A Platinum Open Access Journal for Organic Chemistry

Paper

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Synthesis of 5-acyl-4-methylene-1,2,3,4-tetrahydropyridines

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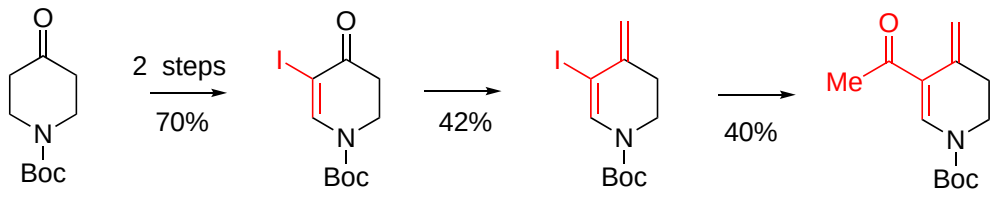
Dedicated to Phil Hodge in recognition of his outstanding contributions to the chemistry of polymers

Received 04-10-2021 **Accepted Manuscript** 05-19-2021 **Published on line** 06-02-2021

Abstract

Several approaches to monocyclic *N*-protected 4-methylene-1,2,3,4-tetrahydropyridines are reported. *N*-Boc-4-methylenepiperidin-3-one was found to be unstable and its enol triflate was not easily accessible. However, *N*-protected 2,3-dihydropyridin-4-ones are readily available by oxidation of the corresponding piperidin-4-ones and can be converted into 5-iodo-2,3-dihydropyridin-4-ones. Methylenation then provided *N*-Boc- and *N*-nosyl-5-iodo-4-methylene-1,2,3,4-tetrahydropyridines. *N*-Boc-5-iodo-2,3-dihydropyridin-4-one and *N*-Boc-5-iodo-4-methylene-1,2,3,4-tetrahydropyridine were converted into the corresponding 5-acetyl-2,3-dihydropyridin-4-one and 5-acetyl-4-methylene-1,2,3,4-tetrahydropyridine by Stille reactions. Methylenation of *N*-Boc-5-ethoxycarbonyl-2,3-dihydropyridin-4-one using the Petasis reagent gave the corresponding 5-ethoxycarbonyl-4-methylene-1,2,3,4-tetrahydropyridine with the 5-acetyl-4-methylenetetrahydropyridine being a side product at higher temperatures.



Keywords: 2,3-Dihydropyridin-4-ones, 4-methylene-1,2,3,4-tetrahydropyridines, Stille reactions, iodination, methylenation

Introduction

N-Protected 5-acyl-4-methylene-1,2,3,4-tetrahydropyridines **1** were identified as intermediates for a synthesis of analogues of the aglycone of the natural product chlorofusin.[1-4] However, monocyclic examples of these compounds were not found in the literature. The parent monocyclic 4-methylene-1,2,3,4-tetrahydropyridines **2** with a removable *N*-protecting group (e.g. Boc, Cbz or Bz) were also not known with the only reported examples being the *N*-methyl-4-methylene-1,2,3,4-tetrahydropyridines **3** (R^1, R^2 = H, Me Bn).[5] These were prepared by deprotonation of the 2,3-dihydropyridinium salts **4** and by elimination of HCN from the 6-cyano-1,2,3,6-tetrahydropyridines **5** but were not isolated as clean compounds and were contaminated by isomeric endocyclic dienes, see Figure 1.

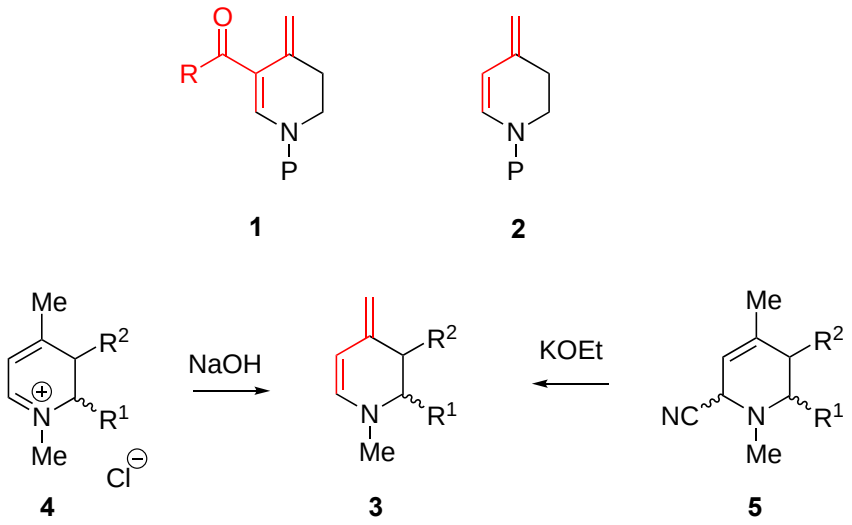


Figure 1. Target 4-methylene-1,2,3,4-tetrahydropyridines **1** and **2** with known literature analogues **3**.

In contrast, 2,3-dihydropridin-4-ones **6** with various *N*-protecting groups (Bz, Bn, Boc) are well known[6-13] including 5-acyl and 5-alkoxycarbonyl derivatives **7** and **8**, see Figure 2.[14,15] These would be useful intermediates in a synthesis of the target compounds **1** and **2** if procedures could be developed for the selective conversion of their 4-carbonyl groups into the required 4-methylene substituents. However, depending on the nature of the *N*-protecting groups, these 4-carbonyl groups are effectively part of a vinylogous amide and selectivity issues were envisaged.

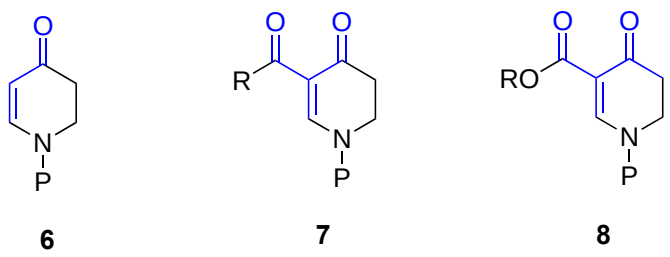


Figure 2. Examples of known 2,3-dihydropyridin-4-ones.

We here report preliminary studies of syntheses of the 4-methylene-1,2,3,4-tetrahydropyridines **1** and **2**.

Results and Discussion

To avoid methylenation of 2,3-dihydropyridin-4-ones, the first studies towards a synthesis of the 5-acyl-4-methylenetetrahydropyridines **1** were predicated on the introduction of the 5,6-double-bond late in the synthesis. 3-Hydroxymethyl-4-methylenepiperidines **9** were identified as suitable intermediates that should be available from 4-methylenepiperidines **10**, see Figure 3.

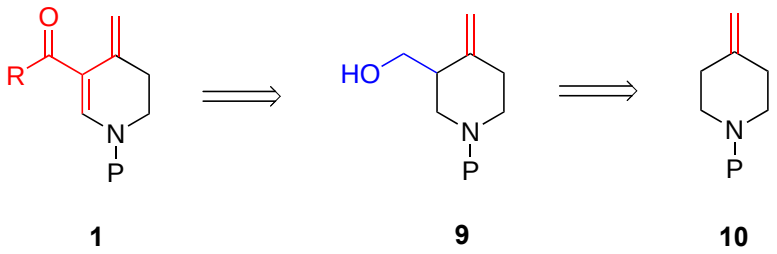
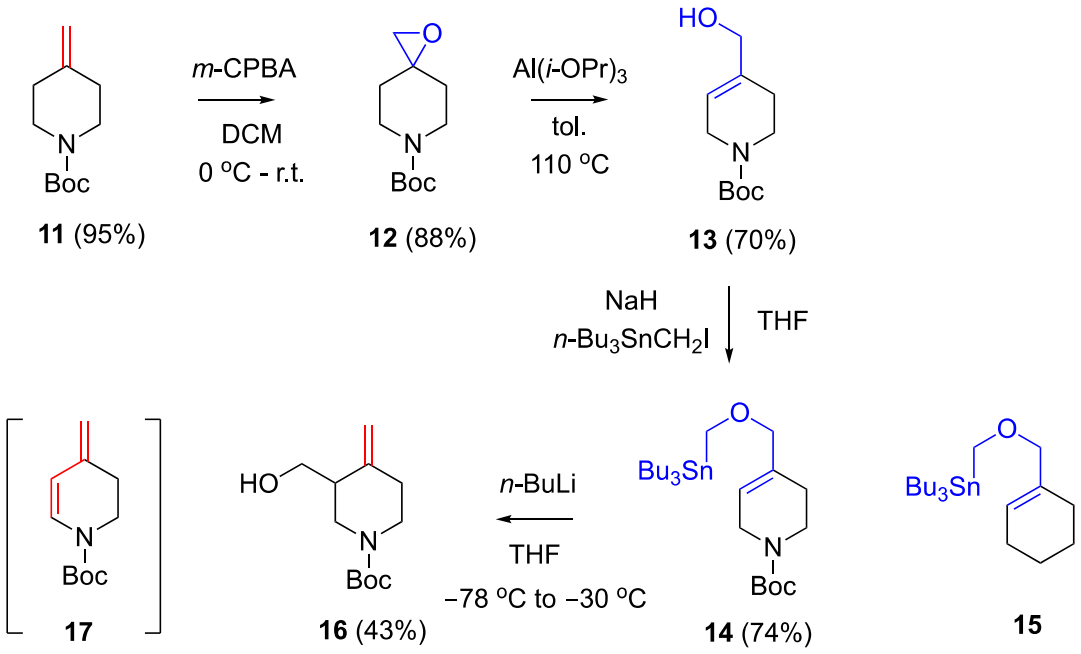


Figure 3. An outline of a possible approach to the target compounds **1**.

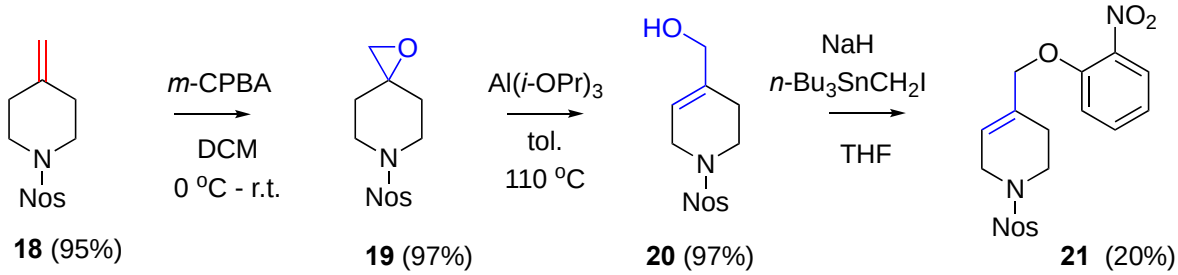
The 4-hydroxymethyl-1,2,5,6-tetrahydropyridine **13** was prepared from the 4-methylenepiperidine **11** via the epoxide **12**.[16] Alkylation using tributyl(iodomethyl)tin gave the (tributyl)stannylmethyl ether **14**. Following the precedent set by the 2,3-Wittig rearrangement of the cyclohexenylmethyl ether **15**,[17-19] the 2,3-Wittig rearrangement of stannylether **14** using *n*-butyllithium at −50 °C to −30 °C gave the 3-hydroxymethyl-4-methylenepiperidine **16** but only in a modest yield (43%). The use of an excess of *n*-butyllithium gave a lower yield of the product **16** (15%) together with a side product identified as the diene **17** (11%) formed by an unexpected 1,4-elimination reaction, see Scheme 1.



Scheme 1. Synthesis of the 3-hydroxymethyl-4-methylenepiperidine **16**.

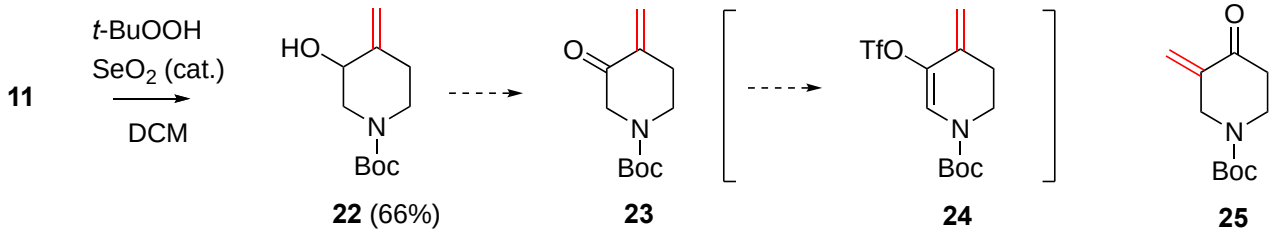
During the course of this work, nosyl protection for the piperidine was investigated and the 4-hydroxymethyl-1,2,5,6-tetrahydropyridine **20** was prepared from the 4-methylenepiperidine **18**.[20] However

attempts to *O*-alkylate this using tributyl(iodomethyl)tin gave the 2-nitrophenyl ether **21** formed by denosylation of the starting material by the sodium salt of another molecule of starting material, see Scheme 2.



Scheme 2. Attempted alkylation of the *N*-nosylated 4-hydroxymethyl-1,2,5,6-tetrahydropyridine **20**.

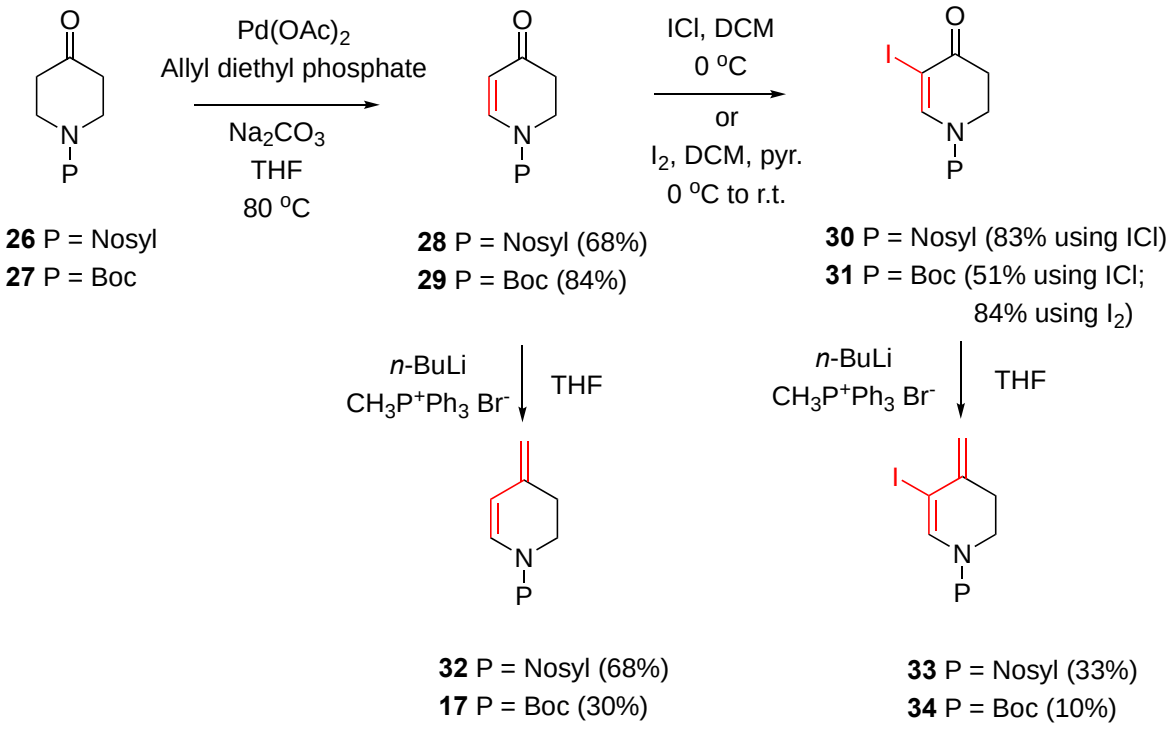
Although further work may have improved the synthesis of the 3-hydroxmethyl-4-methylenepiperidine **16**, it was decided instead to check out alternative approaches to the target 4-methylene-1,2,3,4-tetrahydropyridines **1** and **2**. The enol triflate **24** derived from the 4-methylenepiperidin-3-one **23** was identified as a possible intermediate for the synthesis of the target compounds **1**. However, the attempted oxidation of the known 3-hydroxy-4-methylenepiperidine **22**,[21] see Scheme 3, using several oxidizing agents (Dess-Martin periodinane,[22] PCC, PDC, TPAP, MnO_2) gave complex mixtures of products. The crude reaction mixture obtained from the Dess-Martin oxidation appeared to contain a single, less polar, product, but this gave a mixture on attempted isolation suggesting that the ketone **23** may have been obtained but that it was very unstable. Indeed, the isomeric 3-methylenepiperidin-4-one **25** is known to be unstable and had to be prepared in a large excess and used immediately.[23]



Scheme 3. Attempted preparation of 4-methylenepiperidin-3-one **23**.

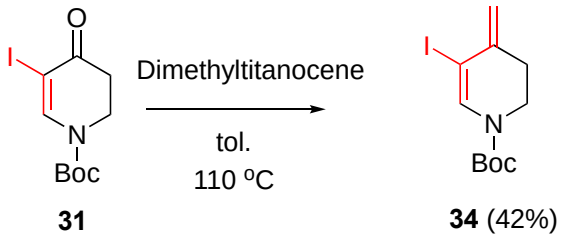
As a third approach to 5-substituted 4-methylene-1,2,3,4-tetrahydropyridines it was decided to see whether methylenation of the corresponding 2,3-dihydropyridin-4-ones, see Figure 2, could be carried out. Several procedures are known for the oxidation of *N*-protected piperidin-4-ones into 2,3-dihydropyridin-4-ones.[24] In our hands, Shvo's palladium(II) acetate catalysed procedure[25] with allyl diethyl phosphate as the oxidant was found to be useful with the oxidation of the *N*-nosyl and *N*-Boc-piperidinones **26** and **27** giving 68% and 84% yields of the 2,3-dihydropyridinones **28** and **29**,[24] respectively. The regioselective iodination of the 2,3-dihydropyridin-4-ones following the precedent set by Comins[26] was then investigated in order to provide access to 5-substituted 4-methylene-1,2,3,4-tetrahydropyridines. In the event, iodination of the *N*-nosyldihydropyridinone **28** using iodine monochloride gave a good yield of the 5-iodo-2,3-dihydropyridin-4-one **30** but better yields of the corresponding *N*-Boc-dihydropyridinone **31** were obtained using iodine,[27] see Scheme 4.

Procedures now had to be evaluated for the conversion of 2,3-dihydropyridin-4-ones into 4-methylene-tetrahydropyridines. Wittig reactions were first investigated. The conversion of the *N*-nosyldihydropyridinone **28** into the 4-methylenetetrahydropyridine **32** using a Wittig reaction proceeded in an acceptable yield of 68%. However, only a 30% yield of the *N*-Boc-4-methylenetetrahydropyridinone **17** was obtained using this procedure and methylenation of the 5-iododihydropyridinones **30** and **31** using Wittig reactions gave only low yields of the 5-iodo-4-methylene-1,2,3,4-tetrahydropyridines **33** and **34**, see Scheme 4.



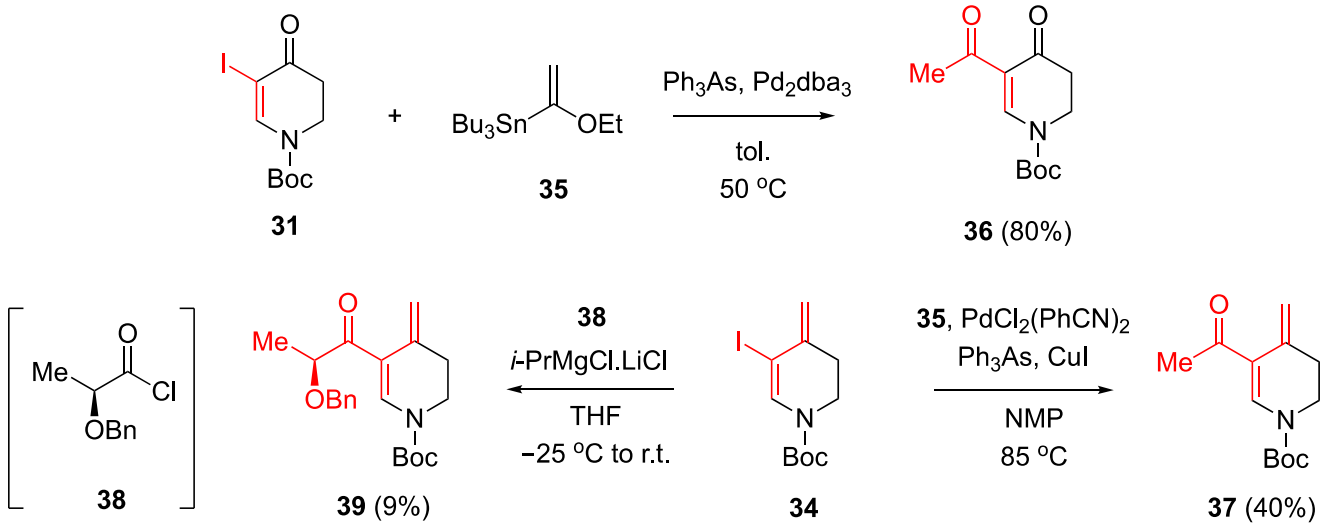
Scheme 4. Preparation of 2,3-dihydropyridinones and their methylenation using Wittig reactions.

Alternative procedures were therefore investigated for the conversions of the 5-iododihydropyridinones **30** and **31** into the 5-iodo-4-methylenetetrahydropyridines **33** and **34**. Using the Petasis reagent (dimethyltitanocene) in toluene at 110 °C,[28-31] a 42% yield of the *N*-Boc-5-iodo-4-methylenetetrahydropyridine **34** was obtained, see Scheme 5. Microwave conditions using the Petasis reagent[32] gave a similar yield but lower yields were obtained using the Tebbe reagent[33-35] and the use of the Nysted reagent[36] gave complex mixtures of products. Only very low yields of the *N*-nosyl-5-iodo-4-methylenetetrahydropyridine **33** were obtained using these organometallic reagents.



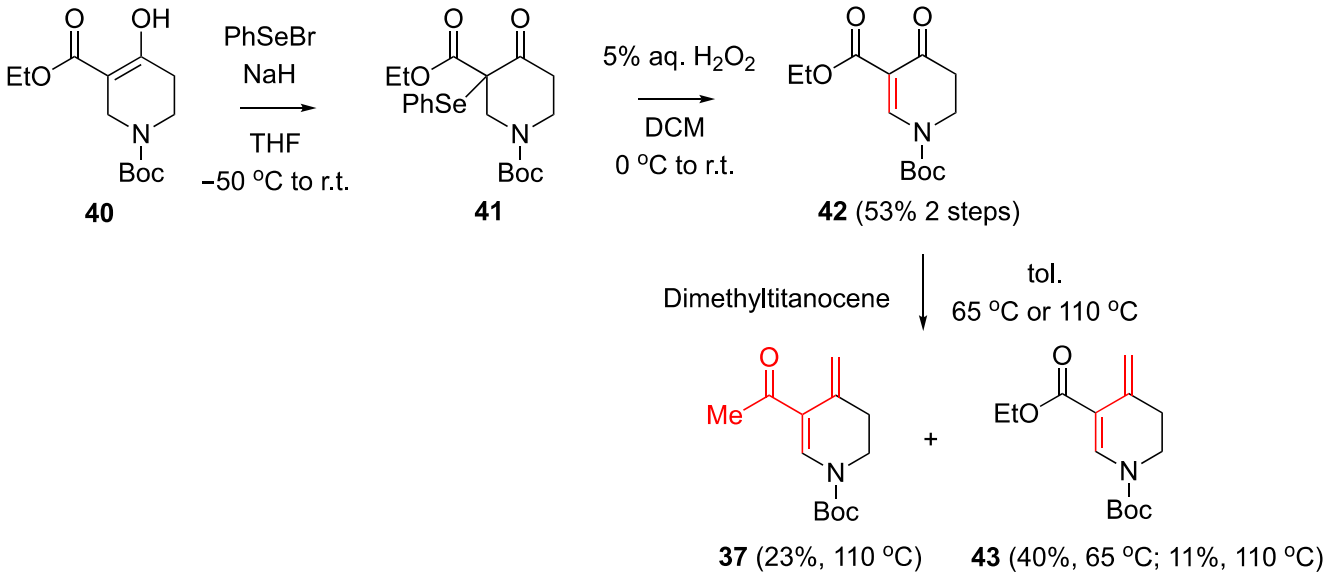
Scheme 5. Preparation of the 5-iodo-4-methylene-1,2,3,4-tetrahydropyridine **34** using the Petasis reagent.

Elaboration of the vinylic iodides **31** and **34** was now investigated. A Stille reaction of the 5-iodo-2,3-dihydropyridin-4-one **31**[37] with the ethoxyvinylstannane **35**[38] using tris(dibenzylideneacetone)dipalladium(0) as the catalyst gave a good yield of the diketone **36**. However, the Stille reaction of the 5-iodo-4-methylenetetrahydropyridine **34** with the ethoxyvinylstannane **35** gave only a 27% yield of the 5-acetyl-4-methylenetetrahydropyridine **37** under these conditions. When bis(benzonitrile)palladium(II) chloride[39] was used as the catalyst, the yield of the acetylated tetrahydropyridine **37** increased to 40%, see Scheme 6, although the yield of the acetylated dihydropyridinone **36** dropped to 56% with this catalyst. Conversion of the iodotetrahydropyridine **34** into the corresponding Grignard reagent[40,41] and acylation with the acid chloride **38** gave the 5-acyl-4-methylenetetrahydropyridine **39** but in only a low yield, see Scheme 6. The 5-iodo-4-methylenetetrahydropyridine **34** showed signs of decomposition after a month at –25 °C in benzene and this instability may account for the lowish yields of the ketones **37** and **39**.



Scheme 6. Preparation of the 5-acyl-4-methylene-1,2,3,4-tetrahydropyridines **37** and **39**.

Finally, the keto-ester **42** was prepared via the selenide **41** from the ester **40**[42,43]and its reaction with the Petasis reagent[28-31] investigated. At 110 °C, a mixture of the 5-acetyl-4-methylenetetrahydropyridine **37** and the expected 5-ethoxycarbonyl-4-methylenetetrahydropyridine **43** was obtained whereas at 65 °C only the ester **43** was isolated (40%), see Scheme 7. Perhaps the ketone **37** had been formed by hydrolysis on work-up of the enol ether formed by reaction of the Petasis reagent with the ethoxycarbonyl group.



Scheme 7. Methylenation of the ketoester **42**.

Conclusions

Approaches to the synthesis of 5-acyl-4-methylene-1,2,3,4-tetrahydropyridines **1** are reported. The synthesis of *N*-Boc-3-hydroxymethyl-4-methylenepiperidine **16** was not particularly efficient and *N*-Boc-4-methylenepiperidin-3-one **23** decomposed on attempted isolation. However, methylenation of 2,3-dihydropyridin-4-ones gave the corresponding 4-methylene-1,2,3,4-tetrahydropyridines albeit with variable yields. Stille reactions of *N*-Boc-5-iodo-2,3-dihydropyridin-4-one **31** and *N*-Boc-5-iodo-4-methylene-1,2,3,4-tetrahydropyridine **34** gave the corresponding 5-acetyl compounds **36** and **37** in 80% and 40% yields, respectively. The Petasis reagent reacted with *N*-Boc-5-ethoxycarbonyl-2,3-dihydropyridin-4-one **42** to give *N*-Boc-5-ethoxycarbonyl-4-methylene-1,2,3,4-tetrahydropyridine **43** together with the corresponding 5-acetyl-tetrahydropyridine **37** at higher temperatures.

Although this work led to the synthesis of the target compound **37** it also pointed the way for further work. For example, it should be possible to improve the synthesis of the 5-acetyl-4-methylenetetrahydropyridine **37** directly by bis-methylenation of the readily available keto-ester **42**. Alternatively, the previously reported elimination of HCN from the 2-cyanotetrahydropyridine **5** and the formation of the 4-methylenetetrahydropyridine **17** from the ether **14** suggest that dehydration of 4-hydroxymethyltetrahydropyridines, e.g. alcohol **13**, may lead to improved access to 4-methylenetetrahydropyridines albeit that further work will be necessary to access more complex examples.

Experimental Section

General. Low resolution mass spectra were recorded on a Micromass Trio 200 spectrometer. High resolution mass spectra were recorded on a Kratos Concept IS spectrometer. Modes of ionisation were electron impact (EI), chemical ionisation using ammonia (CI^+), electrospray (ES) or atmospheric pressure chemical ionization (APCI). Infrared spectra were recorded on a Genesis FTIR as evaporated films on sodium chloride plates.

Proton NMR spectra (^{1}H NMR) were recorded on a Bruker Ultrashield 500 (500 MHz) or a Varian INOVA Unity 300 (300 MHz) spectrometer. Residual non-deuterated solvent was used as the internal standard. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), sextet (sext) or multiplet (m). Coupling constants are quoted in Hertz (Hz). Carbon NMR spectra (^{13}C) were recorded on a Varian INOVA 300 at 75 MHz, or Bruker Ultrashield 500 at 125 MHz using deuterated solvent as the internal standard. Chemical shifts (δ_C) are quoted in ppm downfield from TMS. NMR peak broadening due to rotamers is indicated (br) for some compounds with a Boc-protecting group.

All reactions were carried out under an atmosphere of dry nitrogen in flame-dried flasks unless stated otherwise. Chromatography refers to flash chromatography and was carried out using Merck silica gel 60H (40-60 nm, 230-300 mesh). Petrol refers to the fraction of light petroleum ether that distils between 40 °C and 60 °C at atmospheric pressure and was distilled from 4Å molecular sieves. Ether refers to diethyl ether. Tetrahydrofuran (THF) was dried over sodium/benzophenone and distilled under a nitrogen atmosphere. Dichloromethane (DCM) was dried over calcium hydride and distilled under an atmosphere of nitrogen. Di-isopropylamine was dried over potassium hydroxide pellets and distilled under an atmosphere of nitrogen. Acetonitrile was dried over calcium hydride and distilled under a nitrogen atmosphere. Benzene, toluene, ether and hexane were dried and stored over sodium wire. Triethylamine was stored over potassium hydroxide pellets. *n*-Butyllithium was titrated against a solution of propan-2-ol in xylene with 2,2'-bipyridine as indicator.

***tert*-Butyl 4-(hydroxymethyl)-1,2,5,6-tetrahydropyridine-1-carboxylate (13)**.[44] A mixture of the epoxide **12**[16] (1.98 g, 9.28 mmol) and aluminium isopropoxide (2.87 g, 14.05 mmol) in anhydrous toluene (75 mL) was heated under reflux for 36 h. The reaction was allowed to cool and then poured into aqueous hydrogen chloride (1 M, 25 mL). The aqueous phase was extracted into ether (2 × 25 mL) and the organic extracts were dried (Na_2SO_4) then concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 1 to 3 : 2) gave the title compound **13**[44] as a colourless oil (1.39 g, 70%), R_F = 0.11 (ether : petrol 1 : 1); ν_{max}/cm^{-1} 3435, 2974, 2923, 2859, 1690, 1671, 1423, 1243, 1169, 1114 and 1047; δ_H (500 MHz, $CDCl_3$) 5.68 (1H, m, 3-H), 4.08 and 3.94 (each 2H, m, 2-H and 4-CH), 3.55 - 3.51 (2H, m, 6-H_2), 2.72 (1H, br s, OH), 2.15 (2H, m, 5-H_2) and 1.49 [9H, s, C(CH_3)$_3$]; δ_c (75 MHz, $CDCl_3$) 155.19 (C), 136.72 (CH), 118.90 (br, C), 79.87 (C), 65.86 (CH_2), 42.00 (br, CH_2), 39.49 (br, CH_2), 28.64 (CH_3) and 25.77 (CH_2); *m/z* (CI$^+$) 214 (M$^+$ + 1, 30%) and 114 (100) [Found: *m/z* (EI$^+$) M$^+$, 213.1357. $C_{11}H_{19}NO_3$ requires *M*, 213.1359].

***tert*-Butyl 4-[(tributylstannylmethoxy)methyl]-1,2,5,6-tetrahydropyridine-1-carboxylate (14).** Sodium hydride (365 mg, 9.13 mmol, 60 wt % in mineral oil) was added to the alcohol **13** (650 mg, 3.05 mmol) in THF (20 mL) at rt. After 30 min, iodomethyl(tributyl)tin (1.37 mL, 4.58 mmol) was added. The reaction mixture was stirred at rt for 16.5 h, then further iodomethyl(tributyl)tin (0.45 mL, 1.50 mmol) was added. After stirring for a further 2 d water (10 mL) was added and the mixture was extracted into ether (3 × 20 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (petrol to ether : petrol 3 : 7) gave the *title compound* **14** as a colourless oil (1.16 g, 74%), R_F = 0.65 (ether : petrol 3 : 7); ν_{max}/cm^{-1} 2957, 2925, 2852, 1701, 1460, 1419, 1366, 1286, 1241, 1174, 1112, 1072, 970, 867 and 769; δ_H (500 MHz, $CDCl_3$) 5.62 (1H, m, 3-H), 3.93 (2H, br s, 2-H_2), 3.80 (2H, m, 4-CH_2), 3.68 (2H, m, OCH_2Sn), 3.53 (2H, m, 6-H_2), 2.10 (2H, m, 5-H_2), 1.56-1.48 [6H, m, 3 × C$H_2$$CH_2Sn$], 1.49 [9H, s, C($CH_3$)$_3$], 1.33 (6H, sext, *J* 7.5, 3 × CH_3CH_2), 0.93 (6H, t, *J* 7.5, 3 × CH_2Sn) and 0.91 (9H, t, *J* 7.5, 3 × CH_3); δ_c (75 MHz, $CDCl_3$) 155.07 (C), 134.45 (br C), 120.54 (br CH), 79.58 (C), 78.79 (CH_2), 61.29 (CH_2), 43.45 (br CH_2), 39.90 (br CH_2), 29.35 (CH_2), 28.65 (CH_3), 27.50 (CH_2), 26.01 (CH_2), 13.90 (CH_3) and 9.16 (CH_2); *m/z* (APCI) 418 (M$^+$ − 80, 95%) and 359 (100).

***tert*-Butyl 3-hydroxymethyl-4-methylenepiperidine-1-carboxylate (16)**. *n*-Butyllithium (1.6 M in hexanes, 0.39 mL, 0.62 mmol) was added to the stannylmethyl ether **14** (290 mg, 0.56 mmol) in THF (2 mL) at −78 °C. After 15 min the mixture was allowed to warm to −50 °C, stirred for 12 h, and warmed to −30 °C. After 3 h, water (2 mL) was added, and the mixture allowed to warm to rt then extracted into ether (3 × 10 mL). The organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 6 : 4) gave the *title compound* **15** as a colourless oil (55 mg, 43%), R_F = 0.32 (ether : petrol 6 : 4); ν_{max}/cm^{-1} 3441 (br), 2977, 2934, 2871, 1693, 1671, 1468, 1430, 1366, 1320, 1274, 1242, 1169, 1122, 1038, 947, 894 and 770; δ_H (500 MHz, $CDCl_3$) 4.89 and 4.87 (each 1H, s, 4-CH), 4.05 (1H, br m, 3-CH), 3.98 (1H, m, 2-H), 3.57 (2H, m, 6-H_2), 3.03 (1H, br m, 3-CH'), 2.93 (1H, m, 2-H'), 2.52 (1H, m, 3-H), 2.30 and 2.17 (each 1H, m, 5-H), 2.01 (1H, br s, OH) and 1.57 [9H, s, C(CH_3)$_3$]; δ_c (75 MHz, $CDCl_3$) 156.42 (C), 144.91 (C), 111.75 (CH_2), 80.38 (C), 61.84 (br CH_2), 46.51 (br CH), 46.35 (CH_2), 45.42 (br CH_2), 32.10 (CH_2) and 28.63 (CH_3); *m/z* (CI$^+$) 228 (M^+ + 1, 30%), 189 (20), 172 (40) and 128 (100) [Found: *m/z* (+ES) M^+ + H, 228.1594. $C_{12}H_{22}NO_3$ requires *M*, 228.1594].

An analogous reaction using three equivalents of *n*-butyllithium after stirring at −78 °C for 1 h and then at −50 °C for 19 h, gave the diene **17** (11%), R_F = 0.71 (ether : petrol 1 : 1), that was characterised using a sample prepared later, followed by the title compound **16** (15%).

1-(2-Nitrophenylsulfonyl)-4-methylenepiperidine (18).[20] *n*-Butyllithium (1.6 M in hexanes, 5.1 mL, 7.65 mmol) was added to a suspension of methyltriphenylphosphonium bromide (3.68 g, 10.31 mmol) in THF (30 mL) at 0 °C. After 1 h, 1-(2-nitrophenylsulfonyl)piperidin-4-one **26**[9] (1.46 g, 5.14 mmol) in THF (10 mL) was added *via* a cannula and the reaction mixture allowed to warm to rt and stirred for 19 h. Methanol (30 mL) was added and the mixture concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 1) gave the title compound **18** as an orange gum (1.11 g, 76%), R_F = 0.25 (ether : petrol 1 : 1); ν_{max}/cm^{-1} 3086, 2969, 2920, 2867, 1659, 1552, 1463, 1437, 1370, 1343, 1238, 1166, 1123, 938, 897, 851 and 786; δ_H (300 MHz, $CDCl_3$) 8.04 (1H, m, ArH), 7.76-7.71 (2H, m, ArH), 7.64 (1H, m, ArH), 4.81 (2H, s, 4-CH_2), 3.37 (4H, t, *J* 5.9, 2-H_2 and 6-H_2) and 2.35 (4H, t, *J* 5.8, 3-H_2 and 5-H_2); δ_c (75 MHz, $CDCl_3$) 148.51 (C), 143.31 (C), 133.95 (CH), 132.07 (CH), 131.89 (C), 131.05 (CH), 124.34 (CH), 110.80 (CH_2), 47.76 (CH_2) and 34.48 (CH_2); *m/z* (CI$^+$) 300 (M^+ + 18, 20%), 283 (M^+ + 1, 18%) and 253 (100) [Found: *m/z* (ES) M^+ + NH_4, 300.1015. $C_{12}H_{18}N_3O_4S$ requires *M*, 300.1013].

6-(2-Nitrophenylsulfonyl)-1-oxa-6-azaspiro[2.5]octane (19). *m*-Chloroperbenzoic acid (70 wt %, 480 mg, 2.78 mmol) was added to the 4-methylenepiperidine **18** (505 mg, 1.79 mmol) in DCM (14 mL) at 0 °C and the reaction mixture allowed to warm to rt. After 15 h, saturated aqueous sodium bicarbonate (10 mL) was added and the aqueous phase extracted with DCM (3 × 25 mL). The organic extracts were washed with water (2 × 25 mL), brine (2 × 25 mL) and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue (ether) gave the *title compound* **19** as an orange gum (517 mg, 97%), R_F = 0.29 (ether); ν_{max}/cm^{-1}) 2954, 2925, 2863, 1723, 1545, 1465, 1439, 1368, 1168, 1130, 1042, 946, 914, 850 and 745; δ_H (500 MHz, $CDCl_3$) 8.03 (1H, m, ArH), 7.75-7.73 (2H, m, ArH), 7.65 (1H, m, ArH), 3.73 (2H, dt, *J* 12.7, 4.0, 5-H and 7-H), 3.32 (2H, ddd, *J* 13.3, 10.7, 3.3, 5-H' and 7-H'), 2.73 (2H, s, 2-H_2), 2.09 (2H, ddd, *J* 14.4, 10.7, 4.6, 4-H and 8-H) and 1.51 (2H, dt, *J* 13.7, 3.3, 4-H' and 8-H'); δ_c (75 MHz, $CDCl_3$) 148.55 (C), 134.13 (CH), 131.95 (CH), 131.76 (C), 131.03 (CH), 124.41 (CH), 56.33 (C), 53.90 (CH_2), 44.95 (CH_2) and 32.96 (CH_2); *m/z* (CI$^+$) 316 (M^+ + 18, 100%), 299 (M^+ + 1, 30%), 269 (30) and 112 (20) [Found: *m/z* (ES) M^+ + NH_4, 316.0959. $C_{12}H_{18}N_3O_5S$ requires *M*, 316.0962].

1-(2-Nitrophenylsulfonyl)-1,2,5,6-tetrahydro-4-hydroxymethylpyridine (20). A solution of the epoxide **19** (900 mg, 3.02 mmol) and aluminium isopropoxide (1.85 g, 9.06 mmol) in anhydrous toluene (20 mL) was heated under reflux for 46 h. The mixture was allowed to cool to rt. Ether (20 mL), saturated aqueous

Rochelle's salt (20 mL), and aqueous sodium hydroxide (1 M, 20 mL) were added and the mixture was extracted into ether (3 × 25 mL). The organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue (ether to EtOAc) gave the *title compound* **20** as an orange oil (787 mg, 87%), R_F = 0.30 (EtOAc); ν_{max}/cm^{-1} 3448 br, 2919, 2873, 2860, 2362, 1544, 1365, 1348, 1166, 1047, 953, 920, 778 and 747; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, m, ArH), 7.73-7.71 (2H, m, ArH), 7.65 (1H, m, ArH), 5.72 (1H, m, 3-H), 4.17-4.07 (2H, m, 4-CH_2), 3.93-3.90 (2H, m, 2-H_2), 3.55-3.51 (2H, m, 6-H_2) and 2.27-2.26 (2H, m, 5-H_2); δ_C (125 MHz, $CDCl_3$) 148.68, 136.96, 134.11, 132.09, 132.06, 131.21, 124.55, 117.83, 66.16, 44.75, 43.01 and 21.07; *m/z* (Cl^+) 316 (M^+ + 18, 100%), 206 (30) and 110 (50) [Found: *m/z* (ES) M^+ + H, 299.0707. $C_{12}H_{15}N_2O_5S$ requires *M*, 299.0696].

1-(2-Nitrophenylsulfonyl)-4-(2-nitrophenoxymethyl)-1,2,5,6-tetrahydropyridine (21). Sodium hydride (60 wt % in mineral oil, 45 mg, 1.13 mmol) was added to the alcohol **20** (198 mg, 0.66 mmol) in THF (5 mL) at rt. After 30 min, iodomethyl(tributyl)tin (580 mg, 1.35 mmol) was added and the reaction mixture was stirred at rt for 3.5 d. Water (5 mL) was added and the mixture was extracted into ether (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (EtOAc : petrol 1 : 9 to 7 : 3) gave the *title compound* **21** as a pale brown solid (55 mg, 20%), R_F = 0.24 (ether : petrol 7 : 3); m.p. 131-133 °C; ν_{max}/cm^{-1} 3093, 2914, 2867, 1606, 1545, 1523, 1355, 1278, 1253, 1170, 955, 856 and 747; δ_H (300 MHz, $CDCl_3$) 8.07 (1H, m, ArH), 7.85 (1H, dd, *J* 8.4, 1.8, ArH), 7.75-7.70 (2H, m, ArH), 7.63 (1H, m, ArH), 7.54 (1H, m, ArH), 7.10-7.03 (2H, m, ArH), 5.90 (1H, m, 3-H), 4.57 (2H, s, 4-CH_2), 3.98-3.92 (2H, m, 2-H_2), 3.55 (2H, t, *J* 5.7, 6-H_2) and 2.40-2.30 (2H, m, 5-H_2); δ_c (75 MHz, $CDCl_3$) 151.92 (C), 148.53 (C), 140.14 (C), 134.46 (CH), 134.00 (CH), 131.93 (CH), 131.90 (C), 131.05 (C), 125.96 (CH), 124.41 (CH), 121.08 (CH), 120.98 (CH), 120.72 (CH), 114.92 (CH), 72.01 (CH_2), 44.59 (CH_2), 42.73 (CH_2) and 25.81 (CH_2); *m/z* (+ES) 442 (M^+ + 23, 100%), 236 (55) and 133 (50) [Found: *m/z* (ES) M^+ + Na, 442.0676. $C_{18}H_{17}N_3O_7SNa$ requires M, 442.0679]. A second fraction contained recovered starting material **20** (46 mg, 20%).

1-(2-Nitrophenylsulfonyl)-2,3-dihydropyridin-4-one (28). A mixture of palladium(II) acetate (425 mg, 1.89 mmol), diallyl ethyl phosphate (9.78 g, 50.4 mmol), sodium carbonate (5.58 g, 52.7 mmol) and the piperidin-4-one **26**[9] (8.8 g, 30.95 mmol) in THF (80 mL) was heated at 80 °C for 21 h. The reaction mixture was allowed to cool to rt and was partitioned between DCM (150 mL) and water (150 mL). The aqueous phase was extracted with DCM (3 × 100 mL) and the organic extracts washed with brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate : petrol 1 : 1) gave the *title compound* **28** as a yellow solid (5.9 g, 68%), R_F = 0.36 (EtOAc : petrol 9 : 1), m.p. 99-102 °C; ν_{max}/cm^{-1} 3094, 3022, 2903, 1668, 1600, 1546, 1373, 1283, 1175, 1126, 1075, 1037, 941, 853, 808, 782 and 733; δ_H (300 MHz, $CDCl_3$) 8.16 (1H, m, ArH), 7.91-7.82 (3H, m, ArH), 7.71 (1H, d, *J* 8.4, 6-H), 5.52 (1H, d, *J* 8.4, 5-H), 4.00 (2H, t, *J* 7.2, 2-H_2), 2.65 (2H, t, *J* 7.2, 3-H_2); δ_C (75 MHz, $CDCl_3$) 191.79 (C), 148.26 (C), 143.24 (CH), 135.76 (CH), 132.95 (CH), 131.75 (CH), 130.52 (C), 125.43 (CH), 108.66 (CH), 44.74 (CH_2) and 35.80 (CH_2); *m/z* (Cl^+) 283 (M^+ + 1, 60%), 253 (30) and 98 (100) [Found: *m/z* (ES) M^+ + H, 283.0382. $C_{11}H_{11}N_2O_5S$ requires *M*, 283.0383].

***tert*-Butyl 2,3-dihydropyridin-4-one-1-carboxylate (29)**.[24] A mixture of palladium(II) acetate (680 mg, 3.02 mmol), allyl diethyl phosphate (13.87 g, 71.43 mmol), sodium carbonate (8.2 g, 77.37 mmol) and the piperidin-4-one **27** (11.86 g, 59.52 mmol) in THF (60 mL) was heated under reflux for 21 h. The reaction mixture allowed to cool to rt and was partitioned between DCM (150 mL) and water (150 mL). The aqueous phase was extracted with DCM (3 × 200 mL) and the organic extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 4 : 6) gave the title compound **29** as white solid (9.82 g, 84%), R_F = 0.37 (ether : petrol 7 : 3), m.p. 51-52 °C (lit.[24] 53-54 °C); ν_{max}/cm^{-1} 2977, 2930, 2871, 2365, 2336, 1724, 1669, 1602, 1368, 1343, 1304, 1224, 1156, 1113, 992, 855 and 767; δ_H (500 MHz, $CDCl_3$) 7.79 (1H, br d, *J* 7.5, 6-H), 5.27 (1H, d, *J* 8.3, 5-H), 3.95 (2H, t, *J* 7.4, 2-H_2), 2.52

(2H, t, *J* 7.3, 3-H_2) and 1.52 [9H, s, $C(CH_3)_3$]; δ_C (75 MHz, $CDCl_3$) 193.85 (C), 144.29 (C), 144.28 (CH), 106.88 (CH), 83.67 (C), 41.12 (br CH_2), 35.92 (CH_2) and 28.26 (CH_3); *m/z* (CI^+) 198 (M^+ + 1, 90%) and 98 (100) [Found: *m/z* (ES) M^+ + H, 198.1128. $C_{10}H_{16}NO_3$ requires *M*, 198.1125].

2,3-Dihydro-5-iodo-1-(2-nitrophenylsulfonyl)pyridin-4-one (30). Iodine monochloride (1.0 M in DCM, 41 mL, 41.00 mmol) was added to the dihydropyridinone **28** (5.80 g, 20.55 mmol) in DCM (125 mL) at 0 °C in a foil-covered flask. After 2.5 h, saturated aqueous sodium sulfite (65 mL) and saturated aqueous sodium bicarbonate (65 mL) were added. The reaction mixture was allowed to warm to rt and was stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 × 150 mL) and the organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (ethyl acetate : petrol 4 : 6 to 1 : 1) gave the *title compound* **30** as a yellow solid (6.9 g, 83%), R_F = 0.40 (EtOAc : petrol 9 : 1), m.p. 150-152 °C; ν_{max}/cm^{-1} 3098, 1683, 1578, 1545, 1377, 1279, 1178, 1122, 1078, 1039, 955, 911 and 737; δ_H (300 MHz, $CDCl_3$) 8.24-8.18 (2H, m, 6-H and ArH), 7.95-7.85 (3H, m, ArH), 4.10-4.06 (2H, m, 2-H_2) and 2.90-2.85 (2H, m, 3-H_2); δ_C (75 MHz, $CDCl_3$) 185.88 (C), 148.34 (C), 147.92 (CH), 136.03 (CH), 133.10 (CH), 132.01 (CH), 130.27 (C), 125.67 (CH), 77.80 (C), 45.02 (CH_2) and 34.69 (CH_2); *m/z* (CI^+) 409 (M^+ + 1, 95%) and 224 (100) [Found: *m/z* (ES) M^+ + H,' 408.9334. $C_{11}H_{10}N_2O_5IS$ requires *M*, 408.9350].

***tert*-Butyl 2,3-dihydro-5-iodopyridin-4-one-1-carboxylate (31)**. Iodine (47.0 g, 185.2 mmol) was added to the pyridine-4-one **29** (9.82 g, 49.79 mmol) in DCM (240 mL) and pyridine (110 mL) at 0 °C and the reaction mixture was allowed to warm to rt then stirred for 18 h. Ether (500 mL) was added and the solution washed with a saturated aqueous sodium sulfite (2 × 200 mL) and brine (1 × 200 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 1) gave the *title compound* **31** as a yellow solid (14.29 g, 84%), R_F = 0.53 (ether : petrol 1 : 1), m.p. 134-136 °C; ν_{max}/cm^{-1} 2977, 2932, 2876, 1714, 1673, 1572, 1474, 1374, 1299, 1249, 1139, 1043, 999, 917, 844 and 775; δ_H (300 MHz, $CDCl_3$) 8.39 (1 H, br s, 6-H), 4.11-4.06 (2 H, m, 2-H_2), 2.83-2.78 (2 H, m, 3-H_2) and 1.61 [9 H, s, $C(CH_3)_3$]; δ_c (75 MHz, $CDCl_3$) 187.62 (C), 149.74 (C), 149.70 (CH), 84.66 (C), 75.30 (C), 42.75 (CH_2), 34.74 (CH_2) and 28.27 (CH_3); *m/z* (CI^+) 341 (M^+ + 18, 50%), 324 (M^+ + 1, 60), 241 (40), 224 (45), 115 (60) and 98 (100) [Found: *m/z* (ES) M^+ + H, 324.0095. $C_{10}H_{15}NO_3I$ requires *M*, 324.0091].

4-Methylene-1-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydropyridine (32). *n*-Butyllithium (1.6 M in hexanes, 0.39 mL, 0.62 mmol) was added to a suspension of methyltriphenylphosphonium bromide (276 mg, 0.77 mmol) in THF (2 mL). After 30 min, a solution of the 2,3-dihydropyridinone **28** (109 mg, 0.39 mmol) in THF (1 mL) was added and the mixture stirred for 4.5 h. Methanol was added and the mixture concentrated under reduced pressure. Chromatography of the residue (ether : petrol 3 : 7 then 1 : 1) gave the *title compound* **32** as a pale yellow oil (74 mg, 68%), R_F = 0.43 (ether : petrol 1 : 1); ν_{max}/cm^{-1} 3093, 2952, 2924, 1636, 1595, 1544, 1366, 1268, 1171, 1124, 1084, 953 and 883; δ_H (300 MHz, $CDCl_3$) 8.04 (1H, m, ArH), 7.80-7.69 (3H, m, ArH), 6.73 (1H, d, *J* 8.2, 6-H), 5.68 (1H, d, *J* 8.2, 5-H), 4.92 and 4.76 (each 1H, s, 4-CH), 3.69 (2H, t, *J* 6.2, 2-H_2) and 2.57 (2H, t, *J* 6.2, 3-H_2); δ_c (75 MHz, $CDCl_3$) 148.26 (C), 136.43 (C), 134.37 (CH), 132.16 (CH), 131.92 (CH), 130.81 (C), 125.27 (CH), 124.64 (CH), 111.86 (CH), 111.44 (CH_2), 44.71 (CH_2) and 29.69 (CH_2); *m/z* (CI^+) 281 (M^+ + 1, 100%), 251 (60) and 96 (70) [Found: *m/z* (ES) M^+ + H, 281.0593. $C_{12}H_{13}N_2O_4S$ requires *M*, 281.0591].

***tert*-Butyl 4-methylene-1,2,3,4-tetrahydropyridine-1-carboxylate (17)**. *n*-Butyllithium (1.5 M in hexanes, 0.50 mL, 0.75 mmol) was added to a suspension of methyltriphenylphosphonium bromide (356 mg, 1.00 mmol) in THF (3 mL) and the mixture stirred for 30 min at rt. The dihydropyridinone **29** (93 mg, 0.47 mmol) in THF (1 mL) was added and the reaction mixture stirred for 3.5 h. Methanol was added and the mixture concentrated under reduced pressure. Chromatography of the residue (ether : petrol 3 : 7) gave the *title compound* **17** as a pale yellow oil (27 mg, 30%), R_F = 0.71 (ether : petrol 1 : 1); ν_{max}/cm^{-1} 3055, 2980, 2930, 1694, 1418, 1367, 1266, 1168, 1116, 1069, 994, 863 and 739; δ_H (500 MHz, $CDCl_3$, rotamers) 6.84 (0.4H, br s, 6-H), 6.69 (0.6H, br

d, *J* 7.3, 6-H), 5.41 (0.4H, br s, 5-H), 5.32 (0.6H, br d, *J* 7.3, 5-H), 4.71 and 4.56 (each 1H, s, 4-CH), 3.57 (2H, m, 2-H_2), 2.42 (2H, m, 3-H_2) and 1.43 [9H, s, $C(CH_3)_3$]; δ_c (75 MHz, $CDCl_3$) 142.32 (C), 138.50 (C), 127.02 (CH), 108.95 (CH_2), 108.03 (CH), 81.46 (C), 41.78 (CH_2), 30.02 (CH_2) and 28.54 (CH_3); *m/z* (Cl^+) 196 (M^+ + 1, 20%), 112 (90) and 96 (100) [Found: *m/z* (ES) M^+ + H, 196.1339. $C_{11}H_{18}NO_2$ requires *M*,196.1332].

5-Iodo-4-methylene-1-(2-nitrophenylsulfonyl)-1,2,3,4-tetrahydropyridine (**33)**. *n*-Butyllithium (1.5 M in hexanes, 0.32 mL, 0.48 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (330 mg, 0.92 mmol) in THF (2.5 mL) at rt and the mixture stirred for 50 min. The 5-iododihydropyridinone **30** (120 mg, 0.47 mmol) in THF (2 mL) was added and the reaction mixture stirred for 3 h. Methanol was added and the mixture concentrated under reduced pressure. Chromatography of the residue (ether : petrol 4 : 6) gave the *title compound* **33** as a pale yellow oil (39 mg, 33%), R_F = 0.19 (ether : petrol 4 : 6); ν_{max}/cm^{-1} 3094, 2924, 1685, 1618, 1585, 1543, 1439, 1372, 1270, 1165, 1126, 1085, 960, 909, 852 and 732; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, m, ArH), 7.83-7.72 (3H, m, ArH), 7.30 (1H, s, 6-H), 5.20 and 5.05 (each 1H, s, 4-CH), 3.76 (2H, t, *J* 6.0, 2-H_2) and 2.75 (2H, t, *J* 6.0, 3-H_2); δ_c (75 MHz, $CDCl_3$) 148.30 (C), 137.01 (C), 134.77 (CH), 132.42 (CH), 132.08 (CH), 131.45 (C), 131.06 (CH), 124.89 (CH), 118.83 (CH_2), 78.16 (C), 44.70 (CH_2) and 29.78 (CH_2); *m/z* (EI) 406 (M^+, 100%), 376 (20), 221 (60) and 93 (100) [Found: *m/z* (ES) M^+ + H, 406.9552. $C_{12}H_{12}N_2O_4IS$ requires *M*, 406.9557].

***tert*-Butyl 5-iodo-4-methylene-1,2,3,4-tetrahydropyridine-1-carboxylate (34)**. A solution of the iododihydropyridin-4-one **31** (104 mg, 0.32 mmol) in Petasis reagent (0.15 M in toluene, 4.2 mL, 0.63 mmol) was heated at 110 °C in the dark for 1.5 h then allowed to cool to rt. After concentration under reduced pressure, chromatography of the residue (ether : petrol 1 : 20) gave the *title compound* **34** as an orange oil (43 mg, 42%), R_F = 0.43 (ether : petrol 1 : 15); ν_{max}/cm^{-1} 3090, 2977, 2930, 1714, 1619, 1586, 1371, 1302, 1253, 1159, 1121, 1053, 1010, 994, 944, 871 and 768; δ_H (500 MHz, $CDCl_3$, rotamers) 7.28 (0.4H, br s, 6-H), 7.20 (0.6H, br s, 6-H), 5.00 and 4.86 (each 1H, s, 4-CH), 3.63 (2H, m, 2-H_2), 2.62-2.60 (2H, m, 3-H_2) and 1.43 [9H, s, $C(CH_3)_3$]; δ_c (125 MHz, $CDCl_3$) 151.68, 151.11 (C), 138.84 (C), 134.83 (CH), 116.67, 116.30 (CH_2), 82.62, 82.38 (C), 75.56, 75.30 (C), 43.01, 41.91 (CH_2), 29.92 (CH_2) and 28.58, 28.45 (CH_3); *m/z* (Cl^+) 322 (M^+ + 1, 60%), 222 (100) and 96 (50) [Found: *m/z* (+ES) M^+ + H, 322.0299. $C_{11}H_{17}NO_2I$ requires *M*, 322.0298].

A suspension of iododihydropyridinone **31** (98 mg, 0.30 mmol) and 1-ethyl-3-methylimidazolium hexafluorophosphate (40 mg) in Petasis reagent (0.15 M in toluene, 4.2 mL, 0.63 mmol) was sealed in a microwave vial and heated to 160 °C for 10 min using a Biotage microwave oven. After cooling to rt, the mixture was concentrated under reduced pressure and chromatography of the residue (loaded in DCM / petrol, eluted with ether : petrol 1 : 9) gave the title compound **34** as an orange oil (39 mg, 40%).

Tebbe's reagent (0.5 M in toluene, 0.92 mL, 0.46 mmol) was added to the iododihydropyridinone **31** (103 mg, 0.32 mmol) in THF (1.3 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to rt and was diluted with ether (5 mL). Aqueous sodium hydroxide (1 M, 5 drops) was added slowly (CAUTION: GAS EVOLVED) and, after the release of gas had stopped, the reaction mixture was dried (Na_2SO_4), filtered through a celite pad and concentrated under reduced pressure. Chromatography of the residue (5% ether in petrol) gave the title compound **34** as an orange oil (23 mg, 22%) followed by recovered starting material **31** (8 mg, 8%).

***tert*-Butyl 5-acetyl-2,3-dihydropyridin-4-one-1-carboxylate (36).** A mixture of the iododihydropyridinone **31** (195 mg, 0.60 mmol), $Pd_2(dba)_3$ (20 mg, 0.02 mmol) and triphenylarsine (20 mg, 0.07 mmol) in toluene (3 mL) was degassed using the freeze-thaw method (× 3). (1-Ethoxyethenyl)tributylstannane **35** (290 mg, 0.80 mmol) was added and the reaction mixture heated to 50 °C for 2 h. The reaction mixture was allowed to cool to rt and aqueous hydrogen chloride (1 M, 1.5 mL, 1.5 mmol) was added. After stirring for 14 h the reaction mixture was diluted with water (10 mL) and extracted into EtOAc (3 × 20 mL). The organic extracts were washed with

brine (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 1) gave the *title compound* **36** as a pale brown solid (115 mg, 80%), R_F = 0.20 (ether : petrol 6 : 4), m.p. 104-106 °C; ν_{max}/cm^{-1} 2980, 2933, 1739, 1675, 1563, 1371, 1346, 1308, 1250, 1157, 1131, 1024, 975, 842 and 757; δ_H (300 MHz, $CDCl_3$) 8.76 (1H, s, 6-H), 4.02-3.97 (2H, m, 2-H_2), 2.63-2.58 (2H, m, 3-H_2), 2.51 (3H, s, CH_3) and 1.56 [9H, s, $C(CH_3)_3$] ; δ_C (75 MHz, $CDCl_3$) 195.90 (C), 190.76 (C), 151.52 (CH), 150.82 (C), 116.02 (C), 85.62 (C), 42.73 (CH_2), 36.23 (CH_2), 31.07 (CH_3) and 28.11 (CH_3); *m/z* (Cl^+) 240 (M^+ + 1, 100%) and 140 (80) [Found: *m/z* (+ES) M^+ + H, 240.1226. $C_{12}H_{18}NO_4$ requires *M*, 240.1236].

Alternatively, a mixture of iodopyridinone **31** (200 mg, 0.62 mmol), stannane **35** (460 mg, 1.27 mmol), triphenylarsine (20 mg, 0.07 mmol), copper(I) iodide (16 mg, 0.08 mmol) and $PdCl_2(PhCN)_2$ (13 mg, 0.03 mmol) in NMP (3.3 mL) was degassed with N_2 for 15 min, heated to 83 °C for 15 h, and then allowed to cool to rt. Tetrahydrofuran (10 mL) and aqueous hydrogen chloride (1. M, 1.0 mL, 1.0 mmol) were added and the mixture stirred at rt for 1.5 h. Water (10 mL) was added and the mixture extracted into EtOAc (3 × 25 mL). The organic extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1: 1) gave the title compound **36** as a pale brown solid (79 mg, 56%).

***tert*-Butyl 5-acetyl-4-methylene-1,2,3,4-tetrahydropyridine-1-carboxylate (37).** A mixture of iodo-4-methylenetetrahydropyridine **34** (152 mg, 0.47 mmol), stannane **35** (530 mg, 1.47 mmol), triphenylarsine (19 mg, 0.06 mmol), copper(I) iodide (25 mg, 0.13 mmol) and $PdCl_2(PhCN)_2$ (10 mg, 0.03 mmol) in *N*-methylpyrrolidinone (2.5 mL) was heated at 83 °C for 108 h, then allowed to cool to rt, and partitioned between saturated aqueous ammonium chloride (10 mL) and ether (10 mL). The aqueous phase was extracted with ether (3 × 20 mL) and aqueous potassium fluoride (8 M, 20 mL) added to the organic extracts. The mixture was stirred for 4 h and the organic phase was washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 4) gave the *title compound* **37** as an orange oil (46 mg, 40%), R_F = 0.28 (ether : petrol 3 : 7); ν_{max}/cm^{-1} 3098, 2977, 2934, 1723, 1663, 1628, 1586, 1385, 1371, 1318, 1246, 1220, 1153, 1049, 962, 890 and 769; δ_H (300 MHz, $CDCl_3$) 7.99 (1H, br s, 6-H), 5.87 and 5.02 (each 1H, s, 4-CH), 3.68 (2H, t, *J* 6.5, 2-H_2), 2.45 (2H, t, *J* 6.5, 3-H_2), 2.34 (3H, s, CH_3) and 1.55 [9H, s, $C(CH_3)_3$], δ_C (75 MHz, $CDCl_3$) 196.38 (C), 151.77 (C), 138.31 (CH), 133.41 (C), 117.25 (C), 114.31 (CH_2), 83.43 (C), 43.42 (br, CH_2), 31.55 (CH_2), 28.29 (CH_3) and 27.00 (CH_3); *m/z* (Cl^+) 238 (M^+ + 1, 100%) and 138 (65) [Found: *m/z* (+ES) M^+ + H, 238.1434. $C_{13}H_{20}NO_3$ requires *M*, 238.1438].

Alternatively, a mixture of the iodo-4-methylenetetrahydropyridine **34** (1.10 g, 3.43 mmol), $Pd_2(dba)_3$ (90 mg, 0.10 mmol) and triphenylarsine (78 mg, 0.25 mmol) in toluene (17 mL) was degassed by freeze-thawing (× 3). (1-Ethoxyethenyl)tributylstannane **35** (1.70 g, 4.71 mmol) was added and the reaction mixture heated to 50 °C. After 2 h, further $Pd_2(dba)_3$ (20 mg, 0.02 mmol), triphenylarsine (25 mg, 0.08 mmol) and stannane **35** (850 mg, 2.16 mmol) were added. The reaction mixture was heated at 50 °C for a further 24 h and then allowed to cool to rt. Aqueous hydrogen chloride (1 M, 5.1 mL, 5.1 mmol) was added and the mixture stirred for 2 h then diluted with water (20 mL) and extracted into EtOAc (3 × 50 mL). The organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 3 : 7) gave the title compound **37** as an orange oil (221 mg, 27%).

***tert*-Butyl 5-[(*S*)-2-(benzyloxy)propanoyl]-4-methylene-1,2,3,4-tetrahydropyridine-1-carboxylate (39)**. *i*-Propylmagnesium chloride/lithium chloride (2.0 M in THF, 0.17 mL, 0.33 mmol) was added to the iodo-4-methylenetetrahydropyridine **34** (102 mg, 0.32 mmol) in THF (0.9 mL) at −25 °C. After 5 h, THF (1 mL) and CuCN.2LiCl (1.0 M in THF, 0.35 mL, 0.35 mmol) were added and the reaction mixture was stirred for 15 min before the acid chloride **38** (133 mg, 0.67 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at -25 °C for 1 h, allowed to warm to rt, and stirred for a further 12 h. Saturated aqueous ammonium

hydroxide (2 mL) was added and the mixture extracted into ether (3 × 10 mL). The organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 4) gave the *title compound* **39** as a pale yellow oil (10 mg, 9%), R_F = 0.41 (ether : petrol 1 : 4), ν_{max}/cm^{-1} 2977, 2932, 2877, 1720, 1704, 1582, 1455, 1370, 1313, 1250, 1152, 1060, 1028 and 743; δ_H (300 MHz, $CDCl_3$) 8.45 (1H, s, 6-H), 7.42-7.30 (5H, m, ArH), 5.89 and 5.07 (each 1H, s, 4-CH), 4.81 (1H, m, 2'-H), 4.65 and 4.46 (each 1H, d, *J* 11.5 , Ar*H*CH), 3.80-3.68 (2H, m, 2-H_2), 2.52 (2H, t, *J* 6.3, 3-H_2), 1.53 [9H, s, $C(CH_3)_3$] and 1.53 (3H, d, *J* 7.0, 3'-H_3); *m/z* (CI^+) 358 (M^+ + 1, 100%), 258 (40), 198 (60) and 96 (20) [Found: *m/z* (ES) M^+ + H, 358.2010. $C_{21}H_{28}NO_4$ requires *M*, 358.2013].

***tert*-Butyl 3-ethoxycarbonyl-3-phenylselanylpiperidin-4-one-1-carboxylate (41)**. The enol-ester **40** (4.10 g, 15.11 mmol) in THF (12 mL) was added *via* a cannula over 25 min to a suspension of sodium hydride (60 wt % in mineral oil, 730 mg, 18.25 mmol) in THF (80 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min then allowed to warm to rt. After 45 min, the reaction mixture was cooled to –50 °C and phenylselenyl bromide (4.41 g, 18.7 mmol) in THF (14 mL) was added *via* a cannula over 30 min. After stirring for 2 h at –50 °C, the mixture was allowed to warm to rt and stirred for a further 15 h. The reaction mixture was poured into ice cold, saturated, aqueous potassium carbonate (150 mL) and the mixture extracted into ether (3 × 100 mL). The organic extracts were washed with brine (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give the product **41** (6.3 g) that was used in the next step without purification. Chromatography (ether: petrol 2 : 3) of a sample gave the *title compound* **41** as a white solid, R_F = 0.47 (ether : petrol 1 : 1), m.p. 106-110 °C; ν_{max}/cm^{-1} 3058, 2978, 2933, 2871, 1698, 1477, 1420, 1366, 1277, 1239, 1215, 1165, 1115, 1054, 1022, 970, 861 and 742; δ_H (300 MHz, $CDCl_3$, rotamers) 7.63-7.61 (2H, m, ArH), 7.42-7.30 (3H, m, ArH), 4.81-4.72 (0.13H, m, 2-H), 4.53-4.41 (0.87H, m, 2-H), 4.39-4.14 (3H, m, O*C*H_2CH$_3$ and 6-H), 3.45 (1H, m, 2-H'), 3.34 (1H, m, 6-H'), 2.78-2.60 (2H, m, 5-H_2), 1.40 [9H, br s, $C(CH_3)_3$], 1.20 (3H, br m, OCH_2C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 201.25 (C), 168.09 (br C), 154.10 (C), 138.57 (CH), 130.11 (CH), 129.29 (CH), 125.17 (C), 81.00 (C), 62.52 (CH_2), 61.36 (br C), 52.44 (br CH_2), 43.24 (br CH_2), 40.53 (CH_2), 28.39 (br CH_3) and 14.29 (CH_3); *m/z* (CI^+) 445 (M^+ + 18, 2%), 428 (M^+ + 1, 5%), 272 (30), 233 (80) and 172 (100) [Found: *m/z* (+ES) M^+ + NH_4, 445.1243. $C_{19}H_{29}N_2O_5{}^{80}Se$ requires *M*, 445.1236.

***tert*-Butyl 5-ethoxycarbonyl-2,3-dihydropyridin-4-one-1-carboxylate (42)**. Aqueous hydrogen peroxide [30 wt % in water, 4.5 g, 39.69 mmol, diluted with water (25 mL)] was added the selenide **41** (6.1 g) in DCM (66 mL) at 0 °C and the mixture stirred for 30 min. The reaction mixture was allowed to warm to rt, stirred for a further 1 h, and then poured into saturated aqueous sodium hydrogen carbonate (50 mL). The aqueous phase was extracted with DCM (3 × 25 mL) and the organic extracts were washed with brine (75 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (EtOAc : petrol 1 : 1) gave the *title compound* **42** as a white solid (2.17 g, 53%,from **40**), R_F = 0.17 (EtOAc : petrol 1 : 1), m.p. 140-144 °C; ν_{max}/cm^{-1} 3086, 2981, 2936, 1732, 1697, 1590, 1395, 1372, 1347, 1316, 1250, 1150, 1049 and 766; δ_H (300 MHz, $CDCl_3$) 8.82 (1H, s, 6-H), 4.30 (2H, q, *J* 7.1, O*C*H_2CH$_3$), 4.03 (2H, t, *J* 7.5, 2-H_2), 2.65 (2H, t, *J* 7.5, 3-H_2), 1.61 [9H, s, $C(CH_3)_3$] and 1.36 (3H, t, *J* 7.1, OCH_2C*H*$_3$); δ_c (75 MHz, $CDCl_3$) 188.8 (C), 164.13 (C), 151.44 (CH), 150.71 (C), 108.35 (C), 85.43 (C), 60.86 (CH_2), 42.70 (CH_2), 36.37 (CH_2), 28.13 (CH_3) and 14.54 (CH_3); *m/z* (CI^+) 270 (M^+ + 1, 100%) and 170 (20) [Found: *m/z* (+ES) M^+ + H, 270.1346. $C_{13}H_{20}NO_5$ requires *M*, 270.1336].

***tert*-Butyl 5-ethoxycarbonyl-4-methylene-1,2,3,4-tetrahydropyridine-1-carboxylate (43)**. A solution of the keto-ester **42** (203 mg, 0.75 mmol) in Petasis reagent (0.17 M in toluene, 11 mL, 1.9 mmol) was heated to 65 °C for 22 h in the dark. The reaction mixture was allowed to cool to rt and petrol (20 mL) was added. The titanium residues were removed by filtration and the filtrate concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 4) gave the *title compound* **43** as an orange oil (81 mg, 40%), R_F = 0.49 (ether : petrol 3 : 7); ν_{max}/cm^{-1} 3107, 2980, 2935, 1725, 1708, 1631, 1591, 1371, 1353, 1314, 1238,

1151, 1065, 961, 901 and 772; δ_H (300 MHz, $CDCl_3$) 8.11 (1H, br s, 6-H), 5.82 and 4.98 (each 1H, s, 4-CH), 4.25 (2H, q, *J* 7.1, OCH_2CH_3), 3.70 (2H, t, *J* 6.2, 2-H_2), 2.52 (2H, t, *J* 6.2, 3-H_2), 1.56 [9H, s, $C(CH_3)_3$] and 1.34 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.68 (C), 151.34 (C), 137.11 (CH), 133.83 (C), 112.47 (CH_2), 108.20 (C), 83.13 (C), 60.31 (CH_2), 42.20 (CH_2), 31.52 (CH_2), 28.33 (CH_3) and 14.58 (CH_3); *m/z* (Cl^+) 268 (M^+ + 1, 30%) and 168 (100) [Found: *m/z* (+ES) M^+ + H, 268.1537. $C_{14}H_{22}NO_4$ requires *M*, 268.1543].

A solution of keto-ester **42** (204 mg, 0.75 mmol) and Petasis reagent (0.12 M in toluene, 15 mL, 1.80 mmol) was heated at 110 °C for 2 h. The reaction mixture was allowed to cool and then concentrated under reduced pressure. Chromatography of the residue (ether : petrol 1 : 9, to 3 : 7) gave the ester **43** (23 mg, 11%) followed by the ketone **37** (42 mg, 23%).

Acknowledgements

We thank the EPSRC for a studentship (to A.I.L.)

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