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Study of the oxidation of 3-hydroxypyrroloindoles to pyrrolobenzoxazine alkaloids

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A Gilbert, un bon anniversaire, avec respect et admiration

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ABSTRACT

This report describes a detailed study of the oxidation-Meisenheimer rearrangement of *N*-methyl-3-hydroxy-7-chloropyrroloindoline ethyl ester and the corresponding *O*-Boc and *N*-Boc derivatives. Experimental conditions were found, which allowed the selective Boc protection of either the tertiary alcohol substituent or the NH group of the aminal function. It was shown that both the parent compound and its *O*-Boc derivative yielded a mixture of oxazines and, in some cases, *N*-oxides upon treatment with *m*-CPBA. MS fragmentation (APCI) clearly differentiates formation of *N*-oxides and oxazines. The *N*-Boc derivatives exclusively yielded the *N*-oxides showing that the Meisenheimer rearrangement requires the presence of a high energy lone pair on the neighbouring nitrogen atom. Both the parent compound and the *O*-Boc derivative gave a mixture of rearranged products and *N*-oxide depending on the reaction conditions.

1. Introduction

Paeciloxazin and the related compounds CJ-12662 and CJ-12663 belong to a unique class of natural products made of a pyrrolobenzoxazine alkaloid core esterified with a sesquiterpene diol (Fig. 1).[1] They exhibit interesting antiparasitic and antibiotic properties.

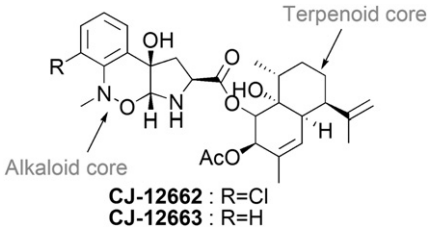
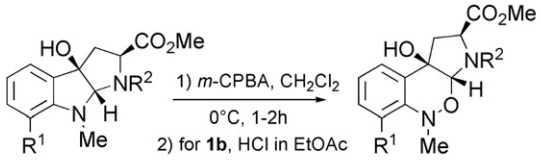


Fig. 1. Structure of terpenoid pyrrolobenzoxazine alkaloids CJ-12662 and CJ-12663.

The pyrrolobenzoxazine alkaloid core of these alkaloids has been efficiently synthesized in 2004 by the groups of Barrett and Baldwin starting from *N*-methylated tryptophan derivatives.[2,3] A key step of their syntheses was the oxidation of 3-hydroxypyrroloindole **1a**,**b**, which led to the target pyrrolobenzoxazine **2a**,**b** after a diastereoselective Meisenheimer rearrangement[4] of an intermediate *N*-oxide (Scheme 1).



Scheme 1. Oxidation of 3-hydroxypyrroloindoles **1** with *m*-CPBA.

Both authors reported satisfactory yields of a single isomer **2a** or **2b**.

These results contrasted with earlier results showing that *m*-CPBA oxidation of physostigmine **3** (as well as the related phenserine, tolserine, cymserine and 2′-ethylphenserine) led to the regioselective insertion of an oxygen atom into the pyrrolidine *C*–*N*

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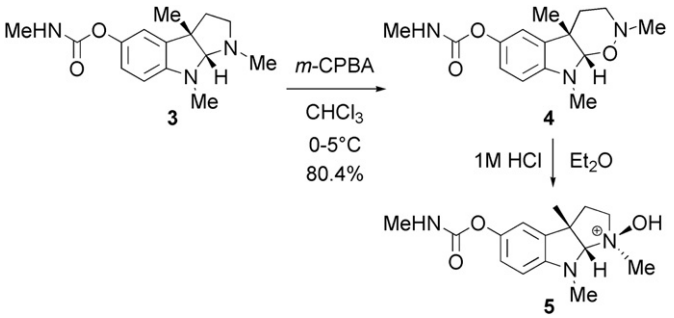
bond to yield hexahydro-1,2-oxazino-[5,6-*b*]-indoles (Scheme 2).[5] Interestingly Brossi et al. observed a pH-dependent tautomerism between *N*-oxides and 1,2 oxazines and were able to induce a retro-Meisenheimer rearrangement by treatment of oxazine **4** with a solution of hydrogen chloride in diethyl ether.[5f,h]



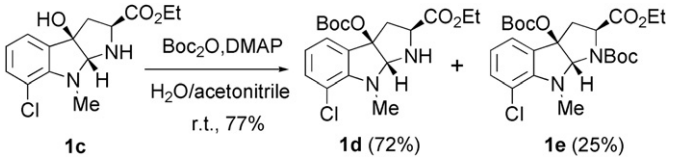
Scheme 2. Oxidation of physostigmine **3** to geneserine **4**.

In the course of a research programme aiming at the preparation of insecticides related to alkaloids CJ-12662 and CJ-12663, we observed that the course of the Meisenheimer rearrangement of 3-hydroxypyrroloindoles was quite sensitive to the nature of the substituents as well as to the reaction conditions. In this report we would like to describe the details of these studies as well as some unexpected observations on the selectivity of the Boc protection reactions.

2. Results and discussion

2.1. Boc protection of hydropyrroloindole 1c

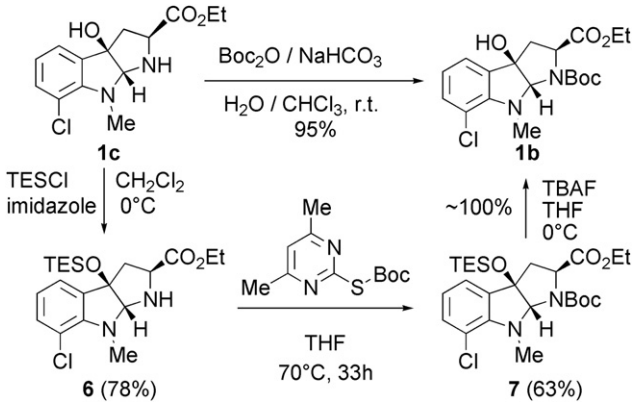
The starting material for these studies was *N*-methyl-3-hydroxy-7-chloropyrroloindoline ethyl ester **1c**, which was supplied to us by Syngenta Crop protection. The compound had been prepared analogously to the procedures described by Barrett and Baldwin.[2,3] Treatment of compound **1c** with Boc_2O in acetonitrile in the presence of 1 equiv of DMAP unexpectedly yielded compound **1d** resulting from a chemoselective acylation of the hindered tertiary alcohol together with some di-Boc product **1e** (Scheme 3). Compound **1d** remained unchanged after prolonged treatment with a large excess of Boc_2O. This suggested that compound **1e** arose from an initially formed *N*-Boc derivative.



Scheme 3. *O*-selectivity of the reaction of **1c** with Boc-anhydride.

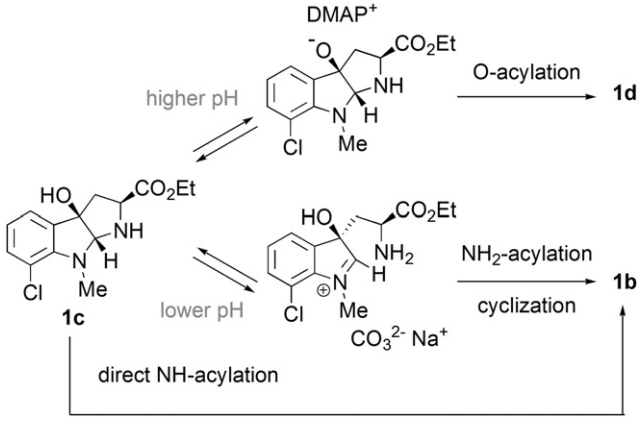
Interestingly the use of a weaker base, such as sodium bicarbonate in a biphasic chloroform–water system led to the almost quantitative protection of the NH group exclusively yielding **1b** (Scheme 4). The structure of **1b** was further confirmed by an independent synthesis following the sequence depicted in the same Scheme 4.

The surprising low reactivity of the NH group probably results from the combination of an anomeric effect n_{NH}/σ^{*}_{C-N} and the presence of electron-withdrawing groups (–NAr, COOEt) on the carbon atoms carried by the NH group. The formation of the *N*-protected compound **1b** at lower pH probably resulted from a lower concentration of reactive alkoxide resulting from the



Scheme 4. *N*-selectivity in the reaction of **1c** with Boc-anhydride.

deprotonation of the tertiary alcohol. Lower pH could also favour the opening of the pyrrolidine ring (C–N cleavage) leading to a primary amine, which would then undergo a facile acylation followed by a ring closure (Scheme 5).



Scheme 5. Possible pathways for the selective formation of **1d** and **1b**.

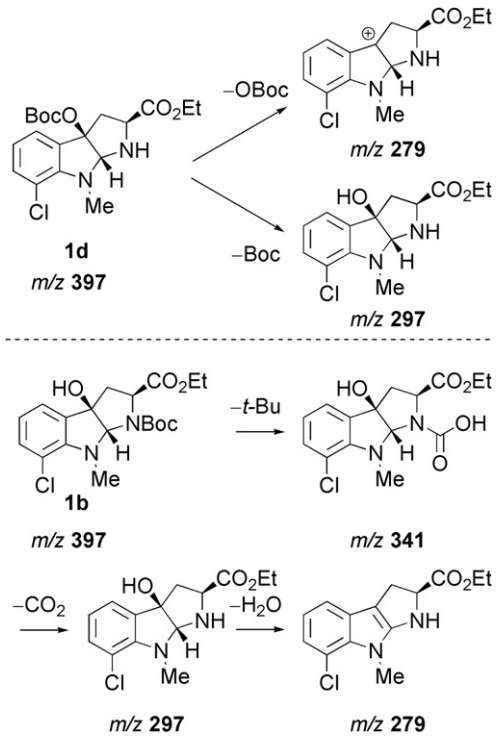
1D NMR (^1H, ^{13}C, DEPT) and 2D NMR (COSY, HMQC) analyses confirmed the structural backbone of **1b** and **1d**, but did not allow to determine the exact position of the Boc group (due to weak correlation in HMBC experiment). On the other hand, MS and MS/MS analyses allowed the full structure elucidation of **1b** and **1d** by showing different fragmentation pathways for the two isomers (Scheme 6).

MS fragmentation of **1d** showed mainly two peaks, characteristic for the loss of Boc (m/z=297) and *O*-Boc (m/z=279) fragments. For compound **1b**, a peak corresponding to the loss of *tert*-butyl group (m/z=341) was also observed. Fragmentation path of this peak (m/z=341), analyzed by MS/MS experiment, gave the two corresponding fragments, typical for the loss of CO_2 (m/z=297) and then H_2O (m/z=279). The loss of *tert*-butyl is characteristic of carbamates.

The peaks at m/z=297 and m/z=279 present in both MS spectra resulted of two different fragmentation pathways as confirmed by MS/MS experiments. X-ray diffraction analyses of crystals **1b** and **1d** confirmed these structural assignments (Fig. 2).

2.2. Oxidation and Meisenheimer rearrangement of pyrroloindoles

The oxidation of *N*-methyl-3-hydroxy-7-chloropyrroloindoline ethyl ester **1c** with *m*-CPBA yielded *a mixture* of Meisenheimer



Scheme 6. Fragmentation pattern of **1d** and **1b**.

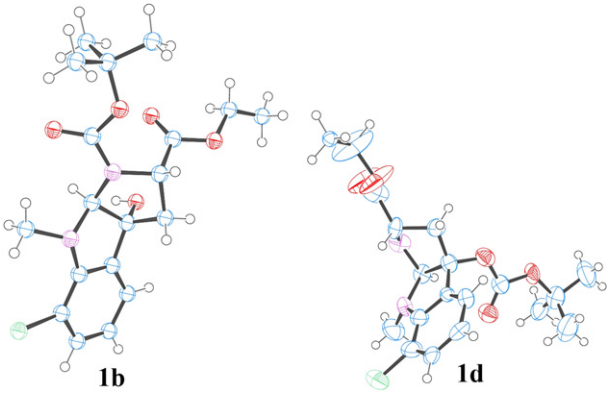
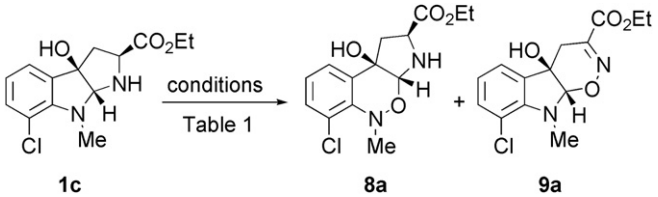


Fig. 2. ORTEP diagrams of **1b** and **1d**.[6]

rearranged products **8a** and **9a** in 30% and 24%, respectively (Scheme 7, Table 1, entry 1).



Scheme 7. Oxidation of **1c**.

This was rather surprising in as much as Baldwin et al. had claimed that hydroxypyrroloindoline methyl ester **1a** (no chlorine atom on the aromatic ring) gave a *single* product related to **8a** resulting from the insertion of oxygen into the indoline ring (see Scheme 1).[3] On the other hand, geneserine **4**, which has a hexahydro-1,2-oxazino-[5,6-*b*]-indole structure related to **9a** had been

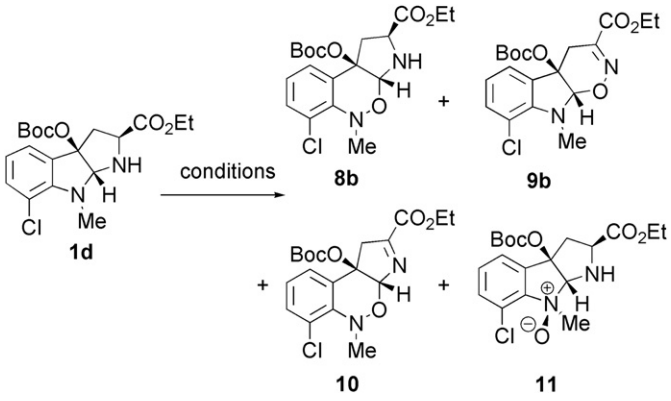
Table 1
Oxidation of **1c**

Entry	Conditions: reagent (equiv)	**8a**[a] (%)	**9a**[a] (%)
1	*m*-CPBA (1.9), −10 °C, CH_2Cl_2, 8 h	30	24
2	*m*-CPBA (1.5), $NaHCO_3$ (2.4), −10 °C, CH_2Cl_2, 7 h	15	23
3	dry *m*-CPBA (4), $KHCO_3$ (4), 0 °C, CH_2Cl_2, 15 h	41	31
4	*m*-CPBA (1.6+0.2), 0 °C, degassed CH_2Cl_2, 24 h	50	37

[a] Pure isolated products.

obtained by oxidation of physostigmine **3** (see Scheme 2). This indicates that subtle structural differences can have a significant impact on the course of the rearrangement. We thus decided to explore the influence of the experimental conditions on the selectivity of the oxidation-rearrangement sequence (Table 1). The use of 2.4 equiv of sodium bicarbonate at −10 °C for 7 h led to a lower yield of rearranged products (entry 2). On the other hand, buffering the mixture by the addition of 4 equiv of potassium bicarbonate resulted in an increase of total yield and a slightly higher proportion of **8a** (entry 3). Degassing the solvent[7] was beneficial: products were formed in 87% total yield in a 1.35/1 ratio in favour of **8a** (entry 4).

We also examined the oxidation of the *O*-Boc-protected *N*-methyl-3-hydroxy-7-chloropyrroloindoline ethyl ester **1d** (Scheme 8, Table 2). In dichloromethane at 0 °C in the presence of potassium bicarbonate, the oxidation was slow but gave a satisfactory yield of rearranged products **8b** and **9b** (Table 2, entry 1). The selectivity in favour of **8b** was slightly higher than with the unprotected compound **1c**. As expected from previous studies on the Meisenheimer rearrangement,[7a,8] the oxidation went much faster in a more polar solvent such acetonitrile. The starting material **1d** had completely disappeared after 30 min (entry 2). However, a significant amount of *N*-oxide **11** was observed. The amount of **11** further increased when lowering the temperature (entry 3). In the absence of potassium bicarbonate, we also observed the formation of **10** (17%) resulting from the oxidation of the pyrrolidine nitrogen of **8b** followed by elimination of one water molecule (entry 4). Both **10** and **11** were not observed in degassed acetonitrile (entry 5).



Scheme 8. Oxidation and Meisenheimer rearrangement of **1d**.

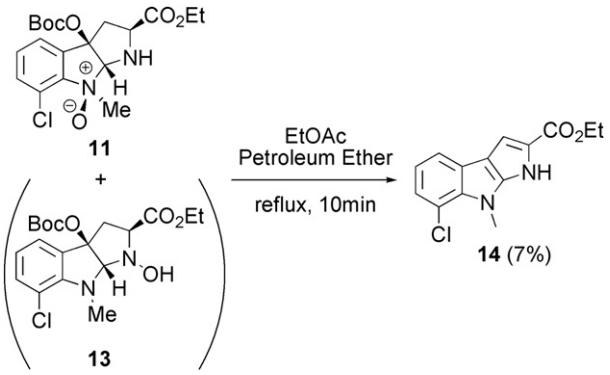
Actually heating compound **11** in ethyl acetate/petroleum ether gave a small amount (7%) of the fully aromatized compound **14** together with unidentified decomposition products (Scheme 9). Starting material **11** was recovered in 63% yield. Compound **14** probably resulted from the elimination of water from a small amount of **13** contaminating **11**.

The oxidation of the Boc-protected compounds **1b** and **1e** was also examined (Scheme 10), which led to the formation of *N*-oxides **12a** and **12b**. None of these *N*-oxides gave the corresponding Meisenheimer rearrangement products upon heating, but instead complex mixtures of unidentified products. However, treatment of

Table 2
Oxidation of **1d**

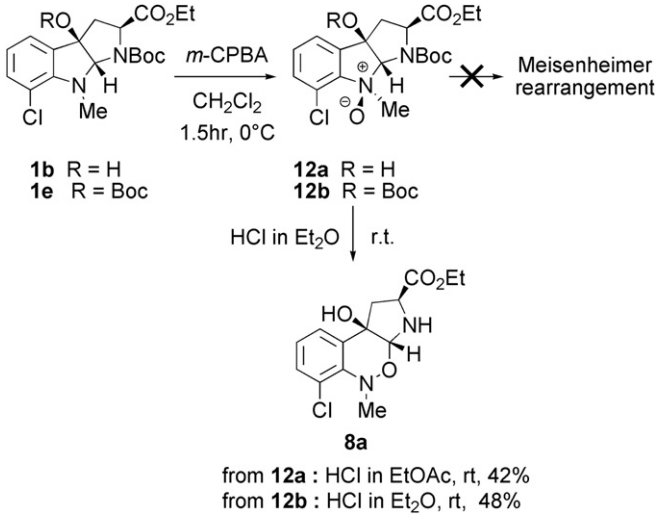
Entry	Conditions: reagent (equiv)	**8**[a] (%)	**9b**[a] (%)	**10**[a] (%)	**11**[a] (%)
1	dry *m*-CPBA (1.8), $KHCO_3$ (4) 0 °C, CH_2Cl_2, 15 h	55	16	—	—
2	*m*-CPBA (1.2), $KHCO_3$ (4), 0 °C, CH_3CN, 0.5 h	36	16	—	24
3	*m*-CPBA (1), $KHCO_3$ (4), −20 °C, CH_3CN, 3 h	52	—	—	40
4	*m*-CPBA (1), −20 °C, CH_3CN, 3 h	34	9	17	23
5	*m*-CPBA (1.6), $KHCO_3$ (4), −20 °C, degassed CH_3CN, 2 h	48	21	—	—

[a] Pure isolated products.



Scheme 9. Attempt of crystallization of **11**.

both **12a** and **12b** with HCl in ethyl acetate or diethyl ether to cleave the Boc protecting group led to the pyrrolobenzoxazine derivative, which was identical to the product **8a** obtained from the Meisenheimer rearrangement of **1c**. The structure of **8a** was confirmed by X-ray diffraction analyses. The formation of *N*-oxide **12a** had not been observed by Barrett et al.[2] because they treated the reaction mixture with HCl in ethyl acetate immediately after work-up.



Scheme 10. Oxidation of Boc-protected *N*-methyl-3-hydroxy-7-chloropyrroloindoline ethyl ester **1b** and **1e**.

2.3. Structure determination of the oxidation products

Great attention was paid to the structural analysis of the oxidation products after purification by column chromatography. In addition to ^1H and ^{13}C NMR spectroscopy, we extensively used mass spectrometry. Atmospheric Pressure Chemical Ionization (APCI) was found particularly useful for the identification of *N*-oxides **11** and **12a**,**b**.[9] from the rearranged products that normally exhibit the same *m*/*z* values. Under these mild conditions, fragmentation of *N*-oxides showed the characteristic cleavage of a single oxygen atom (Fig. 3). In the case of rearranged products, such fragment was not detected.

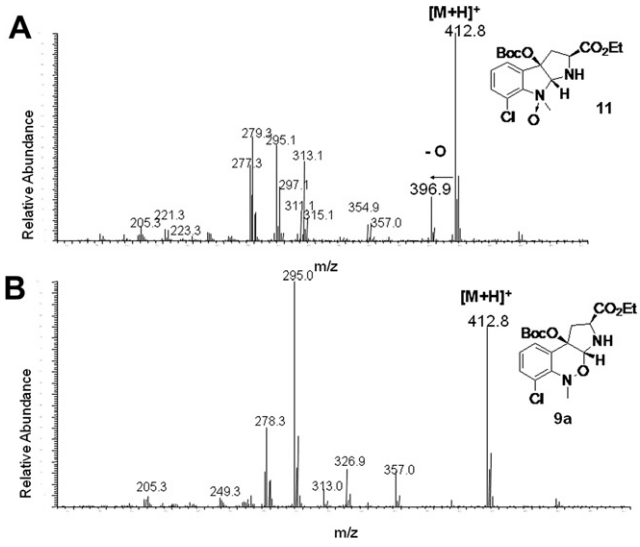
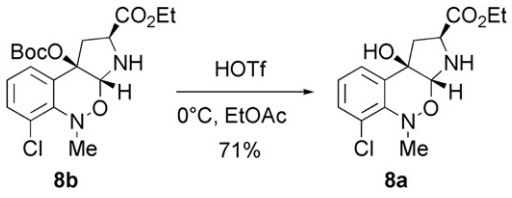


Fig. 3. APCI spectra of **11** (spectrum A) and **8b** (Spectrum B).

We also correlated structures of **8a** and **8b** (Scheme 11).



Scheme 11. Boc removal of **8b** in order to confirm the structure of **8a** previously obtained during the oxidation of **1c**.

Finally, single crystals obtained from from **8a**, **8b**, **9a**, **12a** and **14** were submitted to X-ray diffraction analyses, which confirmed the proposed structures (Fig. 4).

3. Conclusions

Our synthetic studies have revealed an unusual selectivity profile in the Boc protection of 3-hydroxypyrroloindoles. We have indeed shown that subtle modifications of the experimental conditions allowed to selectively protect the tertiary alcohol or the secondary amine group. We have also shown that the oxidation and Meisenheimer rearrangement of 3-hydroxypyrroloindole **1c** carrying a chlorine atom on the aromatic ring was not selective in contrast with earlier observations on the unsubstituted 3-hydroxypyrroloindole. Products resulting from the insertion of an oxygen atom in either of the five-membered rings have been isolated and fully characterized. Also, in some cases we have been able to isolate the intermediate *N*-oxide **11** and **12a**,**b** resulting from the selective oxidation of the tertiary amine group. The rearrangement of the *N*-oxide requires the assistance of lone pair from the neighbouring nitrogen atom: when this nitrogen was protected by a Boc group as in **12a**,**b**, the *N*-oxide was stable. However acid treatment removed the Boc group allowing the rearrangement to occur. We believe that these results have also synthetic value since

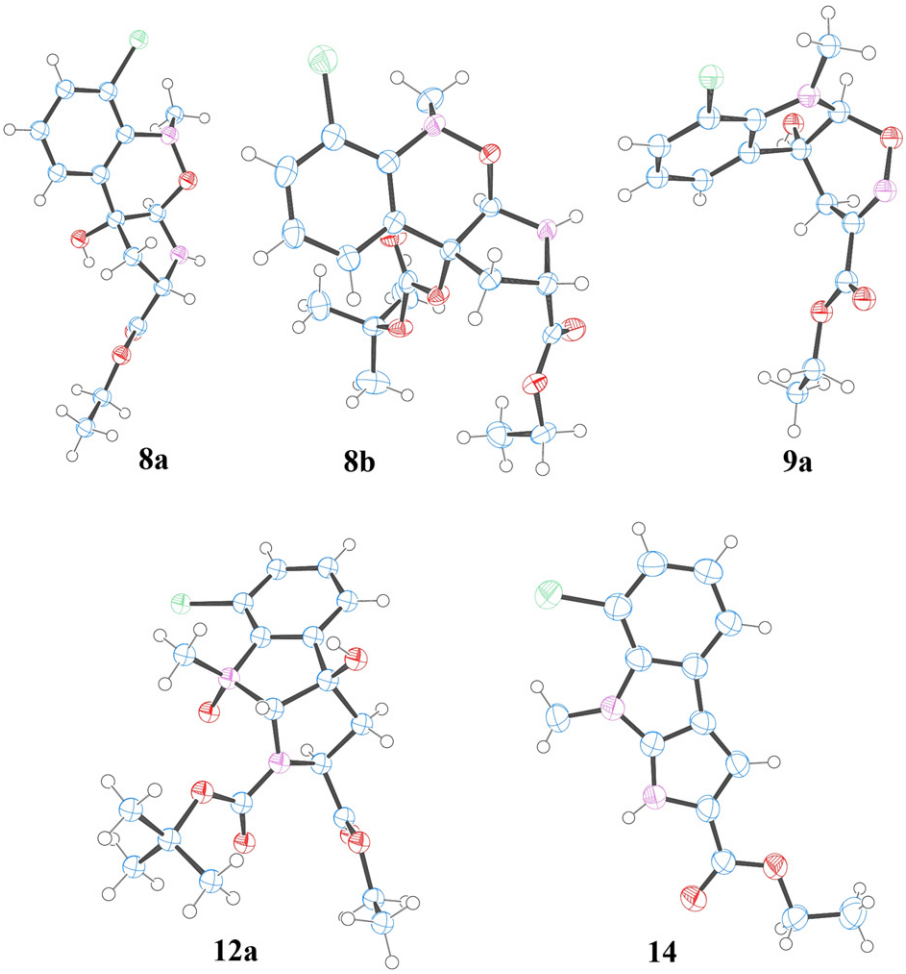


Fig. 4. Ortep diagrams of **8a**, **8b**, **9a**, **12a** and **14**.[6]

the manipulation of O versus N protection combined with the oxidation-Meisenheimer rearrangement sequence allows the preparation of useful quantities of both rearranged structures **8a** and **9a**.

4. Experimental

4.1. General methods

All manipulations were performed under a dry argon atmosphere. Glassware was flame-dried prior to use. Anhydrous CH_2Cl_2 was obtained from distillation over CaH_2. Unless otherwise described, all other materials were obtained from commercial suppliers and used without further purification. *N*-methyl-3-hydroxy-7-chloropyrroloindoline was provided by Syngenta Crop Protection. Enantiomeric purity was 85% as shown by chiral HPLC (using a CHIRALPAK®IA 5 μm-250×50 mm column, eluting with acetonitrile at a flow rate of 120 ml/min at 25 °C. Retention time isomer A, 4.39 min; Isomer B, 7.5 min).

Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silicagel plates ($60F_{254}$) with UV light for detection and *p*-anisaldehyde, ceric-molybdate or potassium permanganate solution and heat as developing agents. E. Merck silicagel (60, particle size 0.040–0.063 mm) was used for flash chromatography.

NMR spectra were recorded with Bruker 300 MHz or 400 MHz instruments fitted with a QNP probe $^{13}C/^{19}F/^{31}P/^{1}H$ and calibrated with residual non-deuterated solvent as an internal reference. Chemical shifts are reported in parts per million downfield from the internal reference. The following abbreviations are used for the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. When possible, ^{1}H and ^{13}C signals were assigned (using an arbitrarily selected numbering) mostly on the basis of distortion enhancement by polarization transfer (DEPT) and 2D-NMR (COSY, HMQC, HMBC) experiments. Due to the co-existence of rotamers, some ^{1}H and ^{13}C signals are doubled. The two chemical shifts are given, and when possible, the rotamer signals were differentiated from each other.

Melting points were measured on Büchi Melting Point B-540 apparatus and were uncorrected.

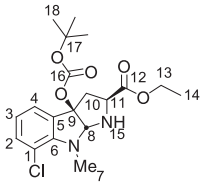
Optical rotation values were measured on a KRUSS P3001 Electronic polarimeter. Concentrations *c* are given in grams for 100 mL of solution. Temperature, concentration and solvent are specified for each compound.

High resolution mass spectra (HRMS) were recorded with a WATERS ESI-TOF LCT Premier spectrometer under electrospray (ESI) conditions. MS and MS/MS analysis were performed on an electrospray ionization-ion trap mass spectrometer LCQ Advantage (Thermo Fisher). The spectrometer was operated in the positive electrospray mode. For ESI-MS experiment each compound was dissolved in methanol and was introduced into the mass spectrometer by direct infusion (10 μl/min) using a syringe pump. The spray voltage was set to 4.5 kV, the capillary temperature was 200 °C, and the capillary voltage was 10 V. MS/MS spectra were

obtained by means of collision-induced dissociation (CID) in the ion-trap, using a normalized collision energy set at 35% of the instrument scale. For APCI experiment the infused solution was mixed with a mobile phase (MeOH/0.1% formic acid) delivered by a Surveyor HPLC system (Thermo Fisher) using a flow rate of 0.5 ml/min. Operating conditions of APCI source were: vaporizer temperature 450 °C, capillary temperature 200 °C, capillary voltage 10 V, corona current 5 μA, sheat gas 60 (arbitrary unit) and auxiliary gas 20 (arbitrary unit). Nitrogen was used for nebulizer gas and auxiliary gas.

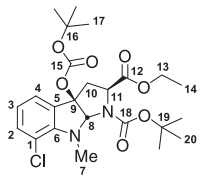
4.2. *O*-Boc protection of 1c: synthesis of 1d and 1e (Scheme 3)

Compound **1c** (1.028 g, 3.46 mmol) was dried in vacuo for 5 min in a 50 mL flask. Then, 4-DMAP (42 mg, 0.346 mmol, 10 mol %) and Boc_2O (1.13 g, 5.19 mmol, 1.5 equiv) and dry acetonitrile (31.5 mL, 0.11 M) were added under argon atmosphere. The suspension was stirred at rt. After 30 min, the reaction mixture became homogeneous and stirring was maintained for 12 h (monitoring by TLC) at rt. The reaction mixture was concentrated (around half of solvent has evaporated) then CH_2Cl_2 (15 mL) was added followed by 0.1 M HCl (7 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were washed twice with brine, then with water and finally dried over Na_2SO_4. Filtration and evaporation of the solvent gave a residue, which was purified through silicagel (petroleum ether/EtOAc 7:1 then 5:1) to give a first fraction **1e** as an oil (428 mg, 25%) and a second fraction **1d** as a white solid (984 mg, 72%).



1d

R_f=0.45 (PE/EA=1:1—$KMnO_4$); mp 81–83 °C; $[\alpha]_D^{24}$ −57.5 (*c* 2.8 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.28 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 7.12 (d, ^3J(H,H)=7.2 Hz, 1H, **4**), 6.66 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.12 (s, 1H, **8**), 4.16 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 3.63 (dd, ^3J(H,H)=9.9, 6.3 Hz, 1H, **11**), 3.30 (br s, 1H, **15**), 3.24 (s, 3H, **7**), 2.66 (dd, ^3J(H,H)=12.6 and 6.3 Hz, 1H, part of AB system, **10a**), 2.50 (dd, ^3J(H,H)=12.6, 9.9 Hz, 1H, part of AB system, **10b**), 1.38 (s, 9H, **18**), 1.23 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=173.8 (**12**), 153.6 (**16**), 149.4 (**6**), 133.8 (**4**), 133.1 (**5**), 124.9 (**2**), 120.7 (**3**), 115.4 (**1**), 94.8 (**8**), 91.8 (**9**), 83.6 (**17**), 62.4 (**11**), 60.2 (**13**), 46.0 (**10**), 36.7 (**7**), 28.8 (**18**), 15.4 (**14**); HRMS (MS ES$^+$, Na) calcd for $C_{19}H_{26}N_2O_5Cl$: 397.1530, found: 397.1522, Δ=2.1 ppm.

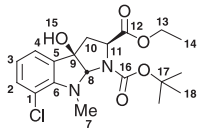


1e

R_f=0.40 (PE/EA=4:1—Ceric Ammonium Molybdate); $[\alpha]_D^{26}$ −127.1 (*c* 8.9 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.34 (d, ^3J(H,H)=7.2 Hz, 0.4H, rotamer of **2**), 7.28 (d, ^3J(H,H)=8.1 Hz, 0.4H, rotamer of **4**), 7.23 (m, 2H, **2**, **4**), 6.91 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 0.4H, rotamer of **3**), 6.85 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.61 (s, 1H, **8**), 5.44 (s, 0.4H, rotamer of **8**), 4.30–4.13 (m, 2.8H, **13**, overlapped with its rotamer), 4.05 (dd, ^3J(H,H)=7.2 and 6.9 Hz, 1H, **11**), 3.45 (s, 3H, **7**), 3.37 (s, 1.2H, rotamer of **7**), 2.78–2.52 (m, 2.8H, **10** overlapped with its rotamer), 1.55 (s, 3.6H, rotamer of **20**), 1.43 (s, 9H, **20**), 1.39 (s, 3.6H, rotamer of **17**), 1.38 (s, 9H, **17**), 1.30 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=173.5 (**12**), 172.5 (rotamer of **12**), 156.4 (**18**), 156.0 (rotamer of **18**), 153.4 (**15**), 149.8 (rotamer of **15**), 151.0 (rotamer of **6**), 149.8 (**6**), 134.5 (**5**), 134.0 (rotamer of **5**), 133.9 (rotamer of **4**), 133.7 (**4**), 124.3 and 123.9 (rotamers of **2** and **3**), 123.2 and 123.1 (**2**, **3**), 119.6 (rotamer of **1**), 118.7 (**1**), 93.1 (rotamer of **8**), 92.4 (**8**), 92.1 (**9**), 91.5 (rotamer of **9**), 84.2 (**16** overlapped with its isomer), 82.9 (rotamer of **19**), 82.2 (**19**), 62.9 (**13**), 62.5 (rotamer of **13**), 61.3 (**11**), 60.8 (rotamer of **11**), 43.4 (**10**), 42.6 (rotamer of **10**), 41.7 (rotamer of **7**), 41.4 (**7**), 29.6 (rotamer of **20**), 29.3 (**20**), 28.8 (**17** overlapped with its rotamer), 15.5 (**14**), 15.4 (rotamer of **14**); HRMS (MS ES$^+$, Na) calcd for $C_{24}H_{34}N_2O_7Cl$: 497.2049, found: 497.2055, Δ=1.2 ppm.

4.3. *N*-Boc protection of 1c: synthesis of 1b (Scheme 4)

4.3.1. Method A. To a solution of **1c** (164 mg, 0.55 mmol) in a mixture chloroform/water 1:1 (3.4 mL), were added $NaHCO_3$ (194 mg, 2.31 mmol, 4.2 equiv) then Boc_2O (253 mg, 1.16 mmol, 2.1 equiv). After 40 h at rt, the reaction was not complete. More $NaHCO_3$ (46 mg, 0.55 mmol, 1 equiv) and Boc_2O (120 mg, 0.55 mmol, 1 equiv) were added and the reaction mixture was stirred for another 30 h. Then, more chloroform was added, the organic layer was separated and the aqueous layer was extracted three times by $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified through silicagel (petroleum ether/ethyl acetate 3:1 then 2.5:1) to yield **1b** as a white solid (206 mg, 0.52 mmol, 94%).

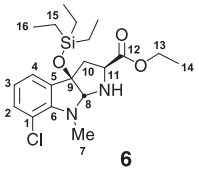


1b

R_f=0.55 (PE/EA=1:1—Ceric Ammonium Molybdate); $[\alpha]_D^{24}$ −65.6 (*c* 4 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.24 (d, ^3J(H,H)=7.2 Hz, 0.6H, rotamer of **2**, **4**), 7.16 (d, ^3J(H,H)=7.8 Hz, 2H, **2**, **4**), 6.86 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 0.3H, rotamer of **3**), 6.80 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.23 (s, 1H, **8**), 5.06 and 5.05 (2× br s, 2×0.3H, rotamers of **8** and **15**), 4.94 (br s, 1H, **15**), 4.29–4.15 (m, 2.6H, **13**, overlapped with its rotamer), 4.05 (dd, ^3J(H,H)=7.5 and 7.2 Hz, 1H, **11**), 3.37 (s, 3H, **7**), 3.31 (s, 0.9H, rotamer of **7**), 2.58–2.34 (m, 2.6H, **10** overlapped with its rotamer), 1.54 (s, 2.7H, rotamer of **18**), 1.43 (s, 9H, **18**), 1.28 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=174.2 (**12**), 173.4 (rotamer of **12**), 156.4 (**16**), 156.0 (rotamer of **16**), 149.0 (rotamer of **6**), 148.0 (**6**), 137.7 and 137.6 (**5** and its rotamer), 133.12 and 133.06 (**4** and its rotamer), 123.8 and 123.4 (rotamers of **2** and **3**), 123.3 (**2**), 122.6 (**3**), 118.9 (rotamer of **1**), 117.8 (**1**), 94.9 (**8**), 94.0 (rotamer of **8**), 87.6 (rotamer of **9**), 86.4 (**9**), 82.4 (rotamer of **17**), 81.8 (**17**), 62.7 (**13**), 62.4 (rotamer of **13**), 62.1 (**11**), 61.6 (rotamer of **11**), 44.5 (**10**), 42.8 (rotamer of **10**), 41.5 (rotamer of **7**), 40.8 (**7**), 29.6 (rotamer of **18**), 29.3 (**18**), 15.5 (**14**), 15.4 (rotamer of **14**); HRMS (MS ES$^+$, Na) calcd for $C_{19}H_{25}N_2O_5NaCl$: 419.1350, found: 419.1345, Δ=1.1 ppm.

*4.3.2. Method B. 4.3.2.1. O-TES-protection of **1c**: synthesis of **6** (Scheme 4).* Compound **1c** (50 mg, 0.17 mmol) was dried under vacuum for 20 min in a 10 mL flask, then treated with, imidazole (27.8 mg, 0.408 mmol, 2.4 equiv) and anhydrous CH_2Cl_2 (0.85 mL, 0.2 M). Then TESCl (34 μL, 0.204 mmol, 1.2 equiv) was added at 0 °C over a period of 10 min and the resulting mixture was brought to rt .

After 14 h, more CH_2Cl_2 was added; the aqueous phase was separated and extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4. Removal of the solvent left a crude residue was purified through silicagel (petroleum ether/EtOAc=6:1 then EtOAc) to yield **6** as an oil (54.4 mg, 0.13 mmol, 78%).

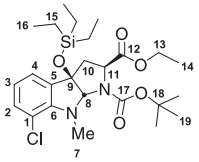


6

R_f=0.3 (Petroleum ether/EtOAc=6:1—Ceric Ammonium Molybdate); $[\alpha]_D^{23}$ −29.7 (*c* 0.6 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.17 (d, ^3J(H,H)=7.8 Hz, 1H, **4**), 7.10 (d, ^3J(H,H)=7.8 Hz, 1H, **2**), 6.69 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 4.77 (s, 1H, **8**), 4.16 (dd, ^3J(H,H)=7.2 and 2.7 Hz, 1H, part of AB system, **13**), 4.13 (dd, ^3J(H,H)=7.2 and 2.7 Hz, 1H, part of AB system, **13**), 3.57 (dd, ^3J(H,H)=8.7 and 6.6 Hz, 1H, **11**), 3.23 (s, 3H, **7**), 2.47 (dd, ^3J(H,H)=12.3 and 6.6 Hz, 1H, part of AB system, **10a**), 2.36 (dd, ^3J(H,H)=12.3 and 8.7 Hz, 1H, part of AB system, **10b**), 1.23 (t, ^3J(H,H)=7.2 Hz, 3H, **14**), 0.85 (t, ^3J(H,H)=7.8 Hz, 9H, **16**), 0.46 (q, ^3J(H,H)=7.8 Hz, 6H, **15**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=174.8 (**12**), 148.1 (**6**), 136.7 (**5**), 133.4 (**4**), 124.8 (**2**), 120.4 (**3**), 115.2 (**1**), 93.7 (**9**), 90.1 (**8**), 62.4 (**13**), 60.7 (**11**), 48.8 (**10**), 36.0 (**7**), 15.5 (**14**), 8.1 (**16**), 7.5 (**15**); HRMS (MS ES$^+$, Na) calcd, for $C_{20}H_{32}N_2O_3SiCl$: 411.1871, found: 411.1851, Δ=4.8 ppm.

4.4. *N*-Boc protection of 6: synthesis of 7 (Scheme 4)

Anhydrous THF (0.2 mL, 0.8 M) and *S*-Boc-2-mercapto-4,6-dimethylpyrimidine (Boc-S) (42 mg, 0.173 mmol, 1.3 equiv) were added to **6** (54.4 mg, 0.133 mmol), which had been dried under vacuum for 5 min. The mixture was refluxed for 21 h, then an additional amount of Boc-S (16 mg, 0.066 mmol, 0.5 equiv) and THF (0.2 mL) were added the reaction mixture was refluxed for another 12 h. Removal of the solvent left a residue, which was dissolved in EtOAc and then washed with 3 mL of a 1% aqueous solution of citric acid (pH ∼2–3). The organic layer was washed with 5% aqueous solution of $NaHCO_3$ (3 mL, pH=8) and brine (pH=7) and finally dried over Na_2SO_4. After filtration and concentration, the residue was purified through silicagel (petroleum ether/EtOAc 10:1 then 6:1) to give **7** as an oil (43.1 mg, 0.084 mmol) in 63% yield.



7

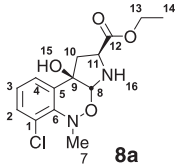
R_f=0.60 (Petroleum ether/EtOAc=6:1—Ceric Ammonium Molybdate); $[\alpha]_D^{23}$ −58.1 (*c* 2 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.28 (d, ^3J(H,H)=7.8 Hz, 0.6H, rotamer of **2**, **4**), 7.22 (d, ^3J(H,H)=7.8 Hz, 2H, **2**, **4**), 6.90 (d, ^3J(H,H)=7.8 Hz, 0.3H, rotamer of **3**), 6.84 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.24 (s, 1H, **8**), 5.11 (s, 0.3H, rotamers of **8**), 4.19 (q, ^3J(H,H)=6.9 Hz, 2H, **13**, overlapped with its rotamer), 4.01 (dd, ^3J(H,H)=7.5 and 7.2 Hz, 1H, **11**), 3.44 (s, 3H, **7**), 3.38 (s, 0.9H, rotamer of **7**), 2.62 (dd, ^3J(H,H)=12.9 and 7.5 Hz, 1H, part of AB system, **10a**), 2.41 (dd, ^3J(H,H)=12.9, 7.2 Hz, 1H, part of AB system, **10b**), 1.54 (s, 2.7H, rotamer of **18**), 1.42 (s, 9H, **18**), 1.29 (t, ^3J(H,H)=7.2 Hz, 3H, **14**), 1.24 (t, ^3J(H,H)=6.9 Hz, 0.9H, rotamer of **14**), 0.88 (t, ^3J(H,H)=7.8 Hz, 11.7H, **16** overlapped with its rotamer), 0.50 (q, ^3J(H,H)=7.8 Hz, 7.8H, **15** overlapped with its rotamer); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=173.4 (**12**), 172.5 (rotamer of **12**), 156.4 (**17**), 155.8 (rotamer of **17**), 148.9 (rotamer of **6**), 148.1 (**6**), 136.83 and 136.76 (**5** and its rotamer), 133.6 (**4** and its rotamer), 124.3 (rotamer of **2**), 123.9 (**2**), 123.2 (rotamer of **3**), 122.5 (**3**), 119.1 (rotamer of **1**), 118.0 (**1**), 94.4 (**8**), 93.7 (rotamer of **8**), 89.3 (rotamer of **9**), 88.3 (**9**), 82.4 (rotamer of **18**), 81.9 (**18**), 62.6 (**13**), 62.3 (rotamer of **13**), 61.6 (**11**), 61.4 (rotamer of **11**), 46.3 (**10**), 44.2 (rotamer of **10**), 41.7 (rotamer of **7**), 41.2 (**7**), 29.6 (rotamer of **19**), 29.3 (**19**), 15.6 (**14**), 15.5 (rotamer of **14**), 8.0 (**16**), 7.5 (**15**); HRMS (MS ES$^+$, Na) calcd, for $C_{25}H_{40}N_2O_5$-SiCl: 511.2395, found: 511.2387, Δ=1.6 ppm.

4.5. Cleavage of TES: synthesis of 1b (Scheme 4)

TBAF (1 M solution in THF, 93 μL, 93 μmol, 1.1 equiv) was added to a solution of **7** (43.1 mg, 0.084 mmol) in anhydrous THF (0.85 mL, 0.1 M) at 0 °C and the solution was stirred at 0–5 °C for 1.5 h. Then CH_2Cl_2 and brine were added at 0 °C and the biphasic mixture was stirred for 20 min. The aqueous layer was extracted twice by CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4. After filtration and removal of the solvent, the residue was purified through silicagel using (petroleum ether/EtOAc 2:1) to quantitatively yield **1b** as an off-white solid (33 mg, 0.084 mmol).

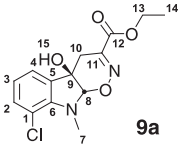
4.6. Oxidation of 1c: synthesis of 8a and 9a (Scheme 7)

To a solution of **1c** (87 mg, 0.29 mmol) in degassed CH_2Cl_2 (3.5 mL) at 0 °C under argon, was added a solution of *m*-CPBA (70% in H_2O, 114 mg, 0.46 mmol, 1.6 equiv) in degassed CH_2Cl_2 (0.5 mL) dropwise over 40 min and the reaction mixture was stirred at −10 °C. After 16 h, a new portion of *m*-CPBA (15 mg, 0.06 mmol, 0.2 equiv) was added to the reaction mixture. After 8 h, the reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$ then with brine. The aqueous layer was extracted by CH_2Cl_2, and the combined organic layer was dried over Na_2SO_4. After filtration and concentration, the crude resdue was purified over silicagel to yield two products in almost 1:1 ratio. The first fraction was the imine **9a** (34 mg, 37% yield). The second compound was the compound **8a** (45 mg, 50% yield).



8a

R_f=0.4 (Petroleum ether/EtOAc 1:1—$KMnO_4$); mp 116–118 °C; $[\alpha]_D^{23}$ +8.3 (*c* 1 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.48 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 7.22 (d, ^3J(H,H)=8.1 Hz, 1H, **4**), 7.04 (dd, ^3J(H,H)=8.1, 7.8 Hz, 1H, **3**), 5.21 (br s, 1H, **8**), 4.14 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 3.87 (m, 1H, **11**), 3.20 (s, 3H, **7**), 2.47 (d, ^3J(H,H)=13.2 Hz, 1H, **10**, part of ABX system), 2.25 (dd, ^3J(H,H)=13.2, 9.3 Hz, 1H, **10**, part of ABX system), 1.22 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=176.7 (**12**), 146.0 (**6**), 136.1 (**5**), 130.8 (**4**), 128.4 (**2**), 126.3 (**3**), 124.6 (**1**), 87.3 (**8**), 77.2 (**9**), 62.5 (**13**), 59.8 (**11**), 43.6 (**10**), 43.1 (**7**), 15.5 (**14**); HRMS (MS ES$^+$, Na) calcd, for $C_{14}H_{18}N_2O_4Cl$: 313.0955, found: 313.0955, Δ=0.0 ppm (Method A); HRMS (MS ES$^+$, Na) calcd for $C_{14}H_{18}N_2O_4Cl$: 313.0955, found: 313.0955, Δ=0 ppm.



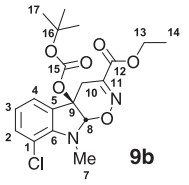
9a

R_f=0.7 (Petroleum ether/EtOAc 1:1—$KMnO_4$); mp 105–107 °C; $[\alpha]_D^{23}$ −28.1 (*c* 1 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6,

TMS): δ=7.16 (d, ^3J(H,H)=7.5 Hz, 1H, **4**), 7.05 (d, ^3J(H,H)=7.8 Hz, 1H, **2**), 6.65 (dd, ^3J(H,H)=7.8, 7.5 Hz, 1H, **3**), 5.37 (br s, 1H, **15**), 5.22 (s, 1H, **8**), 4.22–4.08 (m, 2H, **13**), 3.32 (s, 3H, **7**), 3.29 (d, ^3J(H,H)=15.0 Hz, 1H, **10**, part of AB system), 2.63 (d, ^3J(H,H)=15.0 Hz, 1H, **10**, part of AB system), 1.19 (t, ^3J(H,H)=6.9 Hz, 3H, **14**). ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=163.7 (**12**), 162.2 (**11**), 147.8 (**6**), 136.1 (**5**), 133.6 (**2**), 124.3 (**4**), 121.7 (**3**), 114.7 (**1**), 104.7 (**8**), 80.5 (**9**), 63.5 (**13**), 36.0 (**7**), 32.7 (**10**), 15.2 (**14**); HRMS (MS ES$^+$, Na) calcd for $C_{14}H_{15}N_2O_4$NaCl: 333.0618, found: 333.0617, Δ=0.3 ppm.

4.7. *O*-Boc protection of 9a: synthesis of 9b

To a solution of **9a** (25 mg, 79.5 μmol), in CH_3CN (0.8 mL, 0.1 M) was added, at 0 °C, Boc_2O (26 mg, 0.12 mmol, 1.5 equiv) and 4-DMAP (1 mg, 8 μmol, 10 mol %). The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction monitored by TLC, the reaction mixture was diluted in CH_2Cl_2, then washed with a saturated aqueous solution of ammonium chloride till pH=7. The separated aqueous layer was extracted twice by CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified through silicagel to yield **9b** (14.6 mg, 35.5 μmol, 45%).



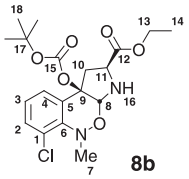
9b

The ^{1}H and ^{13}C NMR spectra were identical to the one of compound **9b** obtained during oxidation of **1d**.

4.8. Oxidation of 1d: synthesis of compounds 8b, 9b, 10, 11 (Scheme 8)

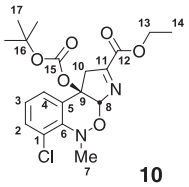
4.8.1. Method A (Table 2, entry 4). To a solution of **1d** (233 mg, 0.588 mmol) in CH_3CN (5.8 mL), was added at −20 °C, a solution of *m*-CPBA (70% in H_2O, 145 mg, 0.588 mmol, 1 equiv) in CH_3CN (1.2 mL) over 20 min (62 μL/min). The reaction mixture was stirred overnight at −20 °C. After completion of the reaction (monitoring by TLC), the reaction mixture was diluted with CH_2Cl_2 (15 mL) and treated with a saturated aqueous solution of $Na_2S_2O_3$ at 0 °C for 15 min. The organic layer was washed with water (pH=7). The combined aqueous phases were extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified through silicagel (petroleum ether/diethyl ether, 3:1; 2:1 then 1:1). The first fraction contained **9b** as an oil (22.8 mg, 57.5 μmol, 9%), the second fraction contained **11** as an oil (54.9 mg, 0.133 mmol, 23%), the third fraction contained **8b** as an off-white solid (81.4 mg, 0.20 mmol, 34%), and the fourth fraction contained **10** as an oil (40.8 mg, 0.10 mmol, 17%).

4.8.2. Method B (Table 2, entry 5). To a solution of **1d** (237 mg, 0.59 mmol) and $KHCO_3$ (238 mg, 2.38 mmol, 4 equiv) in degassed CH_3CN (10 mL) was added at −20 °C, a solution of *m*-CPBA (77% solution in H_2O, 165.2 mg, 0.95 mmol, 1.6 equiv) in CH_3CN (2.5 mL) over 1 h (43 μL/min). During addition, the solution turned pink then became slowly yellow after complete addition (2 h). Then, the reaction mixture was diluted in CH_2Cl_2 (15 mL) and treated with a saturated aqueous solution of $Na_2S_2O_3$ at 0 °C for 20 min. The separated organic layer was washed with water (pH=7). The combined aqueous phases were extracted by CH_2Cl_2 three times. Combined organic layers were dried over Na_2SO_4. After filtration and concentration, the crude mixture was purified through silicagel using petroleum ether/diethyl ether=3:1, 2.5:1 and 2:1. The first fraction contained **9b** as an oil (51.3 mg, 0.125 mmol, 21%) and the second fraction contained the compound **9a** as an off-white solid (118 mg, 0.285 mmol, 48%).



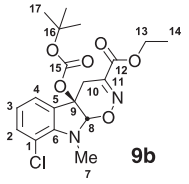
8b

R_f=0.4 (Petroleum ether/EtOAc 1:1—$KMnO_4$); mp 92–94 °C; $[\alpha]_D^{23}$ −45.8 (*c* 5.4 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.24 (d, ^3J(H,H)=7.5 Hz, 1H, **4**), 7.17 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 6.75 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.14 (br s, 1H, **8**), 4.14 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 3.53 (dd, ^3J(H,H)=11.1 and 6.0 Hz, 1H, **11**), 3.35 (s, 3H, **7**), 2.73 (dd, ^3J(H,H)=12.3 and 11.4 Hz, 1H, **10**, part of ABX system), 2.45 (dd, ^3J(H,H)=12.6 and 5.7 Hz, 1H, **10**, part of ABX system), 1.37 (s, 9H, **18**), 1.22 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=171.5 (**12**), 153.6 (**15**), 150.0 (**6**), 134.6 (**5**), 133.7 (**2**), 124.0 (**4**), 122.1 (**3**),116.5 (**1**), 97.7 (**8**), 90.8 (**9**), 83.9 (**17**), 66.7 (**11**), 62.2 (**13**), 41.7 (**10**), 40.3 (**7**), 28.8 (**18**), 15.4 (**14**); HRMS (MS ES$^+$, Na) calcd for $C_{19}H_{25}N_2O_6$NaCl: 435.1299, found: 435.1281, Δ=4.1 ppm.



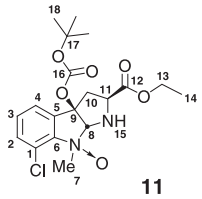
10

R_f=0.15 (Petroleum ether/Et_2O 1:1.5—Ceric Ammonium Nitrate); $[\alpha]_D^{23}$ −172.2 (*c* 1 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.49 (d, ^3J(H,H)=7.5 Hz, 1H, **4**); 7.29 (d, ^3J(H,H)=7.8 Hz, 1H, **2**), 6.89 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.77 (s, 1H, **8**), 4.19 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 3.62 (d, ^3J(H,H)=18.6 Hz, 1H, **10**, part of ABX system), 3.56 (s, 3H, **7**), 3.55 (d, ^3J(H,H)=18.6 Hz, 1H, **10**, part of ABX system), 1.42 (s, 9H, **17**), 1.24 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=160.3 (**12**), 153.4 (**15**), 148.3 (**6**), 134.8 (**2**), 133.5 (**5**), 131.3 (**11**), 125.5 (**4**),123.4 (**3**), 117.6 (**1**), 103.2 (**8**), 84.9 (**16**), 83.6 (**9**), 62.4 (**13**), 42.8 (**10**), 40.8 (**7**), 28.8 (**17**), 15.4 (**14**); HRMS (MS ES$^+$, Na) calcd for $C_{19}H_{23}N_2O_6$NaCl: 433.1142, found: 433.1162, Δ=4.5 ppm.



9b

R_f=0.5 (Petroleum ether/EtOAc 1:1.5—$KMnO_4$); $[\alpha]_D^{23}$ −79.7 (*c* 1.5 in chloroform); ^{1}H NMR (300 MHz, acetone-d_6, TMS): δ=7.32 (d, ^3J(H,H)=7.5 Hz, 1H, **4**), 7.17 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 6.74 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 5.65 (s, 1H, **8**), 4.28–4.14 (m, 2H, **13**), 3.52 (d, ^3J(H,H)=Hz, 1H, **10**, part of AB system), 3.40 (s, 3H, **7**), 2.97 (d, ^3J(H,H)=15.0 Hz, 1H, **10**, part of AB system), 1.38 (s, 9H, **17**), 1.24 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=163.4 (**12**), 162.8 (**15**), 152.9 (**11**), 149.5 (**6**), 134.6 (**2**), 132.0 (**5**), 125.0 (**4**), 121.9 (**3**), 115.1 (**1**), 101.8 (**8**), 88.2 (**9**), 84.7 (**16**), 63.8 (**13**), 36.6 (**7**), 31.7 (**10**), 15.2 (**14**); HRMS (MS ES$^+$, Na) calcd, for $C_{14}H_{23}N_2O_6$NaCl: 433.1142, found: 433.1147, Δ=1.1 ppm.



11

R_f=0.5 (Petroleum ether/Et_2O 1:1.5—$KMnO_4$); $[\alpha]_D^{23}$ −80.6 (*c* 3.7 in chloroform); ^1H NMR (300 MHz, acetone-d_6, TMS): δ=7.23 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 7.17 (d, ^3J(H,H)=6.9 Hz, 1H, **4**), 6.75 (dd, ^3J(H,H)=7.8 and 7.8 Hz, 1H, **3**), 5.13 (s, 1H, **8**), 4.14 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 3.56 (dd, ^3J(H,H)=11.1, 6.0 Hz, 1H, **11**), 3.35 (s, 3H, **7**), 2.73 (t, ^3J(H,H)=11.7 Hz, 1H, part of AB system, **10a**), 2.45 (dd, ^3J(H,H)=12.6, 6.0 Hz, 1H, part of AB system, **10b**), 1.37 (s, 9H, **18**), 1.22 (s, 3H, **14**); ^{13}C NMR (75 MHz, acetone-d_6, TMS): δ=171.4 (**12**), 153.6 (**16**), 149.9 (**6**), 134.6 (**5**), 133.7 (**4**), 124.0 (**2**), 122.1 (**3**), 116.4 (**1**), 97.7 (**8**), 90.8 (**9**), 83.9 (**17**), 66.6 (**11**), 62.2 (**13**), 41.7 (**10**), 40.2 (**7**), 28.8 (**18**), 15.4 (**14**); HRMS (MS ES$^+$, Na) calcd, for $C_{19}H_{26}N_2O_6Cl$: 413.1479, found: 413.1483, Δ=0.9 ppm.

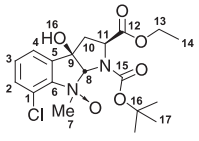
4.9. *O*-Boc-removal of 8b: access to 8a

To a solution of **8b** (21.2 mg, 51 μmol) in dry ethyl acetate (0.5 mL, 0.1 M) at 0 °C, was added triflic acid (9 μL, 0.102 mmol, 2 equiv) and the reaction mixture was stirred for 1 h. Then, a solution of 2,6-di*tert*butyl-4-methyl-pyridine (20.9 mg, 0.102 mmol, 2 equiv) in dry ethyl acetate (0.2 mL), was added at 0 °C and the mixture was stirred for 20 min. After base addition, precipitation and pink colour solution were observed. Then, the reaction mixture was concentrated at rt. The crude residue was purified through silicagel using CH_2Cl_2/acetone 30:1 then 25:1 as eluent. The first fraction contained unreacted **8b** (3.5 mg, 16%), and **8a** (11.3 mg, 36 μmol, 71%) was isolated as a second fraction.

The ^1H and ^{13}C NMR spectra were identical to the one of compound **8a** obtained during oxidation of **1c**; HRMS (MS ES$^+$, Na) calcd for $C_{14}H_{18}N_2O_4Cl$: 313.0955, found: 313.0950, Δ=1.6 ppm.

4.10. Oxidation of 1b: synthesis of 12a (Scheme 10)

To a solution of **1b** (137 mg, 0.346 mmol) in CH_2Cl_2 (2 mL, 0.17 M) was slowly added, at 0 °C, a solution of *m*-CPBA (70% solution in H_2O, 85 mg, 0.346 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 1.5 h at 0 °C. After removal of the solvent under reduced pressure at rt the residue was purified through silicagel (CH_2Cl_2/CH_3OH 95:5, 9:1, 8:1 then 7:1) to yield **12a** as an off-white solid (88.5 mg, 0.214 mmol, 62%).



12a

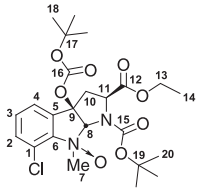
R_f=0.15 (CH_2Cl_2/CH_3OH=95:5—Ceric Ammonium Molybdate); mp 162–164 °C (decomp.); $[\alpha]_D^{22}$ −46.9 (*c* 4.9 in chloroform); ^1H NMR (300 MHz, CD_3OD, TMS): δ=7.59–7.44 (m, 3.9H, **2**, **3**, **4** and rotamers), 5.87 (br s, 1H, **8**), 5.79 (br s, 0.3H, rotamer of **8**), 4.90 (br s, 1H, **16**), 4.73 (dd, ^3J(H,H)=10.2 and 2.1 Hz, 1H, **11**), 4.29–4.24 (m, 2.6H, **13**, overlapped with its rotamer), 4.05 (s, 3H, **7**), 4.04 (s, 0.9H, rotamer of **7**), 2.67–2.59 (dd, ^3J(H,H)=14.1 and 10.2 Hz, 1.3H, **10** overlapped with its rotamer, part of ABX system), 2.40–2.35 (dd, ^3J(H,H)=14.1 and 10.2 Hz, 1.3H, **10** overlapped with its rotamer, part of ABX system), 1.60 (s, 2.7H, rotamer of **17**), 1.51 (s, 9H, **17**), 1.33 (t, ^3J(H,H)=7.2 Hz, 3.9H, **14** overlapped with its rotamer); ^{13}C NMR (75 MHz, CD_3OD, TMS): δ=173.0 (**12**), 172.6 (rotamer of **12**), 155.7 (**15**), 154.5 (rotamer of **15**), 144.5 (**6**), 144.2 (rotamer of **6**), 140.9 (**5**), 140.8 (rotamer of **5**), 134.5 (rotamer of **4**), 134.3 (**4**), 133.5 (rotamer of **2**), 133.4 (**2**), 126.1 (rotamer of **3**), 126.0 (**3**), 124.03 (rotamer of **1**), 124.00 (**1**), 102.3 (**8** overlapped with its rotamer), 85.2 and 84.7 (rotamers of **9** and **16**), 83.8 and 83.6 (**9** and **16**), 64.6 (**11**), 64.4 (rotamer of **11**), 62.7 (**13**), 62.7 (rotamer of **13**), 58.2 (**7**), 57.7 (rotamer of **7**), 43.8 (**10**), 43.3 (rotamer of **10**), 28.6 (rotamer of **17**), 28.4 (**17**), 14.6 (**14**), 14.5 (rotamer of **14**); HRMS (MS ES$^+$, Na) calcd for $C_{19}H_{26}N_2O_6Cl$: 413.1479, found: 413.1488, Δ=2.1 ppm.

4.11. Treatment of 12a with HCl: synthesis of 8a (Scheme 10)

A 1 M HCl solution in ethyl acetate (4.8 mL, 4.8 mmol, 15 equiv) was added at 0 °C to *N*-oxide **12a** (132.7 mg, 0.32 mmol) and the solution left overnight at rt. After evaporation of the solvent under vacuum at rt, the residue was dissolved in CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ was added to reach pH=8. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified through silicagel (petroleum ether/ethyl acetate 1:1) to yield compound **8a** (42.5 mg, 0.136 mmol, 42%).

4.12. Oxidation of 1e: synthesis of 12b (Scheme 10)

To a solution of **1e** (183 mg, 0.368 mmol) in CH_2Cl_2 (2.2 mL, 0.17 M) was slowly added, at 0 °C, a solution of *m*-CPBA (70% solution in H_2O, 91 mg, 0.368 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) and the reaction mixture was stirred for 1.5 h at 0 °C. After completion of the reaction monitored by TLC, the solvent was removed under reduced pressure in cold (without dipping flask in water bath of rotavapor) and crude residue was purified through silicagel using CH_2Cl_2/CH_3OH 9:1 to yield a first fraction containing unreacted **1b** (25 mg, 0.050 mmol, 14%), and a second fraction containing **12b** as an oil (163 mg, 0.318 mmol, 86%).



12b

R_f=0.60 (CH_2Cl_2/CH_3OH=9:1—Ceric Ammonium Molybdate); $[\alpha]_D^{23}$ −79.1 (*c* 5 in chloroform); ^1H NMR (300 MHz, CD_3OD, TMS): δ=7.63–7.37 (m, 3.6H, **2**, **3**, **4** and rotamers), 6.44 (br s, 1H, **8**), 6.31 (br s, 0.2H, rotamer of **8**), 4.72–4.64 (dd, ^3J(H,H)=8.4 and 3.9 Hz, 1.2H, **11** overlapped with its rotamer), 4.34–4.20 (m, 2.4H, **13**, overlapped with its rotamer), 4.09 (s, 3H, **7**), 4.02 (s, 0.6H, rotamer of **7**), 2.72 (m, 2.4H, **10** overlapped with its rotamer), 1.59 (s, 1.8H, rotamer of **20**), 1.49 (s, 9H, **20**), 1.42 (br s, 10.8H, **18** overlapped with its rotamer), 1.33 (t, ^3J(H,H)=7.2 Hz, 3.6H, **14** overlapped with its rotamer); ^{13}C NMR (75 MHz, CD_3OD, TMS): δ=172.4 (**12**), 171.8 (rotamer of **12**), 155.2 (**15**), 154.3 (rotamer of **15**), 153.0 (rotamer of **16**), 152.9 (**16**), 144.9 (**6**), 144.7 (rotamer of **6**), 137.4 (**5**), 137.3 (rotamer of **5**), 135.4 (rotamer of **4**), 134.9 (**4**), 133.6 (**2**), 133.5 (rotamer of **2**), 125.1 (**1** overlapped with its rotamer), 121.2 (**3**), 121.0 (rotamer of **3**), 98.8 (rotamer of **8**), 98.7 (**8**), 91.2 (rotamers of **9**), 89.7 (**9**), 85.4 (**17**), 85.0 (rotamer of **17**), 84.1 (rotamer of **19**), 84.0 (**19**), 63.6 (rotamer of **11**), 63.5 (**11**), 63.0 (rotamer of **13**), 62.9 (**13**), 57.9 (**7**), 57.8 (rotamer of **7**), 42.7 (**10**), 42.2 (rotamer of **10**), 28.5 (rotamer of **20**), 28.4 (**20**), 27.9 (**18** overlapped with its rotamer), 14.6 (**14**), 14.5 (rotamer of **14**); HRMS (MS ES$^+$, Na) calcd for $C_{24}H_{34}N_2O_8Cl$: 513.1993, found: 513.2004, Δ=2.1 ppm.

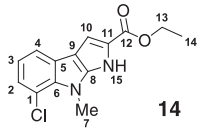
4.13. Treatment of 12b with HCl: synthesis of 8a (Scheme 10)

To a dry *N*-oxide **12b** (163 mg, 0.32 mmol) was introduced HCl (2 M in Et_2O, 5 mL, 10 mmol, 30 equiv) at rt and the reaction mixture

was stirred for 21 h. Reaction mixture was concentrated under reduced pressure in cold bath, dried in high vacuum for 10 min and under argon atmosphere, a new amount of HCl (2 M in Et_2O, 5 mL, 10 mmol, 30 equiv) was introduced and the tightly closed flask was stirred for 8 h at rt. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 then washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted three times by CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification through silicagel using Petroleum ether/EtOAc 1:1 led to compound **8a** (47.7 mg, 0.15 mmol, 48%).

4.14. Thermal behaviour of 12a (Scheme 9)

N-oxide **11** (47 mg, 0.11 mmol) was recrystallized in a mixture of ethyl acetate and petroleum ether at reflux for 10 min then standing at rt. Crystals of **14** (2.1 mg, 7.7 μmol, 7%) were formed among recovered *N*-oxide **11** (30 mg, 0.07 mmol, 63%).



14

Mp 222–224 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$, TMS, 40 °C): δ=9.70 (br s, 1H, **15**), 7.59 (d, ^3J(H,H)=7.8 Hz, 1H, **4**), 7.26 (m, 1H, **10**, overlapped with $CDCl_3$), 7.16 (d, ^3J(H,H)=7.5 Hz, 1H, **2**), 7.05 (dd, ^3J(H,H)=7.8 and 7.5 Hz, 1H, **3**), 4.39 (q, ^3J(H,H)=7.2 Hz, 2H, **13**), 4.19 (s, 3H, **7**), 1.42 (t, ^3J(H,H)=7.2 Hz, 3H, **14**); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 40 °C): δ=162.4 (**12**), 144.2 (**6**), 136.9 (**8**), 124.3 (**5**), 123.7 (**2**), 121.4 (**11**), 120.8 (**3**), 118.1 (**4**), 116.8 (**1**), 108.9 (**9**), 108.0 (**10**), 60.4 (**13**), 33.6 (**7**), 14.6 (**14**); HRMS (MS ES$^+$, Na) calcd, for $C_{14}H_{14}N_2O_2Cl$: 277.0744, found: 277.0753, Δ=3.3 ppm.

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References and notes

1. (a) Perry, D. A.; Maeda, H.; Tone, J. UK Pat. Appl. 2 240 100, 1991; (b) Kojima, Y.; Yamauchi, Y.; Kojima, N.; Bishop, B. F. Pat. Coop. Treaty WO 95/19363, 1995. See also: Kanai, Y.; Fujimaki, T.; Kochi, S.; Konno, H.; Kanazawa, S.; Tokumasu, S. *J. Antibiot.* **2004**, *57*, 24–28.
2. Didier, C.; Critcher, D. J.; Walshe, N. D.; Kojima, Y.; Yamauchi, Y.; Barrett, A. G. M. *J. Org. Chem.* **2004**, *69*, 7875–7879.
3. Schwaebisch, D.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. M.; Baldwin, J. E. *Chem. Commun.* **2004**, 2252–2253.
4. Meisenheimer, J. *Chem. Ber.* **1919**, *52*, 1667–1677.
5. (a) Hootelé, C. *Tetrahedron Lett.* **1969**, *10*, 2713–2716; (b) Robinson, B.; Moorcroft, D. *J. Chem. Soc. C* **1970**, 2077–2078; (c) Nakagawa, M.; Kaneko, T.; Yoshikawa, K.; Hino, T. *J. Am. Chem. Soc.* **1974**, *96*, 624–625; (d) Nakagawa, M.; Yoshikawa, K.; Hino, T. *J. Am. Chem. Soc.* **1975**, *97*, 6496–6501; (e) Nakagawa, M.; Okajima, H.; Hino, T. *J. Am. Chem. Soc.* **1976**, *98*, 635–637; (f) Yu, Q.-S.; Yeh, H. J. C.; Brossi, A.; Flippen-Anderson, J. L. *J. Nat. Prod.* **1989**, *52*, 332–336; (g) Node, M.; Hao, X.-J.; Nishide, K.; Fuki, K. *Chem. Pharm. Bull.* **1996**, *44*, 715–719; (h) Yu, Q.-S.; Zhu, X.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2002**, *45*, 3684–3691; (i) Bremner, J. B.; Browne, E. J.; Davies, P. E. *Aust. J. Chem.* **1980**, *33*, 1335–1343; (j) Khuthier, A.-H.; Al-Kazzaz, A.-K. S.; Al-Rawi, J. M. A.; Al-Iraqi, M. A. *J. Org. Chem.* **1981**, *46*, 3634–3638; (k) Khuthier, A.-H.; Al-Mallah, K. Y.; Hanna, S. Y.; Abdulla, N.-A. I. *J. Org. Chem.* **1987**, *52*, 1710–1713; (l) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S.; Kurihara, T. *Tetrahedron* **1996**, *52*, 14563–14576.
6. Crystallographic data (excluding structure factors) for compounds **1b**, **1d**, **8a**, **8b**, **9a**, **12a** and **14** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. 732762, 732767, 732765, 732763, 732761, 732764 and 837158, respectively. Copies of the data can be obtained, free of charge, on the application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail:deposit@ccdc.cam.ac.Uk).
7. (a) Kurihara, T.; Sakamoto, Y.; Takai, M.; Ohuchi, K.; Harusawa, S.; Yoneda, R. *Chem. Pharm. Bull.* **1993**, *41*, 1221–1225; (b) Majumdar, K. C.; Jana, G. H. *J. Org. Chem.* **1997**, *62*, 1506–1508; (c) Bergbreiter, D. E.; Walchuk, B. *Macromolecules* **1998**, *31*, 6380–6382; (d) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874–875.
8. (a) Henry, D. W.; Leete, E. *J. Am. Chem. Soc.* **1957**, *79*, 5254–5256; (b) Bremner, J. B.; Browne, E. J.; Davies, P. E.; van Thuc, L. *Aust. J. Chem.* **1980**, *33*, 833–841; (c) Bremner, J. B.; Browne, E. J.; Davies, P. E.; Raston, C. L.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 1323–1334; (d) Fall, Y.; Van Bac, N.; Langlois, Y. *Tetrahedron Lett.* **1986**, *27*, 3611–3614; (e) Nordmann, R.; Gull, P. *Helv. Chim. Acta* **1986**, *69*, 246–250; (f) Bremner, J. B.; Browne, E. J.; Engelhardt, L. M.; Greenwood, C. S.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 1815–1826; (g) Bremner, J. B.; Browne, E. J.; Engelhardt, L. M.; Gunawardana, I. W. K.; White, A. H. *Aust. J. Chem.* **1988**, *41*, 293–303; (h) Bailey, P. D.; McDonald, I. M.; Rosair, G. M.; Taylor, D. *Chem. Commun.* **2000**, 2451–2452; (i) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 8279–8283; (j) Penkett, C. S.; Simpson, I. D. *Tetrahedron Lett.* **2001**, *42*, 3029–3032.
9. (a) Tong, W.; Chowdhury, S. K.; Chen, J.-C.; Zhong, R.; Alton, K. B.; Patric, J. E. *Rapid Commun. Mass Spectrom.* **2001**, *15*, 2085–2090; (b) Ma, S.; Chawdhury, S. K.; Alton, K. B. *Anal. Chem.* **2005**, *77*, 3676–3682.