*RS,RS*) and (*SR,RS*)-Oxiran-2-ylmethyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 18

A solution of freshly distilled ammonia (100 mL), THF (15 mL), bis(methoxyethyl)amine (1.50 mL, 10.2 mmol) and sodium (151 mg, 6.56 mmol) was stirred at −78 °C for 45 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (309 mg, 1.23 mmol) in THF (15 mL) was followed by stirring for a further 30 minutes. Addition of isoprene (1.0 mL) [reaction colour changed to dark red] was followed by addition of (±)-epibromohydrin (410 μL, 4.79 mmol) [reaction colour changed to brown] to the rapidly stirring solution. Stirring at −78 °C was continued for 15 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (10 mL) and 2 M HCl (30 mL) were added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (691 mg). Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated **18** as a colourless oil and as a 1.5 : 1 mixture of diastereoisomers (342 mg, 1.11 mmol, 90%). $\delta_H$ [* = major isomer] 7.49* + 7.46 (2 × dd, 1H, *J* 6.9, *J* 1.6), 6.55* + 6.52 (2 × dd, 1H, *J* 10.1, *J* 1.6), 5.53 + 5.41* (2 × s, br, 1H), 5.21 (dd, 1H, *J* 10.1, *J* 1.9), 5.08 + 5.05 (2 × sp, 2H, *J* 6.2), 3.11–3.06* + 3.00–2.94 (2 × m, 1H), 2.77 + 2.75* (2 × d, 1H, *J* 4.1), 2.47 + 2.46* (2 × d, 1H, *J* 2.7), 2.10* + 2.03 (ABX, 1H, *J* 14.8, *J* 7.1), 1.69 (ABX, 1H, *J* 14.8, *J* 4.0), 1.28 + 1.24 (2 × d, 12H, *J* 6.2); $\delta_C$ 171.91 + 171.77, 165.70, 141.66 + 141.56, 123.61 + 123.45, 111.99 + 111.74, 98.29 + 98.15, 69.87 + 69.83, 66.31 + 66.25, 61.98 + 61.35, 47.87 + 47.35, 46.15, 44.05 + 43.89, 22.05, 21.60 + 21.58, 21.55 + 21.52 (2); *m*/*z* 310 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{16}H_{23}NO_5$ ($+H^+$) requires 310.1654, found 310.1651 (1.0 ppm); IR (film)/$cm^{-1}$ 3412 (m, br), 2982 (m, C–H), 2938 (m, C–H), 1721 (m, (C=O)-O*i*Pr), 1677 (w), 1637 (m), 1102 (s).

### (*RS,RS*) and (*SR,RS*)-Oxiran-2-ylmethyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 18

A solution of naphthalene (890 mg, 6.91 mmol), sodium (136 mg, 5.91 mmol) and THF (40 mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (319 mg, 1.27 mmol) was added in THF (15 mL) and stirring was continued for a further 50 minutes. Addition of (±)-epibromohydrin (460 μL, 5.38 mmol) to the rapidly stirring solution over a period of 20 seconds was followed by continued stirring for 3 minutes before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a brown then to a light orange solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column) and 90 : 10 hexanes–acetone isolated **18** as a pale yellow oil and as a mixture of diastereoisomers (338 mg, 1.09 mmol, 84%).

**(*RS*)-2-Allyl-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 19**

A solution of freshly distilled ammonia (60 mL), THF (10 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (110 mg, 4.79 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (276 mg, 1.10 mmol) in THF (15 mL) was followed by stirring for a further 30 minutes. Addition of isoprene (0.5 mL) [reaction colour changed to brown–red] was followed by rapid addition of allyl chloride (270 μL, 3.31 mmol) [no colour change] to the rapidly stirring solution. Stirring at −78 °C was continued for 12 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (40 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow liquid (513 mg). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated **19** (contaminated with a small amount (5%) of starting material **10**) as a pale yellow oil (319 mg, 1.09 mmol, 99%). $\delta_H$ 7.43 (dd, 1H, *J* 6.6, *J* 1.4), 6.47 (dd, 1H, *J* 10.1, *J* 1.4), 5.67–5.55 (m, 1H), 5.46 (s, br, 1H), 5.21–4.96 (m, 5H), 2.48 (ABX, 1H, *J* 13.8, *J* 7.8), 2.40 (ABX, 1H, *J* 13.8, *J* 6.9), 1.25 + 1.21 (2 × d, 12H, *J* 6.2); $\delta_C$ 171.84, 165.90, 141.77, 130.15, 122.97, 120.30, 112.31, 97.94, 69.54, 66.20, 62.08, 45.85, 22.09 (2), 21.69, 21.62; *m*/*z* 294 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{16}H_{23}NO_4$ ($+H^+$) requires 294.1705, found 294.1705 (0 ppm); IR (film)/$cm^{-1}$ 3341 (s, br, N–H), 2980 (s, C–H), 1735 (s, (C=O)O*i*Pr), 1686 (s), 1671 (s), 1638 (s), 1233 (s), 1100 (s), 919 (m).

**(*RS*)-2-(3-Chloropropyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 20**

A solution of freshly distilled ammonia (125 mL), THF (10 mL), bis(methoxyethyl)amine (2.40 mL, 16.3 mmol) and sodium (263 mg, 11.4 mmol) was stirred at −78 °C for 45 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (779 mg, 3.10 mmol) in THF (15 mL) was followed by stirring for a further 25 minutes. Addition of isoprene (1.00 mL) [no major colour change] was followed by rapid addition of $I(CH_2)_3Cl$ (1.50 mL, 11.6 mmol) [reaction colour changed to deep orange] to the rapidly stirring solution. Stirring at −78 °C was continued for 9 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (10 mL) and 2 M HCl (30 mL) were added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (1.60 g). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated **20** as a colourless oil (986 mg, 2.98 mmol, 96%). $\delta_H$ 7.45 (d, 1H, *J* 6.0), 6.52 (d, 1H, *J* 10.0), 5.22 (s, br, 1H), 5.18 (d, 1H, *J* 10.0), 5.06 + 5.05 (2 × sp, 2H, *J* 6.3), 3.61–3.49 (m, 2H), 2.00–1.62 (m, 4H), 1.28 + 1.24 (2 × d, 12H, *J* 6.3); $\delta_C$ 172.49, 165.81, 142.05, 123.30, 111.59, 97.40, 69.58, 66.15, 62.07, 44.54, 38.62, 26.31, 21.99 (2), 21.53, 21.46; *m*/*z* 330 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{16}H_{24}NO_4Cl$ ($+H^+$) requires 330.1472, found 330.1480 (2.4 ppm); IR (film)/$cm^{-1}$ 3319 (s, br, N–H), 2981 (s, C–H), 2936 (s, C–H), 1733 (s, (C=O)O*i*Pr), 1683 (s), 1639 (s), 1581 (s), 1249 (s), 1100 (s), 733 (m).

**(*RS*)-2-(3-Chloropropyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 20**

A solution of naphthalene (1.00 g, 7.79 mmol), sodium (172 mg, 7.46 mmol) and THF (40 mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (323 mg, 1.29 mmol) was added in THF (20 mL) and stirring was continued for a further 45 minutes. Rapid addition of $I(CH_2)_3Cl$ (550 μL, 5.12 mmol) to the rapidly stirring solution over a period of 10 seconds was followed by continued stirring for a further 10 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a brown then to a light orange solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column) and 95 : 5 hexanes–acetone isolated **20** as a yellow oil (381 mg, 1.23 mmol, 96%).

**(*RS*)-2-(4-Chlorobutyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 21**

A solution of freshly distilled ammonia (125 mL), THF (20 mL), bis(methoxyethyl)amine (2.00 mL, 13.5 mmol) and sodium (319 mg, 13.9 mmol) was stirred at −78 °C for 45 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (1.01 g, 4.02 mmol) in THF (30 mL) was followed by stirring for a further 25 minutes. Addition of isoprene (1.50 mL) [no major colour change] was followed by rapid addition of $I(CH_2)_4Cl$ (1.80 mL, 14.7 mmol) [reaction colour changed to deep orange] to the rapidly stirring solution. Stirring at −78 °C was continued for 10 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (10 mL) and 2 M HCl (30 mL) were added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (2.54 g). Gradient column chromatography on silica eluting with 95 : 5 hexanes–acetone followed by 90 : 10 hexanes–acetone isolated **21** as a pale yellow oil (1.38 g, 4.01 mmol, 100%). $\delta_H$ 7.44 (d, 1H, *J* 6.6), 6.48 (d, 1H, *J* 10.2), 5.36 (s, br, 1H), 5.16 (d, 1H, *J* 10.2), 5.04 + 5.03 (2 × sp, 2H, *J* 6.3), 3.50 (t, 2H, *J* 6.6), 1.81–1.65 (m, 3H), 1.62–1.48 (m, 2H), 1.43–1.31 (m, 1H), 1.26 + 1.22 (2 × d, 12H, *J* 6.3); $\delta_C$ 172.62, 165.87, 141.78, 123.00, 112.16, 97.84, 69.57, 66.23, 62.34, 44.47, 40.55, 32.20, 22.08 (2), 21.64, 21.59, 20.14; *m*/*z* 344 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{17}H_{26}NO_4Cl$ ($+H^+$) requires 344.1628, found 344.1628 (0 ppm); IR (film)/$cm^{-1}$ 3322 (w, br N–H), 2980 (s, C–H), 2938 (m, C–H), 1732 (s, (C=O)O*i*Pr), 1682 (s), 1638 (s), 1580 (m), 1372 (m), 1304 (m), 1245 (s), 1098 (s), 734 (m).

**(*RS*)-2-(4-Chlorobutyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 21**

A solution of naphthalene (984 mg, 7.64 mmol), sodium (175 mg, 7.62 mmol) and THF (40 mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (326 mg, 1.30 mmol) was added in THF (20 mL) and stirring was continued for a further 45 minutes. Addition of $I(CH_2)_4Cl$ (600 μL, 4.90 mmol) to the rapidly stirring solution over a period of 10 seconds was followed by continued stirring for a further 10 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a brown then to a light orange solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column) and 92.5 : 7.5 hexanes–acetone isolated **21** as a colourless oil (405 mg, 1.18 mmol, 91%).

**(*RS*)-2-(5-Chloropentyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 22**

A solution of freshly distilled ammonia (60 mL), THF (10 mL), bis(methoxyethyl)amine (1.00 mL, 6.77 mmol) and sodium (123 mg, 5.33 mmol) was stirred at −78 °C for 30 minutes, by which time the solution had turned deep blue in colour. Addition of the pyridine diester **10** (406 mg, 1.62 mmol) in THF (15 mL) was followed by stirring for a further 20 minutes. Addition of isoprene (0.50 mL) [no major colour change] was followed by rapid addition of $I(CH_2)_5Cl$ (1.47 g, 6.31 mmol) [reaction colour changed to deep orange] to the rapidly stirring solution. Stirring at −78 °C was continued for 15 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction colour changed to light yellow]. The reaction was allowed to warm to room temperature and ammonia was allowed to evaporate overnight. Water (10 mL) and 2 M HCl (30 mL) were added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a yellow oil (1.34 g). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated **22** as a yellow oil (563 mg, 1.57 mmol, 97%). $\delta_H$ 7.45 (dd, 1H, *J* 7.5, *J* 1.5), 6.50 (dd, 1H, *J* 9.9, *J* 1.5), 5.18 (dd, 1H, *J* 9.9, *J* 1.8), 5.18 (s, br, 1H), 5.06 + 5.05 (2 × sp, 2H, *J* 6.2), 3.53 (t, 2H, *J* 6.6), 1.81–1.71 (m, 3H), 1.60–1.36 (m, 5H), 1.28 + 1.24 (2 × d, 12H, *J* 6.2); $\delta_C$ 172.78, 165.90, 141.94, 122.84, 112.20, 97.52, 69.39, 66.13, 62.40, 44.71, 41.21, 32.23, 26.57, 22.06, 22.05 (2), 21.59, 21.54; *m*/*z* 358 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{18}H_{28}NO_4Cl$ ($+H^+$) requires 358.1785, found 358.1776 (2.5 ppm); IR (film)/$cm^{-1}$ 3322 (s, br, N–H), 2980 (s, C–H), 2938 (s, C–H), 2866 (s, C–H), 1734 (s, (C=O)O*i*Pr), 1685 (s), 1642 (s), 1582 (m), 734 (m).

**(*RS*)-2-(5-Chloropentyl)-1,2-dihydropyridine-2,5-dicarboxylic acid diisopropyl ester 22**

A solution of naphthalene (876 mg, 6.80 mmol), sodium (157 mg, 6.84 mmol) and THF (40 mL) was sonicated at room temperature for 1 hour, by which time a deep green colour had been generated. The reaction was cooled to −78 °C, pyridine diester **10** (295 mg, 1.17 mmol) was added in THF (20 mL) and stirring was continued for a further 45 minutes. Addition of $I(CH_2)_5Cl$ (1.18 g, 5.09 mmol) to the rapidly stirring solution over a period of 15 seconds was followed by continued stirring for a further 15 seconds before addition of saturated ammonium chloride solution (5 mL) [reaction changed colour to a brown then to a light orange solution with a white precipitate]. The reaction was allowed to warm to room temperature and was stirred under an inert atmosphere overnight. The reaction was dry-loaded onto silica and gradient column chromatography on silica eluting with neat hexanes (until naphthalene had been flushed from the column) and 90 : 10 hexanes–acetone isolated **22** as a pale yellow oil (394 mg, 1.10 mmol, 94%).

**(*RS*)-2,3-Dihydroindolizine-6,8a(1*H*)-dicarboxylic acid diisopropyl ester 23**

Compound **20** (430 mg, 1.30 mmol) and DBU (220 μL, 1.47 mmol) in DCM (25 mL) were stirred at room temperature before being heated at reflux for 16 hours. Evaporation of solvent and addition of DCE (20 mL) and DBU (880 μL, 5.88 mmol) was followed by heating at reflux for a further 36 hours. On cooling, water (30 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a black oil (3.51 g). Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **23** as an off-white solid (363 mg, 1.24 mmol, 95%). $\delta_H$ 7.54 (s, br, 1H), 6.51 (dd, 1H, *J* 9.6, *J* 1.1), 5.14 (d, 1H, *J* 9.6), 5.06 + 4.98 (2 × sp, 2H, *J* 6.1), 3.83–3.53 (m, 2H), 2.51–2.39 + 2.16–2.02 (2 × m, 2H), 1.91–1.76 (m, 2H), 1.24 (d, 6H, *J* 6.1), 1.24 + 1.23 (2 × d, 6H, *J* 6.1); $\delta_C$ 172.50, 165.87, 142.83, 122.99, 109.78, 99.16, 68.68, 68.48, 65.91, 51.01, 37.84, 22.10, 22.08, 21.59, 21.50, 20.69; *m*/*z* 294 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{16}H_{23}NO_4$ ($+H^+$) requires 294.1705, found 294.1702 (1.0 ppm); IR (film)/$cm^{-1}$ 2978 (m, C–H), 1731 (s, (C=O)O*i*Pr), 1683 (s), 1623 (s), 1554 (m), 1276 (s), 1085 (s); mp 62–63 °C.

**(*RS*)-2,3-Dihydroindolizine-6,8a(1*H*)-dicarboxylic acid diisopropyl ester 23**

To compound **20** (232 mg, 0.70 mmol) in THF (30 mL) was added NaH (64.1 mg, ~1.60 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was then heated at reflux for 5 hours. On cooling, water (30 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a brown oil (217 mg). Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **23** as an off-white solid (174 mg, 0.59 mmol, 84%).

**(*RS*)-6,7,8,9-Tetrahydroquinolizine-3,9a-dicarboxylic acid diisopropyl ester 24**

Compound **21** (1.13 g, 3.28 mmol), DBU (2.50 mL, 16.7 mmol) and acetone (40 mL) were heated at reflux for 36 hours. A second portion of DBU (220 μL, 1.47 mmol) was added and the reaction was heated at reflux for a further 12 hours. On cooling, water (40 mL) and 2 M HCl (30 mL) were added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a brown oil (1.27 g). Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated compound **24** as a yellow oil (890 mg, 2.90 mmol, 88%). $\delta_H$ 7.26 (s, br, 1H), 6.36 (dd, 1H, *J* 9.8, *J* 1.4), 4.81 (d, 1H, *J* 9.8), 5.06 + 5.04 (2 × sp, 2H, *J* 6.3), 3.67–3.59 (m, 1H), 3.34–3.26 (m, 1H), 2.38–2.27 (m, 1H), 1.93–1.78 (m, 2H), 1.73–1.57 (m, 2H), 1.43–1.29 (m, 1H), 1.28 + 1.26 (2 × d, 6H, *J* 6.3), 1.23 (d, 6H, *J* 6.3); $\delta_C$ 170.28, 165.73, 147.81, 122.56, 113.98, 95.90, 68.83, 65.85, 65.85, 52.42, 35.65, 25.19, 22.07 (2), 21.65, 21.50, 21.45; *m*/*z* 308 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{17}H_{25}NO_4$ ($+H^+$) requires 308.1862, found 308.1869 (2.3 ppm); IR (film)/$cm^{-1}$ 2981 (m, C–H), 2937 (m, C–H), 1727 (s, (C=O)O*i*Pr), 1680 (m), 1635 (m), 1253 (m), 1099 (s).

**(*RS*)-7,8,9,10-Tetrahydropyrido[1,2-*a*]azepine-3,10a(6*H*)-dicarboxylic acid diisopropyl ester 25**

To compound **22** (202 mg, 0.56 mmol) in THF (25 mL) was added KHMDS (213 mg, 1.07 mmol) and 18-crown-6 ether (251 mg, 0.95 mmol) at −78 °C. The reaction was allowed to warm to room temperature and was stirred for 16 hours. On cooling, water (10 mL) and saturated $NaHCO_3$ solution (10 mL) were added and organics were extracted with DCM (3 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to give a brown oil (246 mg). Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **25** as a colourless oil (82.8 mg, 0.26 mmol, 46%). $\delta_H$ 7.37 (s, br, 1H), 6.50 (dd, 1H, *J* 9.6, *J* 1.4), 5.03 + 4.97 (2 × sp, 2H, *J* 6.3), 4.79 (d, 1H, *J* 9.6), 3.51–3.29 (m, 2H), 2.23–2.14 (m, 1H), 1.91–1.71, 1.60–1.40 and 1.31–1.24 (3 × m, 7H), 1.22 + 1.20 (2 × d, 12H, *J* 6.3); $\delta_C$ 172.81, 165.78, 146.89, 124.24, 113.76, 97.61, 68.60, 67.57, 65.93, 53.21, 40.74, 31.06, 29.09, 22.39, 22.10, 22.09, 21.63, 21.48; *m*/*z* 322 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{18}H_{27}NO_4$ ($+H^+$) requires 322.2018, found 322.2020 (0.6 ppm); IR (film)/$cm^{-1}$ 2978 (s, C–H), 2930 (s, C–H), 2858 (m, C–H), 1731 (s, (C=O)O*i*Pr), 1683 (s), 1637 (s), 1568 (s), 1425 (m), 1354 (m), 1298 (s), 1242 (s), 1163 (s), 1107 (s), 969 (m).

**(*RS*)-1-*tert*-Butoxycarbonyl-2-methylpyridine-2,5(2*H*)-dicarboxylic acid diisopropyl ester 26**

Compound **15** (795 mg, 2.98 mmol), DMAP (cat.), $NEt_3$ (1.25 ml, 8.97 mmol), $(Boc)_2O$ (0.856 mg, 3.92 mmol) and $CH_3CN$ (30 mL) were heated at 50 °C for 24 hours. A second portion of

$(Boc)_2O$ (860 mg, 3.92 mmol) was added and the reaction was stirred for a further 16 hours at 50 °C. On cooling, water (30 mL) was added and organics were extracted with DCM (4 × 40 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a black oil (1.22 g). Flash column chromatography on silica eluting with 90 : 10 hexanes–$Et_2O$ isolated the title compound **26** as a colourless solid (1.02 g, 2.77 mmol, 93%). $\delta_H$ 7.83 (s, br, 1H), 6.28 (d, 1H, *J* 9.9), 5.14 (d, 1H, *J* 9.9), 5.03 + 4.97 (2 × sp, 2H, *J* 6.3), 1.61 (s, 3H), 1.45 (s, 9H), 1.21 (d, 12H, *J* 6.3); $\delta_C$ 170.55, 164.80, 151.34, 135.20, 121.88, 118.70, 105.17, 83.78, 69.16, 67.36, 63.81, 27.78 (3), 21.83 (2), 21.54 (2), 21.38; *m*/*z* 385 ($MNH_4^+$); HRMS (CI, *m*/*z*) for $C_{19}H_{29}NO_6$ ($+H^+$) requires 368.2073, found 368.2066 (1.9 ppm); IR (film)/$cm^{-1}$ 2980 (m, C–H), 1737 (s, (C=O)O*i*Pr), 1704 (s, N(C=O)O*t*Bu), 1371 (m), 1334 (m), 1247 (s), 1104 (s); mp 101–103 °C.

### (*RS*)-1-*tert*-Butoxycarbonyl-2-methyl-3,4-dihydropyridine-2,5(2*H*)-dicarboxylic acid diisopropyl ester 27

A solution of compound **26** (131 mg, 0.36 mmol) and 10% Pd/C (cat.) in THF (10 mL) was stirred under an atmosphere of hydrogen at balloon pressure for 36 hours. Solids were removed by filtration, washed with DCM (3 × 30 mL) and the combined filtrates were concentrated *in vacuo* to yield a colourless oil (138 mg). Flash column chromatography on silica eluting with 80 : 20 hexanes–$Et_2O$ isolated the title compound **27** as a colourless oil (118 mg, 0.32 mmol, 90%). $\delta_H$ 8.01 (s, br, 1H), 5.03 + 5.00 (2 × sp, 2H, *J* 6.3), 2.55–2.42 (m, 1H), 2.27–2.21 (m, 1H), 2.00–1.79 (m, 2H), 1.46 (s, 9H), 1.41 (s, 3H), 1.23 + 1.19 (2 × d, 12H, *J* 6.3); $\delta_C$ 172.58, 166.68, 150.77, 135.28, 106.65, 83.02, 68.49, 67.15, 59.74, 32.13, 27.91 (3), 21.86, 21.69 (2), 21.62 (2), 17.43; *m*/*z* 370 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{19}H_{31}NO_6$ ($+H^+$) requires 370.2229, found 370.2230 (0.3 ppm); IR (film)/$cm^{-1}$ 2980 (m, C–H), 1727 (s, br (C=O)-O*i*Pr), 1698 (s, N(C=O)O*t*Bu), 1642 (m), 1272 (m), 1226 (m), 1157 (s), 1105 (s).

### (*RS*,*RS*) and (*SR*,*RS*)-Oxiran-2-ylmethyl-1,2,3,4-tetrahydropyridine-2,5-dicarboxylic acid diisopropyl ester 28

A solution of compound **18** (305 mg, 0.98 mmol) and 10% Pd/C (cat.) in THF (20 mL) was stirred rapidly under an atmosphere of hydrogen at balloon pressure for 2 hours. Solids were removed by filtration, washed with DCM (3 × 30 mL) and the combined filtrates were concentrated *in vacuo* to yield a yellow oil. Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **28** as a colourless oil and as a 1.5 : 1 mixture of diastereoisomers (280 mg, 0.90 mmol, 91%). $\delta_H$ [* = major isomer] 7.47–7.40 (m, 1H), 5.28 + 5.21* (2 × d, 1H, *J* 6.3), 5.05 + 4.99 (2 × sp, 2H, *J* 6.3), 2.99–2.87 (m, 1H), 2.73 (t, 1H, *J* 4.7), 2.48–1.50 (m, 7H), 1.24 + 1.19 (2 × d, 12H, *J* 6.3); $\delta_C$ 172.87, 167.71, 140.60, 96.20, 69.37, 65.75, 58.20, 47.70, 46.44, 40.14, 28.77, 22.00 (2), 21.47, 21.37, 17.96; *m*/*z* 312 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{16}H_{25}NO_5$ ($+H^+$) requires 312.1811, found 312.1808 (1.0 ppm); IR (film)/$cm^{-1}$ 3374 (s, br, N–H), 2980 (s, C–H), 2934 (s, C–H), 1731 (s, (C=O)O*i*Pr), 1678 (s), 1630 (s), 1497 (m), 1297 (m), 1218 (s), 1104 (s).

### (*RS*)-2,3,7,8-Tetrahydroindolizine-6,8a(1*H*)-dicarboxylic acid diisopropyl ester 29

A solution of compound **23** (295 mg, 1.00 mmol) and 10% Pd/C (cat.) in toluene (15 mL) was stirred rapidly under an atmosphere of hydrogen at balloon pressure for 15 minutes. Solids were removed by filtration, washed with DCM (3 × 30 mL) and the combined filtrates were concentrated *in vacuo* to yield a yellow solid (315 mg). Flash column chromatography on silica eluting with 95 : 5 hexanes–acetone isolated the title compound **29** as a light yellow solid (296 mg, 1.00 mmol, 100%). $\delta_H$ 7.51 (s, br, 1H), 5.00 + 4.98 (2 × sp, 2H, *J* 6.3), 3.78–3.65 (m, 1H), 3.38 (q, br, 1H, *J* 8.4), 2.60–2.46 (m, 2H), 2.39–2.29 (m, 1H), 2.03–1.67 (m, 4H), 1.31–1.12 (m, 1H), 1.22 + 1.21 (2 × d, 12H, *J* 6.3); $\delta_C$ 173.02, 167.76, 141.99, 95.89, 68.68, 66.91, 65.57, 50.27, 37.05, 29.27, 22.42, 22.18, 22.16, 21.59, 21.54, 19.37; *m*/*z* 296 ($MH^+$); HRMS (EI, *m*/*z*) for $C_{16}H_{25}NO_4$ requires 295.1784, found 295.1782 (0.7 ppm); IR (film)/$cm^{-1}$ 2978 (s, C–H), 2936 (m, C–H), 2874 (m, C–H), 1732 (s, (C=O)O*i*Pr), 1679 (s), 1615 (s), 1270 (s), 1180 (s), 1111 (s), 1088 (s); mp 82–83 °C.

### (*RS*)-1,2,6,7,8,9-Hexahydroquinolizine-3,9a-dicarboxylic acid diisopropyl ester 30

A solution of compound **24** (634 mg, 2.06 mmol) and 10% Pd/C (cat.) in toluene (20 mL) was stirred rapidly under an atmosphere of hydrogen at balloon pressure for 20 minutes. Solids were removed by filtration, washed with DCM (3 × 30 mL) and the combined filtrates were concentrated *in vacuo* to yield a yellow oil. Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **30** as a pale yellow oil (564 mg, 1.82 mmol, 88%). $\delta_H$ 7.26 (s, 1H), 5.03 + 5.01 (2 × sp, 2H, *J* 6.3), 3.55–3.15 (m, br, 2H), 2.44–2.14 (m, br, 3H), 2.07–1.88 (m, br, 1H), 1.80–1.29 (m, br, 6H), 1.23 + 1.21 (2 × d, 12H, *J* 6.3); $\delta_C$ 171.63, 167.83, 146.49, 95.85, 68.56, 65.58, 65.20, 50.56, 34.87, 33.49, 25.26, 22.09, 22.07, 21.63, 21.58, 21.39, 18.33; *m*/*z* 310 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{17}H_{27}NO_4$ ($+H^+$) requires 310.2018, found 310.2020 (0.6 ppm); IR (film)/$cm^{-1}$ 2976 (s, C–H), 2938 (s, C–H), 2859 (s, C–H), 1729 ((C=O)O*i*Pr), 1676 (s), 1628 (s), 1449 (s), 1391 (s), 1391 (s), 1287 (s), 1209 (s), 1125 (s), 1008 (s).

### (*RS*)-1,2,7,8,9,10-Hexahydropyrido[1,2-*a*]azepine-3,10a(6*H*)-dicarboxylic acid diisopropyl ester 31

A solution of compound **25** (94.2 mg, 0.29 mmol) and 10% Pd/C (cat.) in THF (20 mL) was stirred rapidly under an atmosphere of hydrogen at balloon pressure for 1 hour. Solids were removed by filtration, washed with DCM (3 × 30 mL) and the combined filtrates were concentrated *in vacuo* to yield a yellow oil. Flash column chromatography on silica eluting with 90 : 10 hexanes–acetone isolated the title compound **31** as a colourless oil (84.1 mg, 0.26 mmol, 89%). $\delta_H$ 7.35 (s, 1H), 4.97 + 4.95 (2 × sp, 2H, *J* 6.3), 3.45–3.24 (m, 2H), 2.40–2.28 (m, 1H), 2.19–1.89 (m, 3H), 1.86–1.66 (m, 5H), 1.56–1.20 (m, 3H), 1.18 (d, br, 12H, *J* 6.3); $\delta_C$ 173.42, 167.87, 146.78, 94.83, 68.51, 65.51, 64.37, 52.91, 37.52, 30.99, 30.43, 29.25, 22.88, 22.16, 22.13, 21.60, 21.49, 18.40; *m*/*z* 324 ($MH^+$); HRMS (CI, *m*/*z*) for $C_{18}H_{29}NO_4$ ($+H^+$) requires 324.2175, found 324.2176 (0.3 ppm); IR (film)/$cm^{-1}$ 2977 (s, C–H), 2932 (s, C–H), 2854 (s, C–H), 1729 (s, (C=O)O*i*Pr), 1678 (s), 1623 (s), 1166 (s), 1110 (s), 1089 (s).

### X-Ray data for 11, 23 and 29 §

The data for **29** were collected using the RAXIS II in 90 × 4 degree phi oscillations, of 10 minutes per exposure (see Table 2). For **23** and **11**, the data were collected using a Rigaku AFC-5R diffractometer. Data collection and refinement parameters are summarised in the table. The structures were solved by direct methods and for **29** and **23**, all non-H atoms were refined anisotropically. In the case of **11**, C15 was disordered over two sites, A and B, whose occupancies were constrained to sum to 1.0. C15A and C15B, were refined isotropically whilst other non-hydrogen atoms were refined anisotropically. In all three structures, the hydrogen atoms were included in constrained positions.

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§ CCDC reference numbers 159038–159040. See http://www.rsc.org/suppdata/p1/b1/b101662h/ for crystallographic files in .cif or other electronic format.

**Table 2** X-Ray data for **11**, **23** and **29**

| | **29** | **23** | **11** |
|---|---|---|---|
| Empirical formula | $C_{16}H_{25}NO_4$ | $C_{16}H_{23}NO_4$ | $C_{15}H_{23}NO_4$ |
| Formula weight | 295.37 | 293.35 | 281.34 |
| Temperature/K | 293(2) | 296.2 | 296.2 |
| Radiation type | Mo Kα | Mo Kα | Cu Kα |
| Wavelength/Å | 0.7107 | 0.7107 | 1.5418 |
| Crystal system | Triclinic | Triclinic | Monoclinic |
| Space group | *P*-1 | *P*-1 | *C* 2/*c* |
| *a*/Å | 7.310 | 9.886(5) | 25.365(11) |
| *b*/Å | 10.038 | 12.422(5) | 11.860(5) |
| *c*/Å | 12.314 | 7.391(2) | 12.158(6) |
| *α* (°) | 111.20 | 93.16(3) | 90 |
| *β* (°) | 93.03 | 95.88(3) | 116.14(4) |
| *γ* (°) | 95.48 | 111.93(3) | 90 |
| Volume /Å$^3$ | 834.8 | 833.3(6) | 3284(2) |
| *Z* | 2 | 2 | 8 |
| *Dc*/Mg m$^{-3}$) | 1.175 | 1.169 | 1.138 |
| Diffractometer | Rigaku RAXIS II | Rigaku AFC-5R | Rigaku AFC-5R |
| *μ*/mm$^{-1}$) | 0.084 | 0.084 | 0.671 |
| *F*(000) | 320 | 316 | 1216 |
| Crystal size/mm$^3$ | 0.5 × 0.4 × 0.05 | 0.30 × 0.30 × 0.20 | 0.50 × 0.37 × 0.37 |
| Scan Type | $\phi$ | $\omega-2\theta$ | $\omega-2\theta$ |
| Theta range for data collection (°) | 2.19–26.31 | 1.78–5.02 | 3.88–70.10 |
| Index ranges | $-9\leqslant h\leqslant 8$, $-12\leqslant k\leqslant 11$, $-14\leqslant l\leqslant 14$ | $0\leqslant h\leqslant 11$, $-14\leqslant k\leqslant 13$, $-8\leqslant l\leqslant 8$ | $-30\leqslant h\leqslant 30$, $-14\leqslant k\leqslant 14$, $-12\leqslant l\leqslant 13$ |
| Reflections collected | 14636 | 3122 | 2953 |
| Independent reflections | 2152 [*R*(int) = 0.035] | 2937 [*R*(int) = 0.0309] | 2886 [*R*(int) = 0.0220] |
| Absorption correction | None | Psi scans (North *et al.,* 1968) | Psi scans (North *et al.,* 1968) |
| Max. and min. transmission | | 1.000 and 0.933 | 1.000 and 0.846 |
| Structure solution | SIR (Altomare, 1993) | SHELXS86 (Sheldrick, 1985) | SHELXS86 (Sheldrick, 1985) |
| Refinement method | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2152 / 0 / 194 | 2937 / 0 / 194 | 2886 / 0 / 189 |
| Goodness-of-fit on $F^2$ | 1.035 | 1.067 | 1.010 |
| Final *R* indices [$I>2\sigma(I)$] | *R*1 = 0.0377, *wR*2 = 0.1022 | *R*1 = 0.0878, *wR*2 = 0.1722 | *R*1 = 0.0747, *wR*2 = 0.2223 |
| *R* indices (all data) | *R*1 = 0.0456, *wR*2 = 0.1091 | *R*1 = 0.2236, *wR*2 = 0.2176 | *R*1 = 0.1106, *wR*2 = 0.2549 |
| Extinction coefficient | | | 0.0007(2) |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.120 and −0.142 | 0.180 and −0.226 | 0.425 and −0.189 |

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