Ozonolysis of some 8-alkoxyquinolines, and synthesis of a precursor to the non-sedating antihistamine Claritin

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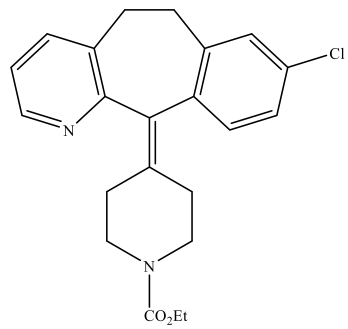
Abstract
3-Formyl-2-methoxycarbonylpyridine and isopropyl 3-formylpyridine-2-carboxylate have each been efficiently accessed in one step *via* the ozonolyses of 8-methoxy- or of 8-isopropoxy-quinoline under near-ambient conditions. The compounds can be utilized as intermediates for syntheses of the tricyclic ketone 8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one, a precursor to the important non-sedating antihistamine Claritin.

Keywords: Alkoxyquinoline, ozonolysis, pyridine, aldehyde, ester

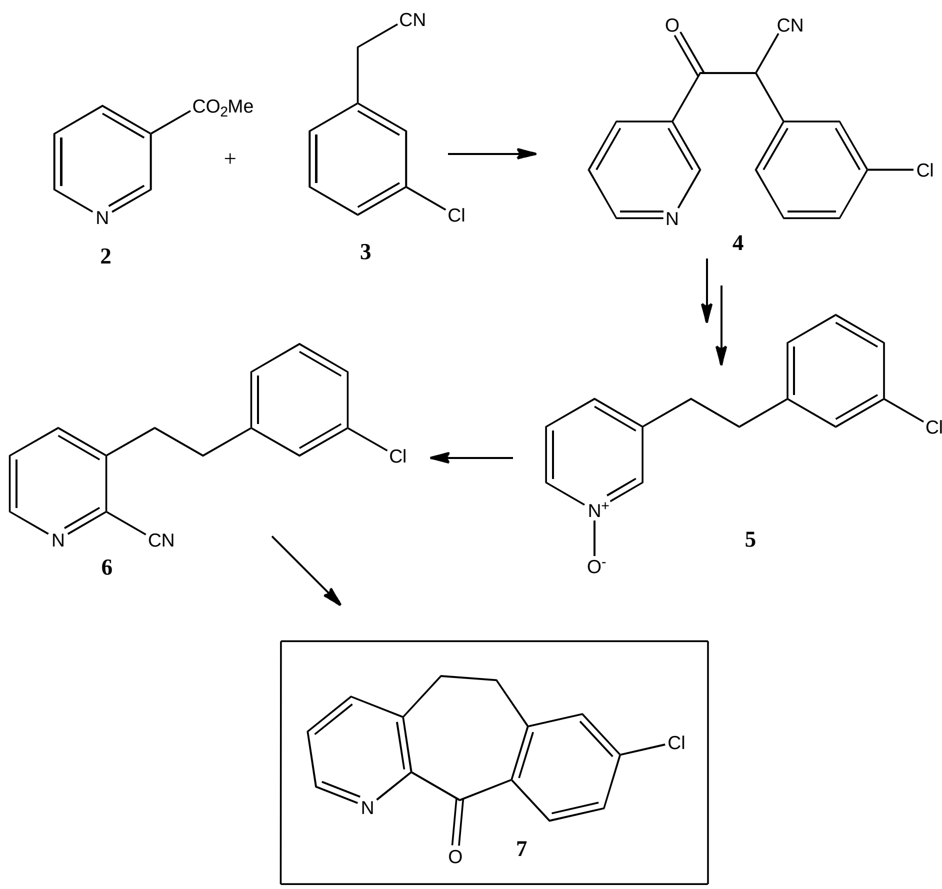
Introduction

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate **1**, is a widely-utilised non-sedating anti-histaminic, anti-allergenic drug that is structurally somewhat related to the tricyclic antidepressants. The compound **1** is sold under trade names such as Claritin,[1] Clarityn[2] and Loratadine. Sales of **1** during 2001 exceeded US $3 billion, making it the fourth-largest selling drug in the world for that year.[3] The drug became a generic product in the USA at the end of 2002, but the $ value of global sales is now far lower than it was. An interesting history of the discovery of Claritin has been published.[4]



1

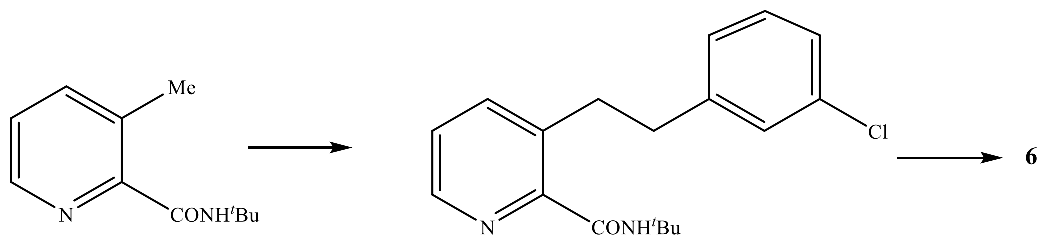
There is an extensive literature that describes synthetic routes to Claritin **1**. Thus (Scheme 1), an initial disclosure[5] was followed by others,[6,7,8] each of which broadly described Claisen-like condensations between an alkyl 3-picolinate **2** and the anion derived from the benzylic nitrile **3** to give the keto-nitrile **4**.



Scheme 1. Early routes to the key tricyclic ketone 7.[5-8]

This was then subjected to series of manipulations to yield the *N*-oxide **5**, which underwent a Reissert-Henze reaction to deliver the pyridyl nitrile **6**. Hydrolysis of **6** to the derived carboxylic acid was followed by Friedel-Crafts ring-closure to give the key tricyclic intermediate **7**. Hydrogen peroxide may[9] be substituted for *m*-CPBA for N-oxidation of the pyridine ring, but the conversion of keto-nitrile **4** into the *N*-oxide **5** by the laborious removal of two activating groups followed by the introduction of another, and the subsequent insertion into the pyridine moiety of a cyano group *via* Reissert-Henze chemistry are all unproductive or unattractive steps that are preferably avoided.

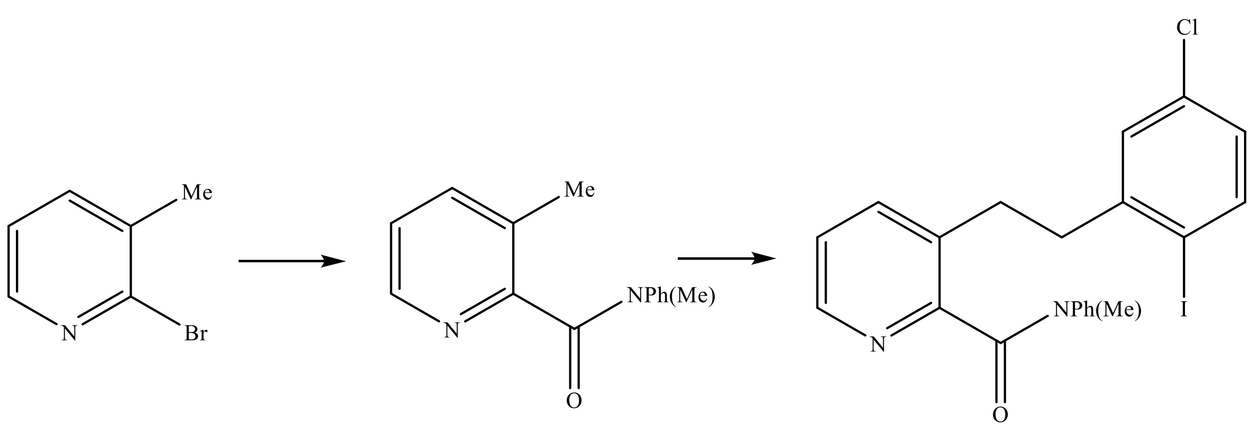
Recognising this, Schumacher *et al.*[10] later (Scheme 2) devised an improved route to Claritin **1** in which the lithiated pyridyl amide **8** was initially alkylated to give **9**, a precursor for the nitrile **6**.



8 **9**

Scheme 2. Second-generation route to the intermediate nitrile **6**.[10]

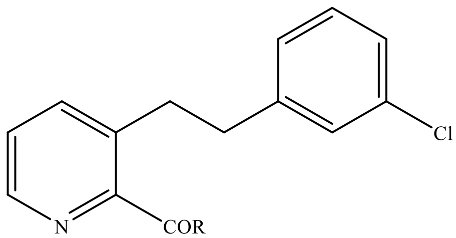
In more recent developments[11,12] amides such as **10** have been obtained (Scheme 3) by Pd-mediated aminocarbonylation of 2-bromo-3-methylpyridine **11**. Lithiation of **10** at low temperature, and alkylation of the derived anion using 5-chloro-2-iodobenzyl bromide gave the diarylethane **12**, which was converted into the tricyclic ketone **7** *via* transmetallation of the iodo function (using RMgX or RLi) and subsequent cyclo-acylation.

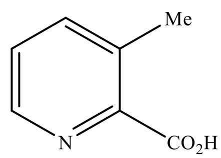


11 **10** **12**

Scheme 3

A variant on this route[13,14] involves the intramolecular cyclisation of a secondary amide **13** using strongly acidic catalysts such as P_2O_5 – CF_3SO_3H to give an imine that is then hydrolysed to yield the ketone **7**.





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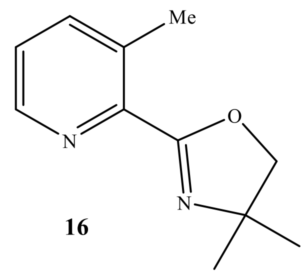


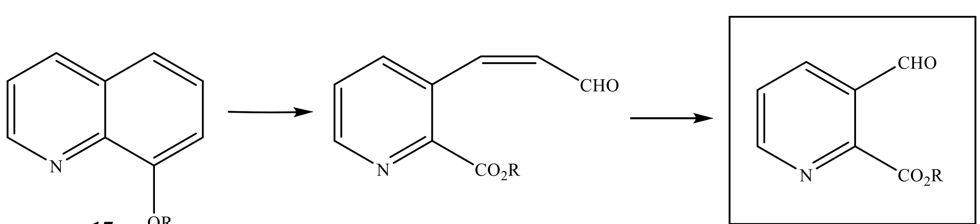
16

13 R = NHR'
15 R = OH

It has been reported[15] that 3-methylpyridine-2-carboxylic acid **14** reacts smoothly with two equivalents of LDA, even at ambient temperatures, to give a dianion that is *C*-alkylated by 3-chlorobenzyl chloride to yield the acid **15**, which can then be cyclised to give **7**. Similarly, the dihydrooxazoline **16** can be mono-lithiated at the 3-methyl group and then alkylated using 3-chlorobenzyl chloride to give[16] another precursor of the tricyclic ketone **7**.

Results and Discussion

In devising possible alternative routes to Claritin **1**, the financial and pharmaceutical potency of which was earlier apparent, it appeared to us that the regioselective ozonolysis of suitable quinoline derivatives under environmentally benign conditions might provide useful differentially functionalised pyridines that would be potentially valuable synthons for the key tricyclic ketone intermediate **7**.



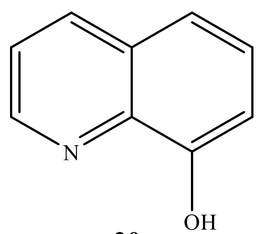
17 **18** **19**

Scheme 4. Selective ozonolysis of an 8-alkoxyquinoline

We considered (Scheme 4) that in an ether **17** derived from 8-hydroxyquinoline, the electron-rich aryl ring would undergo preferential oxidative cleavage by ozone leaving the more electron-deficient pyridine ring intact and provide, *via* secondary cleavage of the (*Z*)-enal **18**, a 2-

carboxyalkylpyridine-3-carboxaldehyde **19** that might then be converted into the key tricyclic ketone **7**.

Some early studies on the exhaustive degradative ozonolysis of alkylquinolines were carried out during the 1940s by Schenck and Bailey.[17,18] More controlled experiments[19] with a number of substituted quinolines that included 8-hydroxyquinoline **20** showed that the initial reaction with ozone took place on the benzenoid ring, and that oxidative work-up yielded pyridine 2,3-dicarboxylic acid **21** (5-95%). Pyridine-2,3-dicarboxaldehyde **22** has[20] also been obtained *via* ozonolysis of quinoline, but yields were very low (<3%). It was later shown[20-22] that the pyridyl ring of quinoline was also attacked by ozone, but only to a minor extent.



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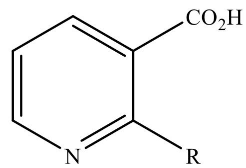
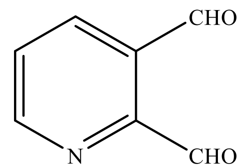


21 R = CO_2H
23 R = H

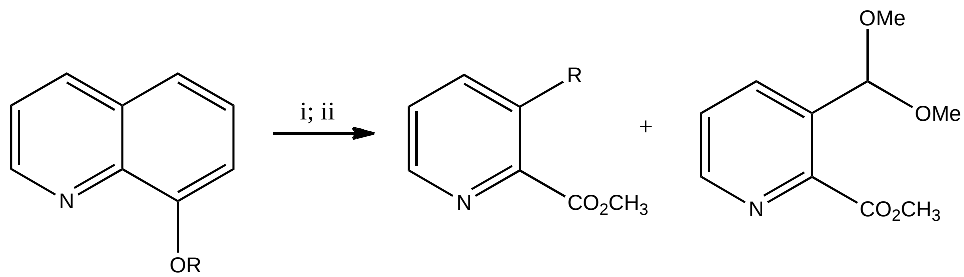


22

Quinoline has been converted into pyridine-3-carboxylic acid **23** by a procedure involving ozonolysis in aqueous nitric acid,[23] but ozonolysis of pyridine in neutral aqueous *tert*-butanol gives[24] the derived *N*-oxide and this type of reaction represents a potential threat to yields where ozonolysis of quinolines to give pyridine free bases is concerned. However, it has been reported[25] that a number of vinylpyridines can be ozonised at –40 ºC in methanol to give modest yields of the derived pyridine carboxaldehydes after reduction of the ozonides with sodium sulfite.

Surprisingly, the literature is almost totally silent regarding the ozonolysis of 8-alkoxyquinolines. In a solitary example it has been reported[26] that 3-ethyl-8-methoxyquinoline is ozonised to yield 5-ethylpyridine-1,2-dicarboxylic acid. The oxidative work-up used in this case clearly precluded the isolation of any aldehyde as product. More recently, Taddei *et al.* have described[27] the successful ozonolysis of three substituted 5-alkoxyquinolines to yield keto-esters as cleavage products in yields ranging from 39-45%.

We initially carried out the ozonolysis of 8-methoxyquinoline **24** in methanol at 0 ºC, using triethylamine to reduce the ozonide that was formed. However, only minor amounts of the desired aldehydo-ester **25** were produced, together with some of the diester **26**. The outcome (Scheme 5) was completely different if dimethyl sulfide (which has been recommended[28] as being a superior reagent for the reduction of ozonides) was used instead of triethylamine, when the aldehyde **25** was isolated in good (81%) yield.



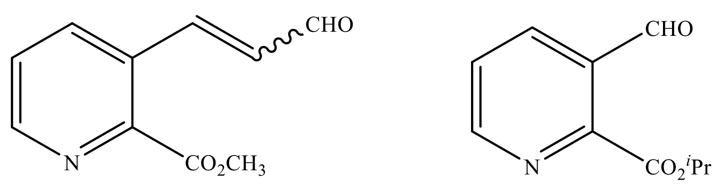
24 R = Me
29 R = ^{i}Pr

25 R = CHO (major)
26 R = CO_2CH_3 (minor)

27 (minor)

Scheme 5. Ozonolysis of 8-methoxyquinoline. Reagents: (i) O_3/MeOH; (ii) Me_2S

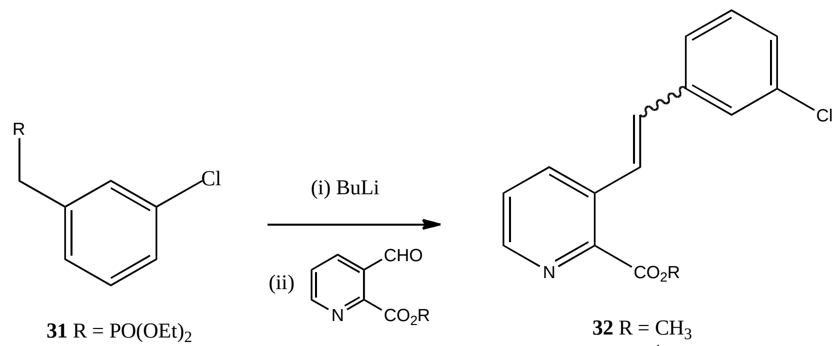
A by-product formed during the ozonolysis of 8-methoxyquinoline **24** was the dimethyl acetal **27**. This may be the source of another minor by-product, the diester **26**, since ozone is known to oxidise acetals to esters.[29]



28 **30**

If the ozonolysis of 8-methoxyquinoline **24** at 0 °C in methanol was interrupted before the calculated amount of ozone had been passed into the reaction mixture the (*E*)- and (*Z*)-isomers of the unsaturated aldehyde **28** could be isolated. These could not be separated by column chromatography because whenever this was attempted the (*Z*)-form of **28** underwent conversion into the (*E*)-isomer, a process that may occur because of traces of acid in the silica gel that was used. The formation of **28** under ozone-limiting conditions is not entirely unexpected, since this reflects initial attack by ozone at the most electron-rich C-C bond of 8-methoxyquinoline **24**. Similar partial ozonolysis reactions of naphthalene have been reported.[30, 31]

8-Isopropoxyquinoline **29** was also successfully ozonised in methanol at 0 °C to give the expected aldehydo-ester **30** in excellent yield after reductive work-up using dimethyl sulfide. An alternative multi-step synthesis of this compound from quinolinic anhydride has been described,[32] but the overall yield obtained using that route was only *ca.* 20%.



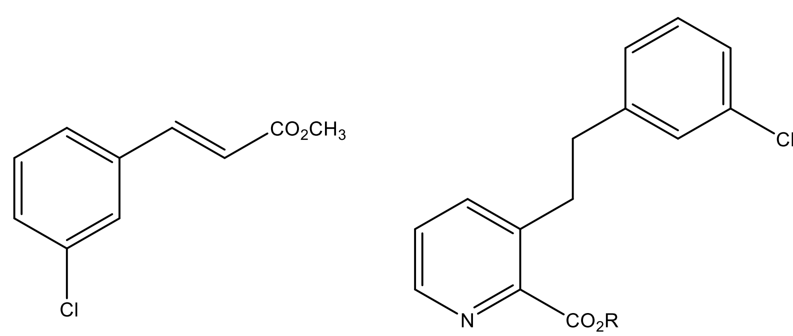
31 R = PO(OEt)$_2$
33 R = Ph$_3$P$^+$Cl$^-$

32 R = CH$_3$
36 R = ^{i}Pr

Scheme 6. Wittig olefination of the aldehydes **25** and **30.**

With easy access to large quantities of the aldehydo-esters **25** and 30 in hand we next explored olefination reactions of the aldehyde **25**. A Horner-Emmons reaction that was attempted between the aldehydo-ester **25** and the anion of the benzylic phosphonate **31** afforded a complex mixture of products from which the desired stilbazole **32** could not be isolated. However (Scheme 6), Wittig olefination of aldehyde **25** using the ylide derived from the phosphonium salt **33** gave a separable mixture of the (*E*)- and (*Z*)-isomers of **32**.

If unpurified aldehyde **25**, obtained directly from the ozonolysis of 8-methoxyquinoline **24**, was used in this Wittig reaction, methyl (*E*)-3-(3-chlorophenyl)prop-2-enoate **34** could be isolated as an additional minor component during chromatography of the product mixture. The precursor to this must be methyl glyoxylate, most likely formed *via* further reaction of ozone with the initially-formed mono-ozonide that leads from 8-methoxyquinoline to the α,β-unsaturated aldehyde **28**.



34

35 R = CH$_3$
37 R = ^{i}Pr

Hydrogenation of (*E*)-/(*Z*)-**32** led to the ethane derivative **35**, which was readily hydrolysed to give the pivotal target acid **15**.

The isopropyl ester **30** was similarly converted by Wittig olefination into the corresponding stilbazole (*E*)/(*Z*)-**36**. Hydrogenation of **36** gave **37**, which was also hydrolysed to yield the acid

15. Conventional intramolecular cyclisation of the acid **15**, *via* its acyl chloride, then delivered the targeted tricyclic ketone **7**.

Conclusions

The useful pyridine aldehydo-esters **25** and **30** have been efficiently obtained from inexpensive 8-alkoxyquinolines *via* simple and relatively "green" ozonolysis reactions carried out under near-ambient conditions. These accessible and differentially-functionalised pyridines have been utilised in syntheses of the tricyclic ketone **7**, which is a precursor of the non-sedating antihistamine Claritin, and should find other applications in the field of heterocyclic chemistry.

Experimental Section

General. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ using a Bruker Avance DPX 400 MHz spectrometer. Coupling constants are recorded in Hz. Assignments were verified where appropriate by ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY, DEPT and HMBC experiments. IR spectra were recorded for Nujol mulls (N) or liquid films (L) between sodium chloride plates using a Mattson FT-IR spectrometer. Mass spectra were obtained under electrospray conditions using a Micromass time-of-flight instrument. Melting points (uncorrected) were measured in unsealed capillary tubes using an Electrothermal IA9100 apparatus. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} 0.2 mm silica gel plates. Column chromatography was carried out using Merck Kieselgel 60 (70-230 mesh) silica gel. Ozonolysis was carried out using a BOC Mark 2 apparatus. All solvents were dried and distilled before use. Organic extracts of reaction products were dried over anhydrous magnesium sulfate.

8-Methoxyquinoline (24). 8-Hydroxyquinoline (4.6 g; 31.7 mmol) and anhydrous potassium carbonate (10.1 g; 73.1 mmol) in DMF (60 mL) were stirred under N_2 at 90 °C for 1 h after which time dimethyl sulfate (**TOXIC!** 3 mL; 31.7 mmol) was added and the mixture was stirred for a further 2 h at 90 ^{o}C. The cooled mixture was then diluted with water (300 mL) and extracted using dichloromethane. The combined organic layers were washed with aqueous potassium hydroxide solution (5%; 100 mL) in portions, and then with water until the washings were no longer alkaline. The extract was dried, filtered and evaporated to give 8-methoxyquinoline **24** (2.67 g; 53%), obtained as an oily solid (lit.[33] mp 46-47 ^{o}C) of sufficient purity for further use, ν_{max} (L) 3391, 3051, 3005, 2955, 2903, 2837, 1616, 1597, 1572, 1501, 1472, 1440, 1424, 1378, 1317, 1263, 1224, 1194, 1174, 1111, 1077, 1031, 994, 823, 792, 753 and 711 cm^{-1}; δ_H 4.07 (3H, s, OC*H*$_3$), 7.04 (1H, d, *J* 8 and *H*-7), 7.35-7.5 (3H, m, *H*-3, *H*-5 and *H*-6), 8.11 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.91 (1H, dd, *J* 4.2 and 1.8, *H*-2) ppm.

Ozonolysis of 8-methoxyquinoline 24: 3-formyl-2-methoxycarbonylpyridine (25). A three-necked flask (250 mL) fitted with a stirring bar and a dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Methoxyquinoline **24** (5.7 g; 35.8 mmol), dissolved in methanol (100 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5% O_3) for 2 h (O_2-flow rate of 1 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (6.6 mL; 90 mmol) was slowly added *via* the dropping funnel while the stirred mixture was continuously cooled in an ice-bath. After a further 30 min, solvents were removed under reduced pressure, the viscous brown oil obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried. Evaporation of the solvent gave crude 3-formyl-2-carbomethoxypyridine **25** (4.8 g; 81%) which could be used without further purification in the following Wittig reaction. An analytical sample of the aldehyde **25** was obtained by extracting the crude oily product using petroleum ether (bp 40-60 °C). 3-Formyl-2-methoxycarbonylpyridine **25** crystallised from the cooled extract and was recrystallised from petroleum ether to give analytically pure material as colourless plates, mp 82-83 °C, ν_{max} (N) 2953, 2924, 2854, 1710, 1693, 1578, 1460, 1426, 1377, 1318, 1263, 1196, 1177, 1088, 1056, 944, 850, 819, 801, 722 and 709 cm^{-1}; δ_H (DMSO-d_6) 3.94 (3H, s, CO_2CH_3), 7.81 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.31 (1H, dd, *J* 7.8 and 1.8, *H*-4), 8.87 (1H, dd, *J* 5 and 1.5, *H*-6) and 10.31 (1H, s, C*H*O) ppm; δ_C (DMSO-d_6) 52.95 (CO_2CH_3), 126.61 (*C*-5), 131.07 (*C*-3), 137.56 (*C*-4), 149.72 (*C*-2), 152.93 (*C*-6), 165.73 (CO_2CH_3) and 191.68 (*C*HO) ppm. HRMS *m/z* 166.0502. Calc. for $[C_8H_7NO_3 + H]^+$: 166.0504.

In some cases where ^{1}H NMR analysis of the crude product revealed significant amounts of impurities, the mixture was chromatographed over silica gel (EtOAc/hexane). In this way, samples of the by-products **26** and **27** were isolated and characterised.

Dimethyl pyridine-2,3-dicarboxylate **26** had mp 54-56 °C (EtOAc) (lit.[34] mp 55-56 °C), ν_{max} (N) 3458, 3162, 3082, 3026, 3010, 2960, 2852, 1736, 1723, 1574, 1451, 1432, 1304, 1286, 1262, 1225, 1196, 1139, 1081, 1057, 958, 845, 782, 763 and 731 cm^{-1}; δ_H 3.94 (3H, s, CO_2CH_3), 4 (3H, s, CO_2CH_3), 7.5 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.18 (1H, dd, *J* 7.5 and 1.5, *H*-4) and 8.77 (1H, d, *J* 4, *H*-6) ppm

Methyl 3-(1',1'-dimethoxymethyl)pyridine-2-carboxylate **27** was obtained as an oil, ν_{max} (L) 3057, 2995, 2953, 2835, 1735, 1639, 1575, 1450, 1427, 1353, 1302, 1249, 1197, 1133, 1119, 1082, 984, 964, 909, 886, 834, 807, 759 and 712 cm^{-1}; δ_H 3.36 (6H, s, OCH_3 groups), 3.97 (3H, s, CO_2CH_3), 6 (1H, s, C*H*$(OCH_3)_2$), 7.44 (1H, dd, *J* 8 and 4.8, *H*-5), 8.06 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.62 (1H, d, *J* 4, *H*-6) ppm; δ_C 52.3 (CO_2CH_3), 53.63 ($CH(OCH_3)_2$), 99.32 (*C*H$(OCH_3)_2$), 125.15 (*C*-5), 134.29 (*C*-3), 135.51 (*C*-4), 147.17 (*C*-2), 148.21 (*C*-6) and 165.95 (CO_2CH_3) ppm. HRMS *m/z* 212.0911. Calc. for $[C_{10}H_{13}NO_4 + H]^+$: 212.0923.

Interrupted ozonolysis of 8-methoxyquinoline 24: (*Z*)- and (*E*)-3-(2-methoxycarbonylpyridin-3-yl)prop-2-enal (28). A three-necked flask (250 mL) fitted with a stirring bar and a dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Methoxyquinoline **24** (7.09 g; 44.6 mmol), dissolved in methanol (100 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5 % O_3) for 3 h (O_2-flow rate of 0.5 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (9.0 mL; 122.7 mmol) was slowly added *via* the dropping funnel while the stirred mixture was continuously cooled in an ice-bath. After a further 60 min, solvents were removed under reduced pressure, the viscous brown oil obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried. Evaporation of solvent gave the crude product mixture as an oil (4.9 g) of which a portion (1.6 g) was chromatographed over silica gel using EtOAc – hexane as eluant. One fraction so obtained (0.4 g) was rechromatographed using EtOAc – hexane to give pure (*E*)-3-(2-methoxycarbonylpyridin-3-yl)prop-2-enal **(*E*)-28** as a solid, mp 117-118 °C (EtOAc/hexane), ν_{max} (N) 2904, 2728, 2672, 1710 (overlapping C=O absorptions), 1580, 1461, 1377, 1312, 1298, 1237, 1196, 1120, 1085, 968, 860, 821, 797, 722, 707 and 685 cm^{-1}; δ_H 4.06 (3H, s, CO_2CH_3), 6.65 (1H, dd, *J* 16 and 7.5, *H*-2), 7.58 (1H, dd, *J* 8 and 4.5, *H*-5'), 8.04 (1H, dd, *J* 8 and 1.5, *H*-4'), 8.38 (1H, d, *J* 16, *H*-3), 8.78 (1H, dd, *J* 4.5 and 1.5, *H*-6') and 9.81 (1H, d, *J* 7.5, *H*-1) ppm; δ_C 52.82 (CO_2CH_3), 126.29 (*C*-5'), 131.51 (*C*-3'), 132.07 (*C*-2), 135.5 (*C*-4'), 145.86 (*C*-2'), 147.59 (*C*-6'), 150.21 (*C*-3), 165.26 (CO_2CH_3) and 192.87 (*C*-1) ppm. HRMS *m/z* 192.0663. Calc. for $[C_{10}H_9NO_3 + H]^+$: 192.0661. (*Z*)-3-(2-methoxycarbonylpyridin-3-yl)prop-2-enal **(*Z*)-28** could never be separated by column chromatography but was clearly present in the crude ozonolysis mixture and had δ_H 3.96 (3H, s, CO_2CH_3), 6.26 (1H, dd, *J* 11.8 and 8, *H*-2), 7.52 (1H, dd, *J* 7.8 and 4.7, *H*-5'), 7.72 (1H, d, *J* 7.5, *H*-4'), 8.08 (1H, d, *J* 11.5, *H*-3), 8.75 (1H, d, *J* 4.5, *H*-6') and 9.62 (1H, d, *J* 8.5, *H*-1) ppm.

8-Isopropoxyquinoline (29). 8-Hydroxyquinoline (14 g; 96.4 mmol) and anhydrous potassium carbonate (34.6 g; 250 mmol) in DMF (150 mL) were stirred under N_2 at 80 °C for 75 min after which time 2-bromopropane (23.5 mL; 250 mmol) was slowly added in two portions. The mixture was stirred at 80 °C for another 3 h and then the cooled contents of the flask were diluted with water (500 mL) and extracted with dichloromethane. The combined organic extracts were washed with aqueous potassium hydroxide solution (5%; 200 mL) in portions and then with water until the washings were no longer alkaline. The dried and filtered extract was evaporated, leaving 8-isopropoxyquinoline **29** (13 g; 85 %) as a viscous oil (lit.[35] mp 41-43 °C), ν_{max} (L) 3458, 3162, 3082, 3026, 3010, 2960, 2852, 1736, 1723, 1574, 1451, 1432, 1304, 1286, 1262, 1225, 1196, 1139, 1081, 1057, 958, 845, 782, 763 and 731 cm^{-1}; δ_H 1.55 (6H, d, *J* 6, $OCH(CH_3)_2$), 4.87 (1H, septet, *J* 6, $OCH(CH_3)_2$), 7.09 (1H, d, *J* 7.5, *H*-7), 7.35-7.5 (3H, m, *H*-3, *H*-5 and *H*-6), 8.13 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.98 (1H, dd, *J* 4 and 1.5, *H*-2) ppm.

Ozonolysis of 8-isopropoxyquinoline 29: isopropyl 3-formylpyridine-2-carboxylate (30). A three-necked flask (250 mL) fitted with a stirring bar and dropping funnel was placed in an ice-bath and connected to the ozoniser. 8-Isopropoxyquinoline **29** (13.0 g; 69.4 mmol), dissolved in methanol (150 mL), was added and the solution was subjected to a stream of ozonised O_2 (containing ~1.5% O_3) during 4.5 h (O_2 flow rate of 2 L/min). Ozone production was discontinued and the system was flushed with O_2 for 20 min to purge excess reagent. Dimethyl sulfide (13 mL; 177.3 mmol) was slowly added *via* the dropping funnel while the mixture was continuously cooled in an ice-bath. After a further 30 min solvents were removed under reduced pressure. The viscous brown oil so obtained was taken up in ethyl acetate (100 mL) and the extract was washed with brine and dried. The crude oily product (13.4 g; 99%) was used without further purification for olefination reactions, but an analytical sample of the aldehyde **30** was obtained by column chromatography (EtOAc/hexane) as an oil (lit.[32] an oil) that had ν_{max} (N) 3068, 2985, 2935, 2879, 1736, 1711, 1579, 1468, 1456, 1439, 1387, 1375, 1344, 1304, 1265, 1240, 1186, 1146, 1103, 1088, 916, 881, 868, 841, 822, 802, 762 and 714 cm^{-1}; δ_H 1.46 (6H, d, *J* 6, OCH(C*H*$_3$)$_2$), 5.4 (1H, septet, *J* 6.3, OC*H*(CH$_3$)$_2$) 7.6 (1H, dd, *J* 7.8 and 4.8, *H*-5), 8.26 (1H, dd, *J* 7.8 and 1.8, *H*-4), 8.89 (1H, dd, *J* 4.5 and 1.5, *H*-6) and 10.58 (1H, s, C*H*O) ppm.

Wittig olefination of aldehyde 25: methyl (*E*)- 3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*E*)-32 and methyl (*Z*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*Z*)-32. 3-Chlorobenzyltriphenylphosphonium bromide **33**[36] (2.4 g; 5.1 mmol) was dissolved under N_2 in freshly distilled anhydrous THF (50 mL) at 0 °C and treated with *n*-butyllithium (2.5M in hexane: 2 mL; 5 mmol). After 30 min the temperature was decreased to –78 °C and the aldehyde **25** (0.8 g; 4.8 mmol), dissolved in THF (10 mL), was added. After 1 h the mixture was warmed to room temperature and stirring was continued overnight. It was then diluted with water (100 mL) and extracted with chloroform. The extract was dried, filtered and evaporated to give a mixture of the (*E*)- and (*Z*)-isomers of the stilbazole **32**, which were separated by column chromatography (EtOAc/hexane).

Methyl (*E*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*E*)-32 had mp 73-74 °C (EtOAc/hexane), ν_{max} (N) 2953, 2922, 2852, 1730 (C=O), 1589, 1456, 1377, 1306, 1281, 1238, 1194, 1140, 1099, 1078, 991, 976, 966, 910, 889, 866, 858, 822, 810, 802, 777, 723, 712, 683 and 675 cm^{-1}; δ_H 3.95 (3H, s, CO$_2$C*H*$_3$), 6.86 (1H, d, *J* 16, *H*-2'), 7.14-7.23 (2H, m, *H*-" and *H*-5"), 7.32 (1H, dt, *J* 7 and 1.5 and 1.5, *H*-6"), 7.37 (1H, dd, *J* 8 and 4.5, *H*-5), 7.42 (1H, d, *J* 2, *H*-2"), 7.82 (1H, d, *J* 16.6, *H*-1'), 7.94 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.53 (1H, d, *J* 3.5, *H*-6) ppm; δ_C 52.42 (CO$_2$*C*H$_3$), 124.65 (*C*-6"), 125.31 (*C*-1'), 125.89, 126.31 (*C*-5 and *C*-2"), 127.78 (*C*-4"), 129.46 (*C*-5"), 131.33 (*C*-2'), 133.96, 134.15 (*C*-3 and *C*-3"), 134.37 (*C*-4), 138.01 (*C*-1"), 145.01 (*C*-2), 147.71 (*C*-6) and 165.74 (*C*O$_2$CH$_3$) ppm. HRMS *m/z* 274.0634. Calc. for [$C_{15}H_{12}ClNO_2$ + H]$^+$: 274.0635.

Methyl (Z)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*Z*)-32 had mp 50-51 °C (EtOAc/hexane), ν_{max} (N) 3384, 3188, 2954, 2924, 2854, 1718 (C=O), 1707, 1593, 1560, 1456, 1412, 1377, 1302, 1282, 1242, 1200, 1142, 1088, 958, 920, 899, 877, 833, 818, 793, 750, 704, 687 and 661 cm^{-1}; δ_H 3.9 (3H, s, CO$_2$C*H*$_3$), 6.61 (1H, d, *J* 12, *H*-2'), 6.81 (1H, d, *J* 7.5, *H*-4"), 6.95-7.01 (3H, m, *H*-1', *H*-2" and *H*-5"), 7.04 (1H, d, *J* 8, *H*-6") 7.17 (1H, dd, *J* 7.8 and 4.7, *H*-5), 7.43 (1H, dd, *J* 7.5 and 1, *H*-4) and 8.52 (1H, d, *J* 4.5, *H*-6) ppm; δ_C 52.21 (CO$_2$*C*H$_3$), 125.3 (*C*-5), 126.75 (*C*-4"), 126.93 (*C*-6"), 128.07, 128.52, 129.01 (*C*-1', *C*-2" and *C*-5"), 129.61 (*C*-2'), 133.66, 134.21 (*C*-3 and *C*-3"), 137.31 (*C*-1"), 138.75 (*C*-4), 145.88 (*C*-2), 147.84 (*C*-6) and 165.41 (*C*O$_2$CH$_3$) ppm. HRMS *m/z* 274.0646. Calc. for [$C_{15}H_{12}ClNO_2$ + H]$^+$: 274.0635.

If the unpurified aldehyde **25**, obtained from the ozonolysis of 8-methoxyquinoline **24**, was used for the above Wittig reaction, methyl (*E*)-3-(3-chlorophenyl)prop-2-enoate **34** could be isolated as an additional minor component during chromatography of the product mixture. This, a low-melting solid (lit.[37] mp 45-46.5 °C), had ν_{max} (N) 3063, 2952, 2925, 2852, 1722, 1641, 1595, 1568, 1467, 1435, 1376, 1317, 1201, 1174, 1106, 1979, 1038, 1015, 982, 884, 860, 788, 744 and 673 cm^{-1}; δ_H 3.83 (3H, s, CO_2CH_3), 6.46 (1H, d, *J* 16, *H*-2), 7.3-7.43 (3H, m, *H*-4', *H*-5' and *H*-6'), 7.52 (1H, s, *H*-2') and 7.64 (1H, d, *J* 16, *H*-3) ppm; δ_C 51.41 (O*C*H$_3$), 118.8 (*C*-2), 125.8 (*C*-6'), 127.34 (*C*-2'), 129.69, 129.71 (*C*-4' and *C*-5'), 134.46 (*C*-3'), 135.72 (*C*-1'), 142.8 (*C*-3) and 166.57 (*C*-1) ppm.

Hydrogenation of methyl (*E*)- and (*Z*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylates 32: methyl 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylate (35). A mixture of (*E*)- and (*Z*)-isomers of the stilbazole **32** (0.4 g; 1.33 mmol) was dissolved in ethyl acetate (10 mL) and 5% Pd/C catalyst (20 mg) was added. The mixture was hydrogenated at 1 atm. until reaction was complete (~ 4 h). Catalyst was removed by filtration and solvent was evaporated to give the ester **35** as a solid that was recrystallised from ethyl acetate/hexane (0.36 g; 89%), mp 54-55 ^oC (EtOAc/hexane), ν_{max} (N) 3066, 3053, 2953, 2922, 2852, 1726 (C=O), 1718, 1599, 1572, 1477, 1464, 1456, 1444, 1429, 1377, 1306, 1294, 1259, 1234, 1201, 1136, 1097, 1076, 968, 889, 868, 849, 820, 804, 769, 725, 702 and 683 cm^{-1}; δ_H 2.94 (2H, m, *H*-2'), 3.25 (2H, m, *H*-1'), 4.02 (3H, s, CO_2CH_3), 7.07 (1H, dd, *J* 6.5 and 2, *H*-6"), 7.18-7.26 (3H, m, *H*-2", *H*-4" and *H*-5"), 7.38 (1H, dd, *J* 7.8 and 4.8, *H*-5), 7.54 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.5 and 1.5, *H*-6) ppm; δ_C 34.55 (*C*-1'), 36.61 (*C*-2'), 52.37 (CO$_2$*C*H$_3$), 125.68 (*C*-5), 125.93, 126.39, 128.24, 129.23 (*C*-2", *C*-4", *C*-5" and *C*-6"), 133.7 (*C*-3"), 138.18 (*C*-3), 139.12 (*C*-4), 142.58 (*C*-1"), 146.38 (*C*-2), 146.88 (*C*-6) and 165.79 (*C*O$_2$CH$_3$) ppm. HRMS *m/z* 276.0798. Calc. for $[C_{15}H_{14}ClNO_2 + H]^+$: 276.0791.

Hydrolysis of methyl 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylate 35 to 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylic acid (15). The methyl ester **35** (0.36 g; 1.31 mmol) was dissolved in ethanol (5 mL) with sodium hydroxide (0.2 g) and water (20 mL) and the mixture was stirred during 48 h. It was then acidified using 1 M HCl and extracted with chloroform. The organic layer was washed with brine, dried, filtered and evaporated to yield a colourless solid that was recrystallised from ethyl acetate to afford 0.3 g (88%) of the acid **15**, mp 125-126 °C,[38] ν_{max} (N) 3475, 3192, 3078, 2953, 2924, 2854, 1658, 1601, 1572, 1508, 1460, 1431, 1377, 1358, 1313, 1290, 1167, 1151, 1103, 1088, 1076, 1057, 1022, 995, 955, 891, 872, 849, 835, 800, 779, 692, 681 and 661 cm^{-1}; δ_H (DMSO-d_6) 2.87 (2H, m, *H*-2'), 3.1 (2H, m, *H*-1'), 7.18 (1H, d, *J* 7.5, *H*-6"), 7.26 (1H, d, *J* 7.8, *H*-4"), 7.28-7.35 (2H, m, *H*-2" and *H*-5"), 7.49 (1H, dd, *J* 7.8 and 4.8, *H*-5), 7.78 (1H, dd, *J* 7.5 and 1, *H*-4), 8.5 (1H, dd, *J* 4.8 and 1.2, *H*-6) and 13.16 (1H, s, CO$_2$*H*) ppm; δ_C 33.74 (*C*-1'), 36.11 (*C*-2'), 125.78 (*C*-5), 126.02, 127.08, 128.21, 130.18 (*C*-2", *C*-4", *C*-5" and *C*-6"), 132.94 (*C*-3"), 136.3 (*C*-3), 139.1 (*C*-4), 143.77 (*C*-1"), 146.68 (*C*-6), 148.65 (*C*-2) and 167.58 (*C*=O) ppm. HRMS *m/z* 262.0620. Calc. for $[C_{14}H_{12}ClNO_2 + H]^+$: 262.0635.

Wittig olefination of aldehyde 30: isopropyl (*E*)- and (*Z*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylates (36). 3-Chlorobenzyltriphenylphosphonium bromide[36] **33** (14 g; 30 mmol) was dissolved under N_2 in freshly-distilled anhydrous THF (60 mL) at 0 ^oC. To this solution was added *n*-butyllithium (2.5M in hexane: 12 mL; 30 mmol) and stirring was continued for 30 min. The temperature was reduced to –70 °C and 3-formyl-2-isopropoxycarbonylpyridine **30** (5.8 g; 30 mmol), in THF (10 mL), was added. After 30 min the mixture was warmed to room temperature and stirring was continued for a further 6 h. The mixture was diluted with water (200 mL), extracted using diethyl ether and the extract was dried, filtered and evaporated. Ether (50 mL) was added to the residue and the mixture was stirred and heated for 1 h and then filtered to remove insoluble triphenylphosphine oxide. The filtrate was evaporated and the oily residue was chromatographed (diethyl ether) to give a yellow oil (4.02 g; 44%) consisting mainly of the (*E*)- and (*Z*)-isomers of the stilbazole **36**. An analytical sample of the (*E*)-isomer could be obtained by further column chromatography (EtOAc/hexane) but the (*Z*)-isomer was always contaminated by traces of the (*E*)-form.

Isopropyl (*E*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*E*)-36 was obtained as a solid that had mp 82-84 °C (EtOAc/hexane), ν_{max} (L) 2923, 2853, 2361, 2343, 1712, 1637, 1610, 1593, 1561, 1506, 1459, 1377, 1353,1293, 1243, 1181, 1148, 1106, 1087, 1060, 956, 909, 870, 850, 806, 772, 737, 709 and 678 cm^{-1}; δ_H 1.49 (6H, d, *J* 6.2, CH(CH_3)$_2$), 5.4 (1H, septet, *J* 6.3, C*H*(CH$_3$)$_2$), 7.01 (1H, d, *J* 16.4, *H*-2'), 7.26-7.37 (2H, m, *H*-4" and *H*-5"), 7.43 (1H, d, *J* 6.8, *H*-6"), 7.51 (1H, dd, *J* 8 and 4.5, *H*-5), 7.54 (1H, s, *H*-2"), 7.82 (1H, d, *J* 16.4, *H*-1'), 8.1 (1H, d, *J* 8.2, *H*-4) and 8.69 (1H, d, *J* 4.1, *H*-6) ppm; δ_C 21.43 (OCH(*C*H$_3$)$_2$), 69.69 (O*C*H(CH$_3$)$_2$), 124.65 (*C*-6"), 125.22 (*C*-1'), 125.62 (*C*-5), 126.38 (*C*-2"), 127.96, 129.58 (*C*-4" and *C*-5"), 131.5 (*C*-2'), 133.56 (*C*-3), 134.34 (*C*-3"), 134.89 (*C*-4), 138.01 (*C*-1"), 147.45 (*C*-2), 147.51 (*C*-6) and 164.8 (*C*O$_2$-*i*Pr) ppm. HRMS *m/z* 302.0960. Calc. for $[C_{17}H_{16}ClNO_2 + H]^+$: 302.0948.

Isopropyl (Z)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylate (*Z*)-36 was obtained as an oil that had ν_{max} (N) 3059, 2962, 2920, 2848, 1716, 1630, 1592, 1560, 1466, 1373, 1298, 1261, 1184, 1144, 1105, 1084, 962, 918, 864, 827, 796, 752, 731, 710, 685 and 654 cm^{-1}; δ_H 1.41 (6H, d, *J* 5.8, CH(CH_3)$_2$), 5.31 (1H, septet, *J* 6.2, C*H*(CH$_3$)$_2$), 6.67 (1H, d, *J* 12.4, *H*-2'), 6.89 (1H, d, *J* 7.3, *H*-4"), 7.02 (1H, d, *J* 12.4, *H*-1'), 7.04-7.09 (2H, m, *H*-2" and *H*-5"), 7.12 (1H, dd, *J* 8 and 1.4, *H*-6"), 7.22 (1H, dd, *J* 7.7 and 4.8, *H*-5), 7.49 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.4 and 1.5, *H*-6) ppm; δ_C 21.35 (CH(*C*H$_3$)$_2$), 69.29 (*C*H(CH$_3$)$_2$), 125.02 (*C*-5), 126.82 (*C*-4"), 126.98 (*C*-6"), 128.3, 128.59, 129.07 (*C*-1', *C*-2" and *C*-5"), 129.4 (*C*-2'), 133.71, 133.76 (*C*-3 and *C*-3"), 137.37 (*C*-1"), 138.65 (*C*-4), 146.99 (*C*-2), 148.04 (*C*-6) and 164.91 (*C*O$_2$-*i*Pr) ppm. HRMS *m/z* 324.0763. Calc. for $[C_{17}H_{16}ClNO_2 + Na]^+$: 324.0767.

Hydrogenation of isopropyl (*E*)- and (*Z*)-3-(2-(3-chlorophenyl)ethenyl)pyridine-2-carboxylates 36: isopropyl 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylate (37). A mixture of the (*E*)- and (*Z*)-stilbazoles **36** (3.2 g; 10.6 mmol), in ethyl acetate (40 mL) with 5**%** Pd/C catalyst (150 mg) was hydrogenated at 1 atm until uptake of hydrogen had ceased (*ca.* 48 h). Removal of catalyst and solvent yielded isopropyl 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylate **37** (2.94 g; 91%) as an oily solid that could not be satisfactorily recrystallised but that had mp 41-43 °C, ν_{max} (N) 3051, 2981, 2935, 2872, 1722 (C=O), 1599, 1572, 1479, 1450, 1439, 1387, 1375, 1354, 1336, 1298, 1232, 1194, 1182, 1146, 1107, 1095, 999, 918, 891, 866, 796, 783, 717, 702, 685 and 667 cm^{-1}; δ_H 1.46 (6H, d, *J* 6, CH(CH_3)$_2$), 2.94 (2H, m, *H*-2'), 3.19 (2H, m, *H*-1'), 5.36 (1H, septet, *J* 6.4, C*H*(CH$_3$)$_2$), 7.06 (1H, dt, *J* 6.6, 1.9 and 1.9, *H*-6"), 7.17-

7.25 (3H, m, *H*-2'', *H*-4'' and *H*-5''), 7.34 (1H, dd, *J* 7.8 and 4.7, *H*-5), 7.50 (1H, dd, *J* 8 and 1.5, *H*-4) and 8.61 (1H, dd, *J* 4.8 and 1.2, *H*-6) ppm; δ_C 21.37 (CH(*C*H_3)$_2$), 34.31 (*C*-1'), 36.53 (*C*-2'), 69.38 (*C*H(CH_3)$_2$), 125.28 (*C*-5), 125.97, 126.31, 128.19, 129.25 (*C*-2'', *C*-4'', *C*-5'' and *C*-6''), 133.72 (*C*-3''), 137.28 (*C*-3), 139.29 (*C*-4), 142.48 (*C*-1''), 146.59 (*C*-6), 147.36 (*C*-2) and 164.97 (*C*O_2*i*-Pr) ppm. HRMS *m/z* 304.1074. Calc. for $[C_{17}H_{18}ClNO_2+H]^+$: 304.1104.

Hydrolysis of isopropyl 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylate 37 to 3-(2-(3-chlorophenyl)ethanyl)pyridine-2-carboxylic acid (15). The isopropyl ester **37** (2.7 g; 8.89 mmol) was dissolved in ethanol (10 mL) with sodium hydroxide (0.7 g; 17.5 mmol) in water (50 mL) and the contents of the flask were refluxed during 5 h. After this time the solution was acidified using 1 M HCl and extracted with chloroform. The extract was washed with brine, dried, filtered and evaporated to give a colourless solid that was recrystallised from ethyl acetate to afford the acid **15** (2.1 g; 90%).

Intramolecular cyclisation of the acid 15: 8-chloro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (7). The acid **15** (0.34 g) was converted into the acyl chloride using thionyl chloride, and this was cyclised according to the published[9] procedure using aluminium chloride as catalyst but with dichloromethane replacing carbon disulfide as solvent to yield the tricyclic ketone **7** (40%), m.p. 106-107 ^oC ($CHCl_3$ – hexane) (lit.[9] 100-101 ^oC), ν_{max} (N) 2927, 2855, 1664, 1644, 1584, 1555, 1453, 1408, 1377, 1356, 1330, 1294, 1229, 1212, 1191, 1166, 1150, 1087, 945, 907, 864, 838, 807, 794, 732 and 681 cm^{-1}; δ_H (DMSO-d_6) 3.11-3.18 (2H, m, *H*-5), 3.2-3.26 (2H, m, *H*-6), 7.47 (1H, dd, *J* 8.5 and 2, *H*-9), 7.51 (1H, s, *H*-7), 7.52 (1H, dd, *J* 8 and 5, *H*-3) 7.85 (1H, dd, *J* 8 and 2, *H*-4) 7.87 (1H, d, *J* 8.5, *H*-10) and 8.59 (1H, dd, *J* 4.8 and 1.7, *H*-2) ppm; δ_C 30.83 (*C*-5), 33.57 (*C*-6), 126.32 (*C*-3), 126.85 (*C*-9), 130.02 (*C*-7), 131.92 (*C*-10), 135.58 (*C*-15), 136.47 (*C*-13), 137.44 (*C*-8), 137.46 (*C*-4), 144.15 (*C*-14), 148.1 (*C*-2), 154.45 (*C*-12) and 193.52 (*C*-11) ppm. HRMS *m/z* 244.0546. Calc. for $[C_{14}H_{10}ClNO + H]^+$: 244.0529.

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References and Notes

1. In the United States of America.
2. In several EU states.

3. See, for example, Hall, S. S. "*Claritin and Schering-Plough: A Prescription for Profit", New York Times on the web*, 11/03/2001, available from http://www.nytimes.com/2001/03/11/magazine/the-claritin-effect-prescription-for-profit.html?module=Search&mabReward=relbias%3As
4. Barnett, A.; Green, M. J. *Chronicles of Drug Discovery*, American Chemical Society, **1993**, 83.
5. Villani, F. J. Belgian Patent 647043, 1964 (to Scherico Ltd.); CA63:80576.
6. Villani, F. J. US Patent 3 357 986, 1967 (to Schering Corporation); CA69:27262.
7. Villani, F. J.; Wefer, E. A.; Mann, T. A.; Mayer, J.; Peer, L.; Levy, A. S. *J. Heterocycl. Chem*., **1972**, *9*, 1203. http://dx.doi.org/10.1002/jhet.5570090602
8. Villani, F. J. US Patent 4 282 233, 1981 (to Schering Corporation); CA95:203761.
9. Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem*. **1971**, *8*, 73. http://dx.doi.org/10.1002/jhet.5570080115
10. Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242. http://dx.doi.org/10.1021/jo00270a041
11. Poirier, M.; Chen, F.; Bernard, C.; Wong, Y.-S.; G. Wu, G. *Org. Lett.* **2001**, *3*, 3795. http://dx.doi.org/10.1021/ol016809d
12. Chen, X.; Poirier, M.; Wong, Y.-S.; Wu, G.-Z. US Patent 5 998 620, 1999 (to Schering Corporation), CA132:12263.
13. Bernard, C.; Casey, M.; Chen, F. X.; Grogan, D. C.; Poirier, M.; Williams, R. P.; Wong, Y.-S.; Wu, G. G. WO 00/30589, 2000 (to Schering Corporation), CA133:4603.
14. Bernard, C.; Casey, M.; Chen, F. X.; Grogan, D. C.; Poirier, M.; Williams, R. P.; Wong, Y.-S.; Wu, G. G. US 6 372 909, 2002, (to Schering Corporation), CA136:309859.
15. Schickaneder, H.; Nikolopoulos, A.; Kocher, C.; Mulcahy, D. WO 00/05215, 2000, (to Russinsky Ltd.), CA132:107883.
16. Cannata, V.; Cotarca, L.; Michieletto, I.; Poli, S. WO 03/040140, 2003, (to Zambon Group S. P. A.) CA 138:385421
17. Schenck, L. M.; Bailey, J. R. *J. Am. Chem. Soc.* **1940**, *62*, 1967. http://dx.doi.org/10.1021/ja01865a019
18. Schenck, L. M.; Bailey, J. R. *J. Am. Chem. Soc.* **1941**, *63*, 1365. http://dx.doi.org/10.1021/ja01850a066
19. Lindenstruth, A. F.; Vanderwerf, C. A. *J. Am. Chem. Soc*. **1949**, *71*, 3020. http://dx.doi.org/10.1021/ja01177a021
20. Wibaut, J. P.; Boer, H. *Rec. Trav. Chim. Pays-Bas* **1955**, *74*, 241.
21. Boer, H.; Sixma, F. J. L.; Wibaut, J. P. *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 509.
22. Sixma, F. J. L. *Rec. Trav. Chim. Pays-Bas* **1952**, *71*, 1124.

23. Sturrock, M. G.; Cline, E. L.; Robinson, K. R.; Zercher, K. A. US 2 964 529, 1960, (to Koppers Co. Inc.), CA55:59566.
24. Andreozzi, R.; Insola, A.; Caprio, V.; D'Amore, M. G. *Water Res.* **1991**, *25*, 655. http://dx.doi.org/10.1016/0043-1354(91)90040-W
25. Callighan, R. H.; Wilt, M. H. *J. Org. Chem.* **1961**, *26*, 4912. http://dx.doi.org/10.1021/jo01070a032
26. O'Murchu, C. *Synthesis* **1989**, 880. http://dx.doi.org/10.1055/s-1989-27423
27. Taddie, D.; Poriel, C.; Moody, C. J. *Arkivoc* **2007**, *(xi)*, 56.
28. Pappas, J. J.; Keaveny, W. P.; Gancher E.; Berger, M. *Tetrahedron Lett*. **1966**, *36*, 4273. Taddie *et al*. (*cf.* reference 26) also obtained superior results when using this reducing agent.
29. Burke, S. D.; Danheiser. R. L. (eds.), *Handbook of Reagents for Organic Synthesis*, Wiley, Chichester, **1999**, 274.
30. Marley, K. A.; Larson, R. A.; Stapleton, P. L.; Garrison, W. J.; Klodnycky, C. M. *Ozone: Science and Engineering*, **1987**, *9*, 23. http://dx.doi.org/10.1080/01919518708552386
31. Larson, R. A.; Garrison, W. J.; Marley, K. A. *Tetrahedron Lett.* **1986**, *27*, 3987. http://dx.doi.org/10.1016/S0040-4039(00)84891-1
32. Ornstein, P. L.; Schaus, J. M.; Chambers, J. W.; Huser, D. L.; Leander, J. D.; Wong, D. T.; Pascal, J. W.; Jones, N. D.; Deeter, J. B. *J. Med. Chem.* **1989**, *32*, 827. http://dx.doi.org/10.1021/jm00124a015
33. Kaufmann A.; Rothlin, E. *Chem. Ber*, **1916**, *49*, 581.
34. Armarego, W. L. F.; Milloy, B. A.; Sharma, S. C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2485. http://dx.doi.org/10.1039/p19720002485
35. Shchukina, M. N.; Savitskaya, N. V. *Zh. Obshchei Khim.* **1952**, *22*, 1218.
36. Acheson R. M.; Harrison, D. R. *J. Chem. Soc. C* **1970**, 1764.
37. Lee, G. D.; Brown, K.C.; Karaman, H. *Can. J. Chem.* **1986**, 64, 1054; Tchilibon, S.; Kim, S.-K.; Gao, Z.-G.; Harris, B. A.; Blaustein, J. B.; Gross, A. S.; Duong, H. T.; Melman, N.; Jacobson, K. A. *Bioorg. Med. Chem.* **2004**, *12*, 2021.
38. The melting point of the acid **15** does not appear to have been reported in either the academic or the Patent literature.

