1-1-2008

# Diastereoselective ritter reactions of chiral cyclic N-acyliminium ions: synthesis of pyrido- and pyrrolo [2,3-d] oxazoles and 4-hydroxy-5-N-acylaminopyrrolidines and 5-hydroxy-6-N-acylaminopiperidines

Ian R. Morgan
*University of Wollongong*, imorgan@uow.edu.au

Arife Yazici
*University of Wollongong*, arife@uow.edu.au

Stephen G. Pyne
*University of Wollongong*, spyne@uow.edu.au

Brian W. Skelton
*University of Western Australia*

## Recommended Citation

# Diastereoselective ritter reactions of chiral cyclic N-acyliminium ions: synthesis of pyrido- and pyrrolo [2,3-d] oxazoles and 4-hydroxy-5-N-acylaminopyrrolidines and 5-hydroxy-6-N-acylaminopiperidines

## Abstract

Pyrido- and pyrrolo[2,3-*d*]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and in situ generated chiral cyclic *N*-acyliminium ions. *cis*-4-Hydroxy-5-acylaminopyrrolidines and *cis*-5-hydroxy-6-acylaminopiperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively.

## Keywords

Diastereoselective, ritter, reactions, chiral, cyclic, Acyliminium, ions, synthesis, pyrido, pyrrolo, oxazoles, Hydroxy, acylaminopyrrolidines, Hydroxy, acylaminopiperidines, CMMB

## Disciplines

Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

## Publication Details

# Diastereoselective Ritter reactions of chiral cyclic *N*-acyliminium ions: Synthesis of pyrido and pyrrolo[2,3-*d*]oxazoles and 4-hydroxy-5-*N*-acylamino-pyrrolidines and 5-hydroxy-6-*N*-acylamino-piperidines

Ian R. Morgan[a], Arife Yazici[a], Stephen G. Pyne[a]* and

Brian W. Skelton[b]

[a]*School of Chemistry, University of Wollongong, Wollongong, New South Wales, 2522, Australia*

[b] *Chemistry M313, School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia, Crawley, Western Australia, 6009, Australia*
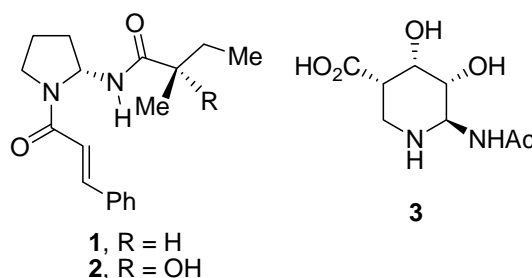
*(spyne@uow.edu.au)*

Pyrido- and pyrrolo[2,3-*d*]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and *in situ* generated chiral cyclic *N*-acyliminium ions. *Cis*-4-hydroxy-5-acylamino-pyrrolidines and *cis*-5-hydroxy-6-acylamino-piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively.
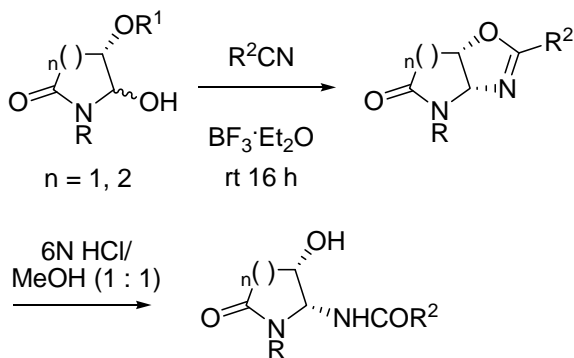
The 2-acylamino-pyrrolidine and piperidine structural motif is found in several biologically active natural and synthetic products. For example, odorine **1**[1], (+)-odorinol **2**[1]and its enantiomer, (-)-odorinol[2] and the aglains[3] are 2-acylamino-pyrrolidine alkaloids isolated from *Aglaia odorata* Lour. (+)-Odorinol **2** showed significant inhibitory activity on P-388 lymphocytic leukemia cell growth.[2] The naturally occurring *N*-iminosugar, siastatin B **3** has neuraminidase and β-glucuronidase inhibition activities.[4] While related 2-acetamido-piperidine derivatives show antimetastatic activity on tumor cells[5] and inhibition of tumor cell heparanase,[6] heperan sulfate 2-*O*-sulfotransferase,[7] *N*-acetylhexosaminidases,[8] influenza virus neuraminidase[9] and glucosidases.[10]



The incorporation of the 2-acetylamino group in these molecules often requires a multi-step sequence and thus a more direct route would be desirable.[8,11] We report here that these types of substituted heterocycles can be conveniently prepared in a highly diastereoselective manner from the Ritter reaction of nitriles and chiral cyclic *N*-acyliminium ions generated *in situ* from the (5*S*)-hydroxy-2-pyrrolidinone and (6*S*)-hydroxy-2-piperidone derivatives **4/5** and **6**, respectively.

Treatment of (4*S*)-**4**[12] in a solution of the nitriles **7a-c** at rt with BF$_3$·Et$_2$O (5 equiv) for 16 h followed by a mild basic work up (saturated aqueous NaHCO$_3$ solution) and purification by column chromatography resulted in formation of the pyrrolo[2,3-*d*]oxazoles **8a-c** in excellent yields (86-93%, Scheme 1, Table 1, entries 1-3). Treatment of (4*S*)-**4** with the nitrile **7d** (3 equiv) at rt in nitromethane solution with BF$_3$.Et$_2$O (5 equiv) for 16 h resulted in formation of the pyrrolo[2,3-*d*]oxazole **8d** in 91% yield (Scheme 1, Table 1, entry 4). Interestingly, treatment of the *O*-benzyl ether analogue of **4**, (4*S*)-**5**,[13] with the nitriles **7b-c** also resulted in formation of the pyrrolo[2,3-*d*]oxazoles **8b-c** in high yields (87% and 80%, respectively, Table 1, entries 5-6). The corresponding *N*-benzylamides **10b-c** were also isolated in yields of 77% and 63%, respectively (Scheme 1).

The 6-membered ring hemi-aminal (5*S*)-**6** (dr = 3 : 1) was prepared from the known *N*-PMB-(3*S*)-hydroxyglutarimide[14,15] by NaBH$_4$ reduction.[16] The major *trans*-isomer of (5*S*)-**6** could be selectively crystallized from the mixture and its structure was established by X-ray crystallographic analysis (Supporting Information). Treatment of the diol (5*S*)-**6** (dr = 3 : 1) with the nitriles **7a-d**, under similar conditions to that of (4*S*)-**4** (BF$_3$·Et$_2$O (5 equiv), rt for 16 h and finally at reflux for 30 min to 3 h), resulted in formation of the corresponding pyrido[2,3-*d*]oxazoles **9a-d** in good to excellent yields (Table 1, entries 7-10). The use of the less nucleophilic 4-nitrobenzonitrile (**7e**) resulted in only recovered hemi-aminal **6** (Table 1, entry 11).

Acid hydrolysis of **8a-b** with 6N HCl/MeOH (1 : 1) at rt for 25 min provided the corresponding *cis*-hydroxy-amides **11a-b**, respectively, in respective yields of 42% and 70%, Scheme 1. This method was less efficient (35-30% yields) for the synthesis of corresponding 6-membered ring analogues **12a-b** from the acid hydrolysis of **9a-b** (Scheme 1). This hydrolysis method also gave several other minor uncharacterizable products by TLC analysis. A much improved yield of 67% for **12b** was achieved by hydrolysis using silica gel and CHCl$_3$/H$_2$O (100 : 1) at rt for 16 h and then at reflux for 2 h. An analogus acid hydrolysis (6N HCl/MeOH (1 : 1) at rt) of the aromatic derivatives **8c-d** or **9c-d** gave only recovered starting material, whereas more forcing conditions (50 °C)

resulted in a complex mixture of products. The stereochemistry of the products **11a** and **11b** was determined to be *cis* based on their the coupling constants $J_{4,5}$, which were 5.0 and 5.6 Hz, respectively. On related systems, $J_{4,5}$ is typically 0-2.5 Hz for the *trans* isomers and 6.0-7.5 Hz for the corresponding *cis*-isomers.[17a,b] The highly crystalline hydroxy-amides **12a-b** were shown to have also have the *cis*-stereochemistry from their single-crystal X-ray structural analysis (Supporting Information).
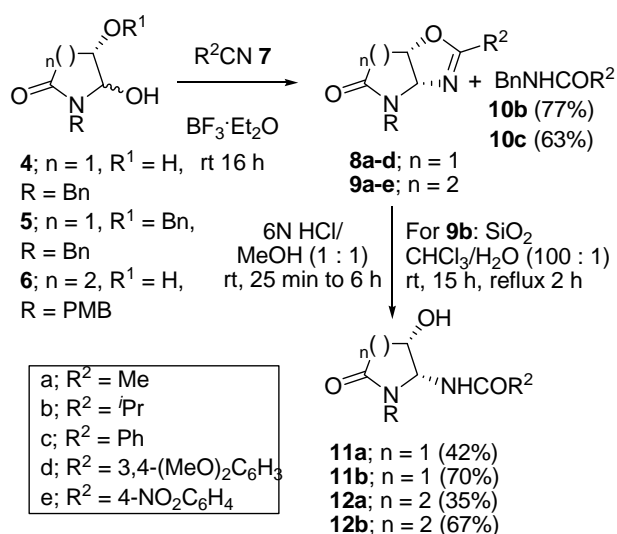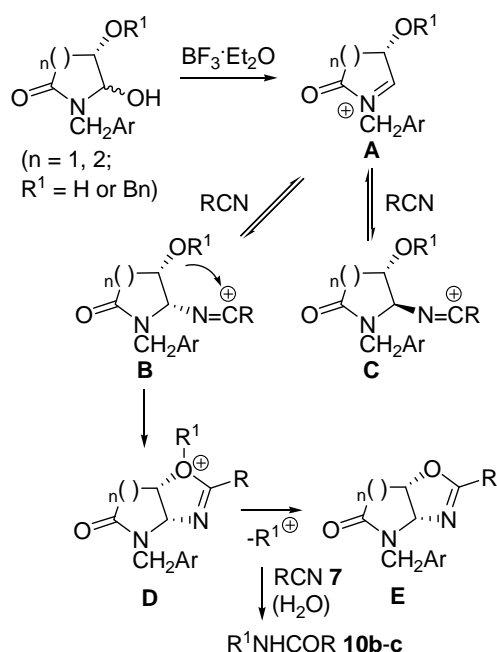
**Scheme 1**



**4**; n = 1, R$^1$ = H, rt 16 h
R = Bn

**5**; n = 1, R$^1$ = Bn,
R = Bn

**6**; n = 2, R$^1$ = H,
R = PMB

a; R$^2$ = Me
b; R$^2$ = $^i$Pr
c; R$^2$ = Ph
d; R$^2$ = 3,4-(MeO)$_2$C$_6$H$_3$
e; R$^2$ = 4-NO$_2$C$_6$H$_4$

**8a-d**; n = 1
**9a-e**; n = 2

**10b** (77%)
**10c** (63%)

6N HCl/
MeOH (1 : 1)
rt, 25 min to 6 h

For **9b**: SiO$_2$
CHCl$_3$/H$_2$O (100 : 1)
rt, 15 h, reflux 2 h

**11a**; n = 1 (42%)
**11b**; n = 1 (70%)
**12a**; n = 2 (35%)
**12b**; n = 2 (67%)

**Table 1**

| Entry | Starting material | Product (yield, %) |
|-------|-------------------|--------------------|
| 1 | **4** | **8a** (93) |
| 2 | **4** | **8b** (90) |
| 3 | **4** | **8c** (86) |
| 4 | **4** | **8d** (91)[a] |
| 5 | **5** | **8b** (87) |
| 6 | **5** | **8c** (80) |
| 7 | **6** | **9a** (99) |
| 8 | **6** | **9b** (91) |
| 9 | **6** | **9c** (58)[b] |
| 10 | **6** | **9d** (79)[a] |
| 11 | **6** | **9e** (0) |

[a] MeNO$_2$ as solvent, 3 equiv of **7d**. [b] Starting **6** was also isolated in 21% recovered yield.

These reactions are notable for providing products with high *cis*-diastereoselectivities. Typically the addition of nucleophiles to the iminium ions generated *in situ* from **4**, **5** and **6** show modest diastereoselectivities.[13,17] To rationalize the high diastereoselectivities and the stereochemical outcomes of these reactions we suggest that attack of the nitriles **7a-d** on the intermediate *N*-acyliminium ion **A** (Ritter reaction)[18,19] is reversible and gives a mixture of the Ritter intermediates **B** and **C** (Scheme 2). Because of its *cis*-stereochemistry intermediate **B** more readily cyclizes to the oxazolidine cationic intermediate **D**. Deprotonation or *O*-debenzylation of **D** gives the oxazolidine **E**. When R$^1$ in **D** is Bn, the benzyl cation that is formed undergoes a Ritter reaction with the nitriles **7b-c** to give the *N*-benzyl amides **10b-c**, respectively (Scheme 2). The optical rotations of compounds **9a-d** and **12a-b**, were notably small or essentially zero, suggesting that **6** may have undergone racemization under the reaction conditions. This was confirmed by converting **12b** to its (*S*)- or (*R*)-Mosher's esters by treating samples of **12b** with (*R*)- or (*S*)-Mosher's acid chloride, respectively. ^{1}H NMR analysis of these derivatives indicated essentially a 1 : 1 mixture of diastereomers were produced.[20] In contrast the optical rotations of compounds **8a-d** and **11a-b**, were relatively large in magnitude. ^{1}H NMR analysis of the analogous Mosher's esters of **11b** indicated high enantiomeric purity (95% ee). It seems likely therefore that hemi-aminal **6** undergoes ring-opening to the corresponding α-hydroxy aldehyde-secondary amide (PMBN(H)COCH$_2$CH$_2$CH(OH)CHO) which undergoes racemization, through a Lewis acid catalysed enolization process of the α-hydroxy aldehyde moiety, prior to re-cyclization back to **6** and then the subsequent Ritter reaction. This does not seem to be a problem in the 5-membered ring series.

**Scheme 2**



R$^1$NHCOR **10b-c**

Under oxidative reaction conditions (MnO$_2$, toluene at reflux) the pyrido[2,3-*d*]oxazole **9c** was converted to the oxazolo[4,5-*b*]pyridin-5(4*H*)-one **13** in 62% yield (Scheme 3). The analogous pyrrolo[2,3-*d*]oxazole **8c** however, failed to provide the corresponding oxidized product when exposed to the same reaction conditions.

**Scheme 3**
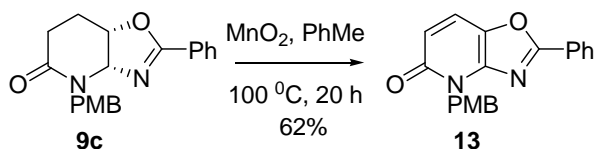


In conclusion, pyrido- and pyrrolo[2,3-*d*]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and chiral cyclic *N*-acyliminium ions. *Cis*-4-hydroxy-5-acylamino-pyrrolidines and *cis*-5-hydroxy-6-acylamino-piperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively. The compounds derived from the 6-membered hemiaminal **6** are obtained in racemic form.

**Experimental**

**General** Unless stated, CDCl$_3$ was used as a solvent for all $^1$H NMR (500 MHz) and $^{13}$C NMR (125 Mz) measurements. All IR spectra were determined as neat samples. All solutions were dried over anhydrous MgSO$_4$. Petrol refers to the hydrocarbon fraction of boiling point 40-60 °C.

**(3a*R*,6a*S*)-4-Benzyl-2-methyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (8a).** To a solution of diol **4** (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 °C was added dropwise BF$_3$·Et$_2$O (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated NaHCO$_3$ solution (10 mL) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined extracts were dried, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc as eluent) to give the title compound (0.103 g, 93%) as a colorless waxy solid. R$_f$ 0.22 (EtOAc). $[\alpha]_D^{23}$ + 21.0 (*c* 0.19, CHCl$_3$). $\upsilon_{max}$/cm$^{-1}$ 1680, 1433, 1308, 1227, 1065, 1024. δ$_H$ 7.34-7.32 (5H, m, Ar*H*), 5.38 (1H, d, *J* = 7.5 Hz), 5.07 (1H, d, *J* = 14.5 Hz), 4.90 (1H, t, *J* = 7.5 Hz), 4.02 (1H, d, *J* = 14.5 Hz), 2.85 (1H, dd, *J* = 7.5, 18.5 Hz), 2.69 (1H, d, *J* = 18.5 Hz), 2.03 (3H, s). δ$_C$ 170.7, 168.8, 135.9, 128.7, 128.6, 127.7, 83.2, 74.48, 44.3, 37.5, 14.1. MS (EI) *m/z* 230 (M$^{+\cdot}$,100%). HRMS (EI) calcd for C$_{13}$H$_{14}$N$_2$O$_2$ (M$^{+\cdot}$) 230.1055, found 230.1057.

**(±)-(5*S*,6*S*)-4-(4-Methoxybenzyl)-3a,4,7,7a-tetrahydro-2-isopropyloxazolo[4,5-*b*]pyridin-5(6*H*)-one (9b).** To a suspension of the diol **6** (150 mg, 0.597 mmol) in isobutyronitrile (10 mL) was added BF$_3$·OEt$_2$ (375 μL, 2.984 mmol) and the resulting homogeneous solution was stirred at rt for 16 h upon which, tlc analysis indicated an incomplete reaction so the solution was heated at reflux for 30 min. The reaction was quenched at 0 °C with saturated NaHCO$_3$ (10 mL) and brine (50 mL) and then allowed to stir for 10 min. The resulting mixture was extracted with EtOAc (3 x 70 mL), dried and concentrated *in vacuo* to yield the crude product. Flash chromatography (Et$_2$O, R$_f$ = 0.31) of the crude product yielded **9b** (164 mg, 0.543 mmol, 91%) as a colorless oil. $\upsilon_{max}$/cm$^{-1}$ 2971, 1655, 1514, 1248, 752. δ$_H$ 7.41 (2H, d, *J* = 8.5 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 5.48 (1H, d, *J* = 14.8 Hz), 5.31 (1H, d, *J* = 9.2 Hz), 4.68-4.72 (1H, m), 3.95 (1H, d, *J* = 14.8 Hz), 3.79 (3H, s), 2.63 (1H, app sept, *J* = 7.0 Hz) 2.39-2.46 (1H, m), 2.23-2.30 (1H, m), 2.18 (1H, ddd, *J* = 14.5, 6.4 and

3.0 Hz), 1.88 (1H, app, tt, *J* = 14.3 and 3.7 Hz), 1.21 (3H, t, *J* = 7.0 Hz), 1.20 (3H, t, *J* = 7.0 Hz). δ$_C$ 174.9, 171.2, 159.0, 129.6, 129.2, 114.0, 78.5, 74.9, 55.2, 46.5, 28.3, 27.1, 25.0, 19.6, 19.5. MS (EI$^+$) *m/z* 302 (M$^+$) 100 %. HRMS (EI$^+$): calcd. for C$_{17}$H$_{22}$N$_2$O$_3$, (M$^+$): 302.1630, found: 302.1623.

**(±)-*N*-((2*R*,3*S*)-1-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)acetamide (11a).** To a solution of oxazoline **8a** (0.020 g, 0.086 mmol) in MeOH (1 mL) at rt was added dropwise 6N HCl (1 mL). The reaction mixture was stirred at rt for 25 min and concentrated *in vacuo*, then diluted with water (5 mL), basidified with solid NaHCO$_3$ to pH 9. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na$_2$SO$_4$) filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% MeOH in EtOAc as eluent) to give the title compound (0.009 g, 42%) as a white solid. R$_f$ 0.24 (5% MeOH in EtOAc). Mp 190-193 °C. $[\alpha]_D^{23}$ -160 (*c* 0.075 MeOH). $\upsilon_{max}$/cm$^{-1}$ 3318, 1577, 1653, 1541, 1446, 1434, 1378, 1275, 1157. δ$_H$ (d$_4$-MeOH) 7.31-7.24 (5H, m), 5.55 (1H, d, *J* = 5.0 Hz), 4.57 (1H, d, *J* = 15.0 Hz), 4.39 (1H, br q, *J* = 6.5 Hz), 4.23 (1H, d, *J* = 15.0 Hz), 2.68 (1H, dd, *J* = 6.5, 17.5 Hz), 2.46 (1H, dd, *J* = 5.0, 17.5 Hz), 1.88 (3H, s). δ$_C$ (d$_4$-MeOH) 174.9, 173.9, 138.2, 129.5, 129.1, 128.5, 67.6, 65.8, 45.0, 39.6, 22.6. MS (EI) *m/z* 248 (M$^+$, 45%). HRMS (EI) cald for C$_{13}$H$_{16}$N$_2$O$_3$ (M$^+$) 248.1160, found 248.1158.

**(±)-(5*S*,6*S*)-*N*-1-(4-methoxybenzyl)-3-hydroxy-6-oxopiperidin-2-yl)isobutyramide (12b).**
**Method 1:** To a solution of the oxazoline **9b** (92 mg, 0.304 mmol) in MeOH/H$_2$O (10 mL of a 9 : 1 v/v mixture) was added three drops of concentrated hydrochloric acid and the solution was stirred at rt for 6 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography [EtOAc to 4% MeOH / EtOAc (R$_f$ = 0.31)] to yield **12b** (35 mg, 0.090 mmol, 30%) as a colorless solid.
**Method 2:** To a solution of the oxazoline **9b** (75 mg, 0.248 mmol) in chloroform (20 mL) was added silica gel (2 g) and water (200 μL) and the resulting suspension was stirred vigorously for 15 h. Tlc analysis indicated only starting material so the reaction was heated at reflux for 2 h. The reaction was cooled and the volatiles were removed *in vacuo*. The silica gel was filtered and washed with EtOAc/MeOH (100 mL of a 2:1 v/v) and then the volatiles were removed. Column chromatography of the crude residue from the silica gel yielded **12b** (53 mg, 0.165 mmol, 67%) showing spectroscopic data consistent with the amide prepared from Method 1 above. The starting oxazoline **9b** was also recovered (15 mg, 0.0496 mmol, 20%). Mp 169-173 °C. $\upsilon_{max}$/cm$^{-1}$ 3288, 2966, 1652, 1615, 1541, 1513, 1468, 1244, 1176, 1033. δ$_H$ 7.17 (2H, d, *J* = 8.6 Hz), 6.83 (2H, d, *J* = 8.6 Hz), 6.37 (1H, d, *J* = 8.8 Hz), 5.47 (1H, dd, *J* = 8.8, 4.1 Hz), 4.84 (1H, d, *J* = 14.6 Hz), 4.02 (1H, d, *J* = 14.6 Hz), 4.00-4.03 (1H, m), 3.76 (3H, s), 3.19 (1H, br s), 2.58 (1H, app dt, *J* = 18.1 and 5.4 Hz), 2.40-2.50 (1H, m), 2.36 (1H, app sept, *J* = 6.9 Hz), 1.85-1.95 (2H, m), 1.14 (3H, d, *J* = 6.9 Hz), 1.13 (3H, d, *J* = 6.9 Hz). δ$_C$ (d$^4$-MeOH) 174.9, 171.2, 158.9, 129.5, 129.2, 114.0, 78.5, 74.9, 55.2, 46.5, 28.3, 27.1, 25.0, 19.6, 19.5. MS (ESI$^-$) *m/z* 319.2 (M - H)$^-$ 100 %. HRMS (ESI$^+$): calcd. for C$_{17}$H$_{25}$N$_2$O$_4$, (M + H)$^+$: 321.1814, found: 321.1821.

**4-(4-Methoxybenzyl)-2-phenyloxazolo[4,5-*b*]pyridin-5(4*H*)-one (13).** To a solution of the oxazoline **9c** (48 mg, 0.143

mmol) in anhydrous toluene (10 mL) was added activated manganese(IV) dioxide (146 mg of 85% activity, 1.43 mmol, 10 eq) and the suspension was heated at 100 °C for 16 h. Tlc analysis indicated an incomplete reaction so a further portion of manganese(IV) dioxide (146 mg, 10 eq) was added at then heated at reflux for 4 h whereupon, tlc analysis showed complete consumption of the oxazoline (the product is fluorescent and the oxazoline is not). The reaction was filtered through a short plug of silica (5 cm), eluted with EtOAc and the volatiles removed *in vacuo*. The crude product was purified by column chromatography [10% EtOAc/Petrol to 50% EtOAc/Petrol ($R_f$ = 0.29)] yielding **13** (28.5 mg, 0.086 mmol, 62%) as a pale yellow solid. Mp 120-122 °C. $\delta_H$ 8.16 (2H, dd, $J$ = 7.5 and 1.5 Hz), 7.62 (1H, d, $J$ = 9.5 Hz), 7.59 (2H, d, $J$ = 9.0 Hz), 7.50-7.56 (4H, m), 6.82 (2H, d, $J$ = 9.0 Hz), 6.44 (1H, d, $J$ = 9.5 Hz), 5.44 (2H, s) and 3.76 (3H, s). $\delta_C$ 163.1, 161.6, 159.2, 133.7, 133.1, 131.8, 130.7, 129.0, 128.8, 127.2, 126.4, 124.3, 116.6, 113.8, 55.2, 45.8. MS (EI$^+$) *m/z* 332 (M$^+$) 100 %; HRMS (EI$^+$): calcd. for $C_{20}H_{16}N_2O_3$, (M$^+$): 332.1160, found: 332.1155.

**Supporting Information Available**. Full experimental procedures and characterisation data as well as copies of the $^1$H NMR and $^{13}$C NMR spectra of all new compounds. Crystal/refinement data and ORTEP plots of compounds **6**, **12a** and **12b** (CCDC #668234, 668235, 668236). This material is available free of charge *via* the Internet as http://pubs.acs.org.

### References

(1) Shiengthong, D.; Ungphakorn, A.; Lewis, D. E.; Massy-Westropp, R. A. *Tetrahedron Lett*. **1979**, *24*, 2247-2250.

(2) Hayashi, N.; Lee, K.-H.; Hall, I. H.; McPhail, A. T.; Huang, H.-C. *Phytochemistry*, **1982**, *21*, 2371-2373.

(3) Nugroho, B. W.; Edrada, R. A.; Wray, V.; Witte, L.; Bringmann, G.; Gehling, M.; Proksch, P. *Phytochemistry*, **1999**, *51*, 367-376.

(4) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, Iizuka, Y. *J. Am. Chem. Soc*. **1996**, *118*, 3051-3052.

(5) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, Iizuka, Y. *J. Med. Chem*. **1997**, *40*, 2626-2633.

(6) Kawase Y; Takahashi M; Takatsu T; Arai M; Nakajima M; Tanzawa K. *J. Antibiot*. **1996**, *49*, 61-64.

(7) Brown, J. R.; Nishimura, Y.; Esko, J. D. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 532-536.

(8) Knapp, S.; Yang, C.; Pabbaraja, S.; Rempel, B.; Reid, S.; Withers, S. G. *J. Org. Chem*. **2005**, *70*, 7715-7720.

(9) Shitara, E.; Nishimura, Y.; Nerome, K.; Hiramoto, Y.; Takeuchi, T. *Org. Lett*. **2000**, *2*, 3837-3840.

(10) Shitara, E.; Nishimura, Y.; Kojima, F.; Takeuchi, T. *Bioorg. Med. Chem. Lett*. **1999**, *7*, 1241-1246.

(11) Babidge, P. J.; Massy-Westropp, R. A.; Pyne, S. G.; Shiengthong, D.; Ungphakorn, A.; Veerachat, G. *Aust. J. Chem*. **1980**, *33*, 1841-5.

(12) Prepared from the known (3*S*)-hydroxysuccinimide (Kočalka, P.; Pohl, R.; Rejmam, D.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 5763-5774) by NaBH$_4$ reduction.

(13) Prepared according to Huang, P.-Q. *Synlett* **2006**, 1133-1149.

(14) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett*. **2003**, *5*, 1927-1929.

(15) Ruan, Y.-P.; Wei, B.-G.; Xu, X.-Q.; Liu, G.; Yu, D.-S.; Liu, L.-X.; Huang, P.-Q. *Chirality*, **2005**, *17*, 595-599.

(16) Morgan, I. R. Yazici, A.; Pyne, S. G. *Tetrahedron*, **2008**, *64*, 1409-1419.

(17) (a) Thaning, M.; Wistrand, L.-G. *J. Org. Chem*. **1990,** *55*, 1406-1408. (b) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett*. **1990**, *31*, 4949-4952. (c) Koot, W.-J.; van Ginkel, R.; Kranenburg, M.; Hiemstra, H. *Tetrahedron Lett*. **1991**, *32*, 401-404. (d) Pilli, R. A.; Russowsky, D. *J. Org. Chem*. **1996**, *61*, 3187-3190. (e) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron*, **1996**, *52*, 2603-2628. (f) Lennartz, M. L.; Sadakane, M.; Steckhan, E. *Tetrahedron*, **1999**, *55*, 14407-14420. (g) Lennartz, M.; Steckham, *Synlett*, **2000**, 319-322. (h) Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett*. **2000**, *41*, 9939-9942. (i) Klitzke, C. F.; Pilli, R. A. *Tetrahedron Lett*. **2001**, *42*, 5605-5608. (j) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem*. **2001**, *66*, 809-823. (k) Washburn, D. G.; Heidebrecht, R. W.; Martin, S. F. *Org. Lett*. **2003**, *5*, 3523-3525. (l) Huang, P.-Q.; Wei, B.-G.; Ruan, Y.-P. *Synlett* **2003**, 1663-1667. (m) Huang, P.-Q.; Lu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett*. **2003**, *5*, 1927-1929. (n) Meng, W.-H.; Wu, T.-J.; Zhang, H.-K.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 3899-3910. (o) Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron*, **2004**, *60*, 10223-10231. (p) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett*. **2005**, *7*, 2825-2828. (q) Othman, R. B.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett*. **2005**, *7*, 5335-5337. (r) Tranchant, M.-J.; Moine, C.; Othman, R. B.; Bousquest, T.; Othman, M.; Dalla, V. *Tetrahedron Lett*. **2006**, *47*, 4477-4480.

(18) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc*., **1948**, *70*, 4045-4048. (b) Ritter, J. J.; Kalish, J. *J. Am. Chem. Soc*., **1948**, *70*, 4048-4050.

(19) Ritter-like reactions using nitriles, and the related Holy reaction using cyanamide, has been employed on sugar acetals and related compounds, providing analogous bicyclic sugar oxazolines. See: (a) Gordon, D. M.; Danishefsky, S. J. *J. Org. Chem*. **1991**, *56*, 3713-3715. (b) Blanco, J. L. J.; Rubino, E. M.; Mellet, C. O.; Fernandez, J. M. G. *Synlett*, **2004**, 2230-2232. (c) Jenkinson, S. F.; Jones, N. A.; Moussa, A.; Stewart, A. J.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett*. **2007**, *48*, 4441-4444 and references cited therein.

(20) The $^1$H NMR spectra of the (*S*)- or (*R*)-Mosher's ester derivatives of **12b** both showed two sets of doublet peaks (1 : 1 ratio) for the benzylic methylene signals $CH_ACH_B$PMP (see Supporting Information).