5-(Alk-1-enyl)-1,2,3,6-tetrahydropyridines as congeners of streptazolin

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The synthesis of 1,3-dienes which are structurally related to streptazolin, a unique natural compound with antibiotic and antifungal activities, is described. Mimicking of two suggested pharmacophoric units leads to compounds with enhanced chemical stability but without any satisfactory gain in antibiotic activity.

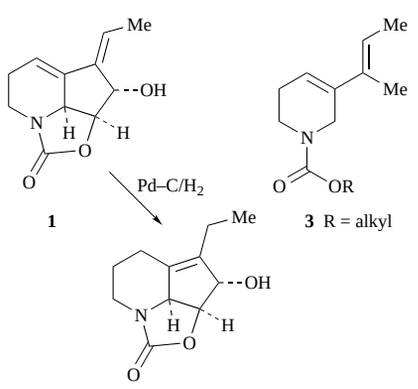
Streptazolin **1**, a unique natural product, was first described by Drautz *et al*. who isolated it from cultures of *Streptomyces viridochromogenes* and demonstrated its antibiotic and antifungal activity.[1,2]

Unfortunately, streptazolin is unstable in the solid state due to its tendency to undergo partial polymerisation. The 1,4-dihydro derivative **2** which is available by catalytic hydrogenation of **1** shows satisfactory stability but has reduced antibiotic activity.[1] Stimulated by its exceptional structure (and the impetus to synthesise a compound which is difficult to handle), three total syntheses of streptazolin have so far been reported. The first one, realised by Kozikowski and Park,[3,4] furnished racemic streptazolin, while Flann and Overman[5] have demonstrated a strategy to the enantiomerically pure compound. Both approaches furnished streptazolin as inseparable mixtures of the ethylidene stereoisomers. Recently Yamada *et al.*[6] reported the stereoselective total synthesis of natural (+)-streptazolin with uniform (*Z*)-ethylidene stereochemistry.

From the pharmaceutical point of view, streptazolin is far from being an ideal antibiotic, since it possesses limited activity and is, moreover, of low stability. Thus, attempts have been made to synthesise derivatives of streptazolin with improved properties.[7,8] Our goal is to produce streptazolin congeners which are available by a simple synthetic approach and have improved pharmacological and physical features.

At first, as described here, we tried to mimic two assumed pharmacophoric moieties of streptazolin, the diene system and the urethane unit, by creating a single ring system with the general structure **3**. As a starting compound for the synthesis we chose arecoline **4** which is commercially available.

Replacement of the *N*-methyl group in **4** by an alkoxycarbonyl group leading to **5** can be directly achieved by heating of arecoline with the appropriate chloroformate in toluene.[9] This starting reaction not only provides advantageous protection of the amino function with regard to the following steps but also offers the opportunity of modifying the pharmacokinetic properties of the target molecule by variation of the urethane moiety using different chloroformates as acylating reagents.



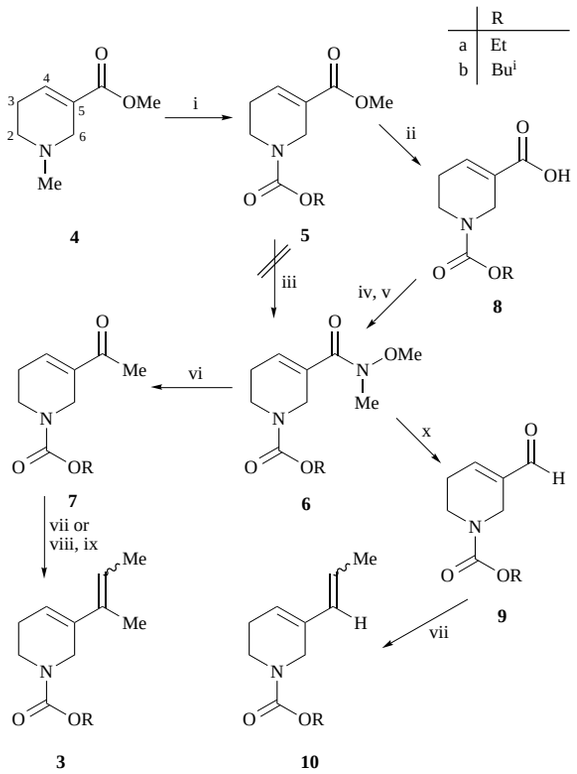
In the subsequent preparation of the ketone **7** by coupling with organometallics, the problem of reactive Grignard or organolithium reagents overadding to the substrate, producing a tertiary alcohol, was encountered. In view of this, we decided to employ Weinreb's strategy to control the exclusive formation of the carbonyl compound by using *N*-methoxy-*N*-methylamides **6** as key intermediates.[10] However, the direct conversion of the ester moiety into the *N*-methoxy-*N*-methylamide by reaction with $(Me_2)AlN(Me)OMe$[11] failed. Thus, the conventional route *via* hydrolysis of the ester **5** to the acid **8**, with intermediate formation of the acid chloride, and final conversion to the *N*-methoxy-*N*-methylamide **6** was chosen.

The reductive alkylation of **6** was realised by reaction with methyllithium or methylmagnesium bromide to yield the ketone **7** in good yield. Finally, the diene **3** was prepared by Wittig olefination with ethyl(triphenyl)phosphonium bromide. Alternatively, the ketone **7** was alkylated by a second organometallic compound (ethylmagnesium bromide) and then dehydrated with phosphoric acid or hydrochloric acid in tetrahydrofuran to give **3**.

As in the first two total syntheses of the target compound **1**, the dienes **3** were formed as *E/Z* mixtures in the olefination step (see Experimental section). Up to now, attempts to separate the isomers by HPLC have failed. However, the isomer ratio could be determined by GC and additionally deduced from separated peaks of the two isomers in the ^{1}H NMR spectrum. Of course, in contrast to streptazolin, the diene system is not frozen into the *cisoid* conformation. The assignment of the ^{1}H signals to the isomers could be achieved by ^{1}H–^{1}H COSY and ^{1}H–^{13}C correlation experiments. Nevertheless, an unequivocal identification as the *E* or *Z* isomer was prevented by signal overlapping. Unfortunately, the preparation of the 1′-dealkyl derivative **10**, containing a proton capable of coupling with the vicinal 2′-H, did not give additional information about *E/Z* isomerism. Compound **10** was readily available *via* the aldehyde **9** which was synthesised by DIBAL-H reduction of *N*-methoxy-*N*-methylamide **6**

The dienes **3** (and **10**, respectively) show remarkable stability in comparison with streptazolin itself. Compounds **3** and **10** can be stored as solids for several months without degradation.

In plate diffusion tests, the dienes exhibit very limited anti-



Scheme 1 *Reagents and conditions*: i, ROCOCl, toluene, heat; ii, NaOH (2 M); iii, $Me_2AlN(Me)OMe$, Et_2O; iv, $SOCl_2$, heat; v, MeNHOMe·HCl, pyridine, $CHCl_3$; vi, MeLi (MeMgBr), THF, 0 °C; vii, $MeCH_2P(Ph_3)Br$, BuLi, EtO; viii, EtMgBr, Et_2O, heat; ix, H_3PO_4 or HCl, heat; x, DIBAL-H, Et_2O, 0 °C

biotic and antifungal activity. The *in vitro* antibacterial activity was tested against *Staphylococcus aureus*, coagulase-negative *Staphylococcus* and *E. coli*, and the antifungal activity against *Candida albicans*. The best values were detected with **3** against *Candida albicans* (full inhibition of growth at a concentration of 400 μg cm^{-3}).

In conclusion, this work has demonstrated that exclusive mimicking of the diene system and the urethane moiety provides compounds with enhanced stability but without any satisfactory gain in biological activity. In further work, the mimicry of streptazolin will also consider the oxygen functionality of the cyclopentane ring.

Experimental

Mps were determined on a Kofler microscope apparatus. IR Spectra were recorded on a Perkin-Elmer 298 instrument. ^{1}H and ^{13}C NMR Spectra were measured on Bruker AC 80 and Varian Unity-plus 300 instruments [^{1}H NMR: tetramethylsilane as internal standard, *J* values given in Hz; ^{13}C NMR: chemical shifts are given in ppm relative to the resonance of $CDCl_3$ (δ 77.0)].† Mass spectra were determined on a Hewlett Packard GC–MS equipment (HP-5890A, HP-5970C, HP-59970).

1,2,5,6-Tetrahydropyridine-1,3-dicarboxylates 5

General procedure. To a mixture of arecoline **4** (1.55 g, 10 mmol) and potassium carbonate (690 mg, 5 mmol) in dry toluene (30 cm^3), heated under reflux, was added the selected chloroformate (11 mmol) dropwise by means of a syringe. Heating was continued for 3 h, after which the reaction mixture was concentrated *in vacuo* and the residue was partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (2 × 10 cm^3) and the combined organic extracts were washed with hydrochloric acid (2 M; 2 × 10 cm^3) and brine (2 × 10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to yield **5** as a colourless to yellow oil.

1-Ethyl 3-methyl 1,2,5,6-tetrahydropyridine-1,3-dicarboxylate 5a. Prepared by treatment of arecoline **4** with ethyl chloroformate (1.1 cm^3, 11 mmol); a yellow oil (1.80 g, 85%) (Found: C, 56.6; H, 7.35; N, 6.55. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%); ν_{max}(KBr; liquid film)/cm^{-1} 1730 and 1700 (C=O); δ_H(80 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.2, OCH_2CH_3), 2.35 (2 H, m, 3-H), 3.50 (2 H, t, *J* 5.6, 2-H), 3.75 (3 H, s, OCH_3), 4.16 (2 H, q, *J* 2.4, 6-H), 4.16 (2 H, q, *J* 7.2, OCH_2CH_3) and 7.10 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 14.7 (OCH_2CH_3), 24.9 (3-C), 38.7 (2-C), 42.1 (6-C), 51.1 (OCH_3), 60.9 (OCH_2CH_3), 127.7 (5-C), 137.3 (4-C), 155.0 (N–C=O) and 165.0 (C=O); *m/z* 213 (M^+).

1-Isobutyl 3-methyl 1,2,5,6-tetrahydropyridine-1,3-dicarboxylate 5b. Prepared by treatment of arecoline **4** with isobutyl chloroformate (1.5 cm^3, 11 mmol); a yellow oil (1.90 g, 85%) (Found: C, 60.0; H, 7.7; N, 5.8. $C_{12}H_{19}NO_4$ requires C, 59.7; H, 7.9; N, 5.8%); ν_{max}(KBr; liquid film)/cm^{-1} 1720 and 1700 (C=O); δ_H(80 MHz; $CDCl_3$) 0.94 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 1.90 [1 H, sept, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.35 (2 H, m, 3-H), 3.45 (2 H, t, *J* 5.6, 2-H), 3.76 (3 H, s, OCH_3), 3.90 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.17 (2 H, q, *J* 2.4, 6-H) and 7.10 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 18.9 [$OCH_2CH(CH_3)_2$], 25.3 (3-C), 27.8 [$OCH_2CH(CH_3)_2$], 39.2 (2-C), 42.4 (6-C), 51.5 (OCH_3), 71.5 [$OCH_2CH(CH_3)_2$], 128.1 (5-C), 137.6 (4-C), 155.4 (N–C=O) and 165.4 (C=O); *m/z* 241 (M^+).

Hydrolysis of 5 to 8

General procedure. The ester **5** (10 mmol) was suspended in aqueous NaOH (2 M; 30 cm^3) and the suspension was stirred at room temperature for 10–12 h. The resulting solution was carefully acidified with hydrochloric acid (2 M) at 0 °C and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic layers were washed with water (2 × 10 cm^3) and brine (2 × 10 cm^3), dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by recrystallisation or column chromatography.

1-Ethoxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid 8a. Colourless crystals (1.85 g, 90%), mp 73–75 °C (Found: C, 54.45; H, 6.6; N, 6.8. $C_9H_{13}NO_4$ requires C, 54.3; H, 6.6; N, 7.0%); ν_{max}(KBr; liquid film)/cm^{-1} 3160 (OH) and 1720, 1680 (C=O); δ_H(80 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.2, OCH_2CH_3), 2.35 (2 H, m, 3-H), 3.55 (2 H, t, *J* 5.6, 2-H), 4.18 (2 H, q, *J* 2.4, 6-H), 4.18 (2 H, q, *J* 7.2, OCH_2CH_3), 7.30 (1 H, m, 4-H) and 10.02 (1 H, br s, OH); δ_H(20.12 MHz; $CDCl_3$) 14.5 (OCH_2CH_3), 25.4 (3-C), 39.1 (2-C), 42.2 (6-C), 61.6 (OCH_2CH_3), 127.7 (5-C), 139.7 (4-C), 155.6 (N–C=O) and 169.5 (C=O); *m/z* 199 (M^+).

1-Isobutoxycarbonyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid 8b. Colourless crystals (2.10 g, 90%), mp 89–91 °C (Found: C, 58.4; H, 7.4; N, 6.05. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.5; N, 6.2%); ν_{max}(KBr)/cm^{-1} 3160 (OH) and 1730, 1660 (C=O); δ_H(80 MHz; $CDCl_3$) 0.95 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 1.96 [1 H, sept, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.36 (2 H, m, 3-H), 3.56 (2 H, t, *J* 5.6, 2-H), 3.91 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.18 (2 H, q, *J* 2.4, 6-H), 7.20 (1 H, m, 4-H) and 10.08 (1 H, br, OH); δ_C(20.12 MHz; $CDCl_3$) 18.9 [$OCH_2CH(CH_3)_2$], 25.4 (3-C), 27.8 [$OCH_2CH(CH_3)_2$], 39.2 (2-C), 42.2 (6-C), 71.8 [$OCH_2CH(CH_3)_2$], 127.7 (5-C), 139.7 (4-C), 155.7 (N–C=O) and 169.5 (C=O); *m/z* 227 (M^+).

N-Methoxy-*N*-methylcarboxamides 6

General procedure. The carboxylic acid **8** (10 mmol) was refluxed in thionyl chloride (15 cm^3) for 1.5 h. The excess of thionyl chloride was removed by distillation and the residue was dissolved in dry toluene and the solution concentrated *in vacuo* several times to remove residual thionyl chloride. The resulting orange oil was redissolved in dry $CHCl_3$ and treated with *N*-methoxy-*N*-methylhydroxylamine hydrochloride (1.1 g, 11

† The numbering of protons in the ^{1}H NMR spectra runs clockwise around the pyridine ring, as shown in Scheme 1 for compound **4**. This is opposite to the system of nomenclature which runs in the opposite, anticlockwise, direction.

mmol). The solution was then cooled to 0 °C and treated with pyridine (1.80 cm^3, 22 mmol). After the mixture had been stirred at 0 °C for 10 min the ice-bath was removed, and the reaction was allowed to proceed at 20 °C for 1 h. After concentration of the reaction mixture *in vacuo* the residue was partitioned between CH_2Cl_2 and hydrochloric acid (0.5 M); the organic layer was separated, washed with brine (2 × 10 cm^3), dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The resulting amides were purified by column chromatography.

Ethyl 3-(*N*-methoxy-*N*-methylcarbamoyl)-1,2,5,6-tetrahydropyridine-1-carboxylate 6a. Starting from **8a** (2.00 g, 10 mmol), **6a** (1.80 g, 74%) was obtained as a light yellow oil after column chromatography (ethyl acetate) (Found: C, 54.3; H, 7.3; N, 11.3. $C_{11}H_{18}N_2O_4$ requires C, 54.5; H, 7.5; N, 11.6%); ν_{max}(KBr; liquid film)/cm^{-1} 1700 and 1650 (C=O); δ_H(80 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.2, OCH_2CH_3), 2.35 (2 H, m, 3-H), 3.25 (3 H, s, NCH_3), 3.50 (2 H, t, *J* 5.6, 2-H), 3.66 (3 H, s, OCH_3), 4.15 (2 H, q, *J* 2.4, 6-H), 4.15 (2 H, q, *J* 7.2, OCH_2CH_3) and 6.50 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 14.0 (OCH_2CH_3), 24.2 (3-C), 32.7 (NCH_3), 39.0 (2-C), 42.7 (6-C), 60.4 (OCH_3), 60.6 (OCH_2CH_3), 130.0 (4-C), 130.7 (5-C), 154.7 (N–C=O) and 167.7 (C=O); *m/z* 211 ($M^+ - OCH_3$).

Isobutyl 3-(*N*-methoxy-*N*-methylcarbamoyl)-1,2,5,6-tetrahydropyridine-1-carboxylate 6b. Starting from **8b** (2.20 g, 10 mmol), **6b** (1.90 g, 70%) was obtained as an orange oil after column chromatography (ethyl acetate) (Found: C, 57.5; H, 8.45; N, 10.2. $C_{13}H_{22}N_2O_4$ requires C, 57.8; H, 8.2; N, 10.4%); ν_{max}(KBr; liquid film)/cm^{-1} 1700 and 1655 (C=O); δ_H(80 MHz; $CDCl_3$) 0.83 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 1.90 [1 H, septet, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.21 (2 H, m, 3-H), 3.09 (3 H, s, NCH_3), 3.46 (2 H, t, *J* 5.6, 2-H), 3.55 (3 H, s, OCH_3), 3.80 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.12 (2 H, q, *J* 2.4, 6-H) and 6.40 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 18.9 [$OCH_2CH(CH_3)_2$], 24.7 (3-C), 27.7 [$OCH_2CH(CH_3)_2$], 33.3 (NCH_3), 39.4 (2-C), 43.2 (6-C), 61.0 (OCH_3), 71.5 [$OCH_2CH(CH_3)_2$], 130.6 (4-C), 137.9 (5-C), 155.4 (N–C=O) and 168.4 (C=O); *m/z* 239 ($M^+ - OCH_3$).

Ketones 7

General procedure. To a solution of *N*-methoxy-*N*-methylamide (10 mmol) in dry THF (60 cm^3) was added the appropriate organometallic reagent (12 mmol) under argon at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 1.5 h; the reaction was then quenched by addition of cold hydrochloric acid (1 M) to the mixture. The mixture was partitioned between CH_2Cl_2 and water and the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 30 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting ketone **7** was purified by column chromatography (ethyl acetate).

Ethyl 3-acetyl-1,2,5,6-tetrahydropyridine-1-carboxylate 7a. For the preparation of **7a** methyllithium (1.6 M; 7.5 cm^3) was used as the organometallic reagent. Column chromatography afforded **7a** as colourless crystals (1.50 g, 75%), mp 132–134 °C (Found: C, 61.1; H, 7.8; N, 7.2. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.7; N, 7.1%); ν_{max}(KBr)/cm^{-1} 1700 and 1660 (C=O); δ_H(80 MHz; $CDCl_3$) 1.30 (3 H, t, *J* 7.2, OCH_2CH_3), 2.28 (3 H, s, $COCH_3$), 2.40 (2 H, m, 3-H), 3.55 (2 H, t, *J* 5.6, 2-H), 4.12 (2 H, q, *J* 2.4, 6-H), 4.10 (2 H, q, *J* 7.2, OCH_2CH_3) and 6.98 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 14.3 (OCH_2CH_3), 24.7 ($COCH_3$), 25.3 (3-C), 38.9 (2-C), 41.6 (6-C), 61.0 (OCH_2CH_3), 136.8 (5-C), 138.4 (4-C), 155.2 (N–C=O) and 196.7 (C=O); *m/z* 197 (M^+).

Isobutyl 3-acetyl-1,2,5,6-tetrahydropyridine-1-carboxylate 7b. For the preparation of **7b** methyllithium (1.6 M; 7.5 cm^3) was used as the organometallic reagent. Column chromatography yielded **7b** as a yellow oil (2.07 g, 92%) (Found: C, 63.7; H, 8.4; N, 6.1. $C_{12}H_{19}NO_3$ requires C, 63.9; H, 8.5; N, 6.2%); ν_{max}(KBr)/cm^{-1} 1700 and 1660 (C=O); δ_H(80 MHz; $CDCl_3$) 0.89 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.02 [1 H, septet, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.31 (3 H, s, $COCH_3$), 2.37 (2 H, m, 3-H), 3.60 (2 H, t, *J* 5.6, 2-H), 3.86 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.07 (2 H, q, *J* 2.4, 6-H) and 7.01 (1 H, m, 4-H); δ_C(20.12 MHz; $CDCl_3$) 19.1 [$OCH_2CH(CH_3)_2$], 24.8 ($COCH_3$), 25.0 (3-C), 27.9 [$OCH_2CH(CH_3)_2$], 39.3 (2-C), 42.1 (6-C), 71.7 [$OCH_2CH(CH_3)_2$], 137.9 (4-C), 139.0 (5-C), 155.6 (N–C=O) and 196.1 (C=O); *m/z* 225 (M^+).

Isobutyl 3-formyl-1,2,5,6-tetrahydropyridine-1-carboxylate 9b. To a solution of **6b** (270 mg, 1 mmol) in dry THF (20 cm^3), was added DIBAL-H (1 M; 2 cm^3, 2 mmol) by means of a syringe under argon at 0 °C. After 0.5 h the reaction was quenched by the addition of water to the reaction mixture which was then extracted with diethyl ether (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* and the residue was purified by column chromatography (diethyl ether) to give **9b** (200 mg, 95%) as a colourless oil (Found: C, 62.4; H, 8.2; N, 6.6. $C_{11}H_{17}NO_3$ requires C, 62.5; H, 8.1; N, 6.6%); ν_{max}(KBr; liquid film)/cm^{-1} 1700 (C=O); δ_H(300 MHz; $CDCl_3$) 0.88 [6 H, d, *J* 6.9, $OCH_2(CH(CH_3)_2$], 1.71 [1 H, septet, *J* 6.9, $OCH_2CH(CH_3)_2$], 2.41 (2 H, br s, 3-H), 3.55 (2 H, t, *J* 5.6, 2-H), 3.83 [2 H, d, *J* 6.9, $OCH_2CH(CH_3)_2$], 4.10 (2 H, br s, 6-H), 6.71 (1 H, br, 4-H) and 9.36 (1 H, s, CHO); δ_C(20.12 MHz; $CDCl_3$) 19.1 [$OCH_2CH(CH_3)_2$], 26.1 (3-C), 27.9 [$OCH_2CH(CH_3)_2$], 39.7 (2-C), 40.8 (6-C), 71.8 [$OCH_2CH(CH_3)_2$], 137.9 (4-C), 155.6 (N–C=O) and 191.5 (C=O); *m/z* 211 (M^+).

Preparation of dienes 3 (10) by Wittig reaction of 7 (9)

General procedure. To a suspension of carefully dried and pulverised ethyl(triphenyl)phosphonium bromide (3.7 g, 10 mmol) in dry diethyl ether, was added butyllithium (1.6 M; 6.3 cm^3, 10 mmol) under argon at 0 °C. Dissolution of the salt and formation of the red ylide occurred within 15 min. A solution of the carbonyl compound **7** (or **9**) (10 mmol) in dry diethyl ether (40 cm^3) was then added dropwise to the mixture by means of a syringe at room temperature. After the reaction mixture had been stirred under reflux for 4 h, it was cooled to room temperature and filtered to remove triphenylphosphine oxide. The resulting filtrate was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by column chromatography on silica gel.

Ethyl 3-(1-methylprop-1-enyl)-1,2,5,6-tetrahydropyridine-1-carboxylate 3a. Column chromatography (diethyl ether–light petroleum, 1:1) gave a yellow oil (1.50 g, 72%) which consisted of a mixture of geometric isomers **3a** in a ratio of 1:2 (A:B) (Found: C, 69.1; H, 9.2; N, 6.7. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.15; N, 6.7%); ν_{max}(KBr; liquid film)/cm^{-1} 1700 (C=O); δ_H(300 MHz; $CDCl_3$) isomer A: 1.27 (3 H, t, *J* 7.2, OCH_2CH_3), 1.73 (3 H, d, *J* 6.8, 3′-H), 1.77 (3 H, s, 1′-CH_3), 2.23 (2 H, m, 3-H), 3.53 (2 H, m, 2-H), 4.12 (2 H, br s, 6-H), 4.16 (2 H, q, *J* 7.2, OCH_2CH_3), 5.55 (1 H, br s, 2′-H), 5.85 (1 H, br s, 4-H); isomer B: 1.27 (3 H, t, *J* 7.2, OCH_2CH_3), 1.60 (3 H, d, *J* 6.1, 3′-H), 1.77 (3 H, s, 1′-CH_3), 2.23 (2 H, m, 3-H), 3.53 (2 H, m, 2-H), 3.87 (2 H, br, 6-H), 4.16 (2 H, q, *J* 7.2, OCH_2CH_3), 5.34 (1 H, q, *J* 6.4, 2′-H) and 5.55 (1 H, br s, 4-H); δ_C(100.62 MHz; $CDCl_3$) 13.2 (1′-CH_3 of isomer B), 13.9 (3′-C of isomer A), 14.6 (3′-C of isomer B), 14.7 (OCH_2CH_3), 23.4 (1′-CH_3 of isomer A), 25.1 (3-C of isomer B), 25.0 (3-C of isomer A), 40.0 (2-C), 43.7 (6-C of isomer A), 44.7 (6-C of isomer B), 61.1 (OCH_2CH_3), 119.1 (4-C of isomer B), 120.0 (4-C of isomer A), 121.8 (2′-C), 133.5 (1′-C), 135.6 (5-C) and 156.2 (N–C=O); *m/z* 209 (M^+).

Isobutyl 3-(1-methylprop-1-enyl)-1,2,5,6-tetrahydropyridine-1-carboxylate 3b. Column chromatography (diethyl ether–light petroleum, 1:1) gave a colourless oil (1.32 g, 55%) which consisted of a mixture of geometric isomers **3b** in a ratio of 5:3 (A:B) (Found: C, 71.0; H, 9.9; N, 5.9. $C_{14}H_{23}NO_2$ requires C, 70.85; H, 9.8; N, 5.9%); ν_{max}(KBr; liquid film)/cm^{-1} 1690 (C=O); δ_H(300 MHz; $CDCl_3$) isomer A: 0.95 [6 H, d, *J* 6.4, $OCH_2CH(CH_3)_2$], 1.72 (3 H, d, *J* 6.8, 3′-H), 1.78 (3 H, s, 1′-CH_3), 1.95 [1 H, septet, *J* 6.4, $OCH_2CH(CH_3)_2$], 2.25 (2 H, m, 3-H), 3.52 (2 H, m, 2-H), 3.90 [2 H, d, *J* 6.4, $OCH_2CH(CH_3)_2$], 4.13 (2 H, br s, 6-H), 5.55 (1 H, m, 2′-H), 5.85 (1 H, br s, 4-H); isomer

B: 0.95 [6 H, d, *J* 6.4, $OCH_2CH(CH_3)_2$], 1.60 (3 H, d, *J* 6.1, 3′-H), 1.78 (3 H, s, 1′-CH_3), 1.95 [1 H, septet, *J* 6.4, $OCH_2CH(CH_3)_2$], 2.25 (2 H, m, 3-H), 3.52 (2 H, m, 2-H), 3.90 (2 H, hidden, 6-H), 3.90 [2 H, d, *J* 6.4, $OCH_2CH(CH_3)_2$], 5.35 (1 H, q, *J* 6.4, 2′-H) and 5.55 (1 H, m, 4-H); δ_C(100.62 MHz; $CDCl_3$) 13.2 (1′-CH_3 of isomer B), 13.9 (3′-C of isomer A), 14.6 (3′-C of isomer B), 19.1 [$OCH_2CH(CH_3)_2$], 23.5 (1′-CH_3 of isomer A), 24.8 (3-C of isomer B), 25.3 (3-C of isomer A), 28.1 [$OCH_2CH(CH_3)_2$], 4.03 (2-C), 44.0 (6-C of isomer A), 44.8 (6-C of isomer B), 71.4 [$OCH_2CH(CH_3)_2$], 119.3 (4-C of isomer B), 120.0 (4-C of isomer A), 121.8 (2′-C), 133.6 (1′-C), 135.8 (5-C) and 155.8 (N–C=O); *m/z* 237 (M^+).

Isobutyl 3-(prop-1-enyl)-1,2,5,6-tetrahydropyridine-1-carboxylate 10b. Column chromatography (ethyl acetate) gave a green oil (1.25 g, 56%) which consisted of a mixture of geometric isomers **10b** in a ratio of 3:2 (A:B) (Found: C, 70.2; H, 9.3; N, 6.4. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%); ν_{max}(KBr; liquid film)/cm^{-1} 1710 (C=O); δ_H(300 MHz; $CDCl_3$) isomer A: 0.92 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 1.79 (3 H, d, *J* 7.1, 3′-H), 1.92 [1 H, septet, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.22 (2 H, br s, 3-H), 3.50 (2 H, t, *J* 5.5, 2-H), 3.88 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.03 (2 H, br s, 6-H), 5.53 (1 H, m, 1′-H), 5.70 (1 H, br s, 2′-H), 5.72 (1 H, br s, 4-H); isomer B: 0.92 [6 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 1.75 (3 H, d, *J* 6.6, 3′-H), 1.92 [1 H, septet, *J* 6.6, $OCH_2CH(CH_3)_2$], 2.22 (2 H, br s, 3-H), 3.50 (2 H, t, *J* 5.5, 2-H), 3.88 [2 H, d, *J* 6.6, $OCH_2CH(CH_3)_2$], 4.06 (2 H, m, 6-H), 5.55 (1 H, m, 2′-H), 5.70 (1 H, br s, 4-H) and 6.03 (1 H, br d, *J* 15.8, 1′-H); δ_C(20.12 MHz; $CDCl_3$) 14.8 (3′-C of isomer A), 18.1 (3′-C of isomer B), 19.1 [$OCH_2CH(CH_3)_3$], 25.2, 29.7 (3-C), 28.1 [$OCH_2CH(CH_3)_3$], 40.2, 40.6 (2-C), 43.4 (6-C of isomer A), 46.1 (6-C of isomer B), 71.5 [$OCH_2CH(CH_3)_2$], 122.5 (4-C of isomer B), 124.4 (4-C of isomer A), 125.8 (2′-C of isomer B), 128.8 (2′-C of isomer A), 131.4 (1′-C), 133.7 (5-C) and 155.8 (N–C=O); *m/z* 223 (M^+).

Alternative preparation of the diene 3a by reductive alkylation of 7a and subsequent dehydration

To a solution of the ketone **7a** (2.0 g, 10 mmol) in dry diethyl ether (100 cm^3) was added ethylmagnesium bromide (3 M; 4.7 cm^3, 14 mmol) by means of a syringe under argon at room temperature. The solution was refluxed for 4 h and then poured into ice-cooled saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 × 50 cm^3). The combined ethereal layers were washed with water and brine, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting alcohol (1.8 g, 80%) was dissolved in THF (40 cm^3) and hydrochloric acid (2 M; 10 cm^3) and the solution refluxed for 2.5 h. After neutralisation with 2 M aqueous NaOH the mixture was extracted with diethyl ether (3 × 20 cm^3) and the combined extracts were washed with saturated aqueous NH_4Cl and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* furnished a yellowish oil which was purified by column chromatography (diethyl ether–light petroleum, 1:1) to yield **3a** (1.67 g, 65%) (ratio A:B = 4:5).

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