Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 5201–5204
Tetrahedron Letters

Tandem oxime formation—epoxide ring opening sequences for the preparation of oxazines related to the trichodermamides

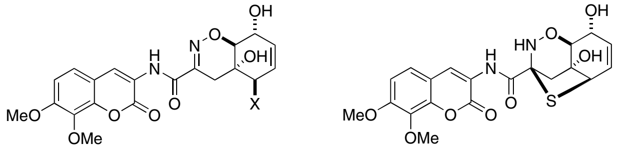
James R. Donald, Michael G. Edwards and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

Received 23 April 2007; revised 14 May 2007; accepted 24 May 2007
Available online 31 May 2007

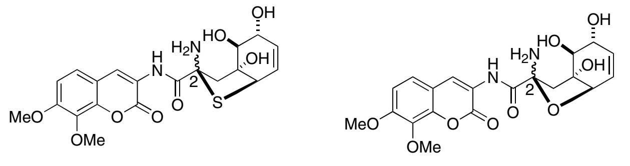
Abstract—A mild and straightforward method for the preparation of 4*H*-5,6-dihydro-1,2-oxazines from keto-epoxides via cyclisation of the intermediate oximes is reported, as is a preparative route to 3-amino-7,8-dimethoxychromen-2-one; these procedures were then employed to prepare a novel analogue of trichodermamide natural products.

Trichodermamides **1** and **2** and the aspergillazines **3**–**7** (Fig. 1) are a family of highly modified heterocyclic dipeptides reported in 2003 and 2005.[1,2] Trichodermamides **1** and **2** were isolated from the marine fungus *Trichoderma virens* by Clardy and colleagues and shown to contain the unusual 4*H*-5,6-dihydro-1,2-oxazine (*O*-alkyl oxime) unit annelated to a highly functionalised cyclohexene ring.[1] Subsequently, Capon et al. isolated the related aspergillazines **3**–**7** from the fungus *Aspergillus unilateralis*.[2] Aspergillazine A **3** has a tricyclic Eastern portion based on a highly substituted, fused tetrahydrothiophene-tetrahydro-1,2-oxazine-cyclohexene containing the unusual S–C–N–O connectivity and four contiguous stereocentres.



Trichodermamide A (X = OH), **1**
Trichodermamide B (X = Cl), **2**

Aspergillazine A **3**



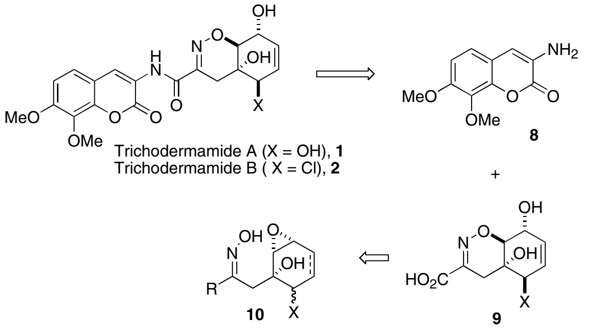
Aspergillazines B and C (C2-epimers)
4, 5

Aspergillazines D and E (C2-epimers)
6, 7

Figure 1. The trichodermamides and aspergillazines.

Given the structural novelty of these compounds, together with their interesting and only partially explored biological activities, we decided to develop routes for their synthesis. We were particularly interested in the synthesis of trichodermamides **1** and **2** and aspergillazine A **3**. To the best of our knowledge, there were no reported synthetic endeavours in this area until the recent publication by Wan, Doridot and Joullié on model studies towards trichodermamides.[3] We therefore present our own preliminary studies in this Letter.

Our synthetic approach is illustrated retrosynthetically in Scheme 1 using the trichodermamides **1** and **2**. Amide disconnection generates amino-coumarin **8** and a bicyclic dihydro-1,2-oxazine carboxylic acid **9** containing four stereocentres.



Scheme 1.

---

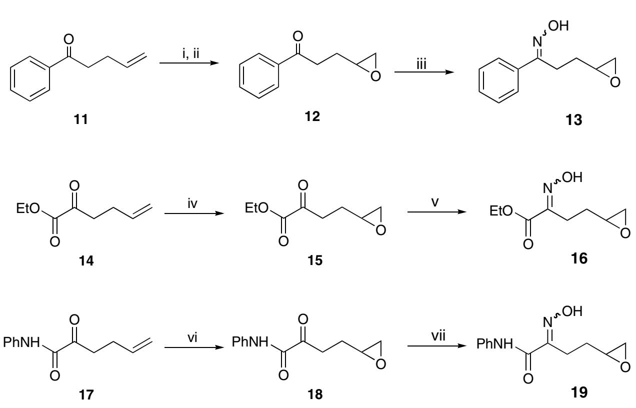
* Corresponding author. E-mail: rjkt1@york.ac.uk

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.145

Many methods have been reported for the preparation of 4*H*-5,6-dihydro-1,2-oxazines, the majority of which fall into two general classes: (i) pericyclic reactions such as hetero-Diels–Alder cycloadditions[4,5] or the 1,2-oxaza-Cope rearrangement[6] and (ii) the O-alkylation of oximes by an internal electrophile such as iodonium ions,[7] seleniranium ions[8] or alkyl chlorides.[9] We were interested in developing a variant of the latter category in which oxazine formation is achieved by the intramolecular opening of epoxides by an adjacent oxime (e.g., **10** → **9**, Scheme 1). When we commenced this project, there were only two reports of dihydro-1,2-oxazine preparation by epoxide ring opening,[10] although the Joullié group employed an intramolecular example in their recent publication.[3]

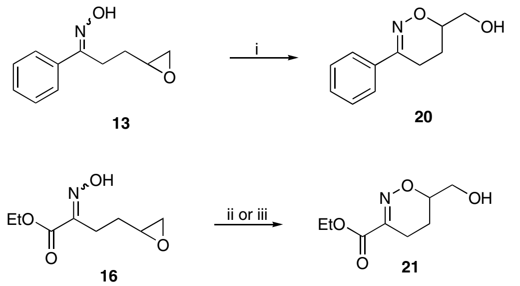
To commence this study, γ,δ-epoxy-oximes were required in order to test the oxazine formation process (Scheme 2). Phenyl ketone **11**[11] was chosen as the initial model system as it was assumed that oxime formation would favour the desired *E*-oxime isomer on steric grounds. In addition, oxazine **20** derived from oxime **13** is a known compound.[10b] After much experimentation, epoxide **12**[12] was obtained by the conversion of alkene **11** into the corresponding bromohydrin followed by treatment with caesium carbonate.[13] Epoxide **12** was found to be rather unstable and its conversion to oxime **13** proved problematic under a range of classical oximination conditions. However, on treatment with hydroxylamine hydrochloride in buffered acetic acid,[14] oxime **13** was obtained in a best yield of 39% as what appeared to be a single isomer, although the reaction was capricious.

α-Keto-ester **14**[15] was efficiently epoxidised using DMDO and product **15** could be purified by Kugelrohr distillation. Epoxide **15** readily underwent condensation with hydroxylamine in aqueous acetonitrile[16] to give oxime **16** in good yield (as a single isomer according to ^{1}H NMR spectroscopy).[17] Amide **17** was readily prepared[18] and epoxidised using DMDO in a similar manner. However, the conversion of α-keto-amide **18** into oxime **19** proved problematic with a best yield of <20%. For this reason, subsequent studies involved the oximination of keto-esters with amide formation at a later stage.



Scheme 2. Reagents and conditions: (i) NBS, THF/H_2O, rt, 16 h, 73%; (ii) Cs_2CO_3, MeCN, rt, 3 h, 86%; (iii) $H_2NOH \cdot HCl$, KOAc, AcOH buffered to pH 6, rt, 26 h, 39%; (iv) DMDO, Me_2CO, rt, 6 h, 95%; (v) $H_2NOH \cdot HCl$, NaOAc, MeCN/H_2O (3:1), rt, 2.5 h, 76%; (vi) DMDO, Me_2CO, rt, 6 h, 86%; (vii) $H_2NOH \cdot HCl$, NaOAc, EtOH, Δ, 2 h, 19%.

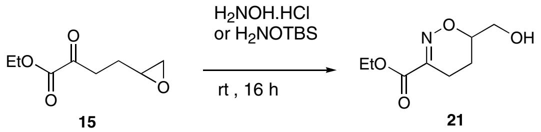
The conversion of oximes into oxazines proved to be more facile than expected (Scheme 3). Oxime **13** underwent spontaneous cyclisation on standing at room temperature to give oxazine **20** in quantitative yield; oxazine **20** was identified by comparison with published ^{13}C NMR data (δ_C 155.2, C=N), lit.[10b] (δ_C 155.1).



Scheme 3. Reagents and conditions: (i) Standing, quantitative; (ii) K_2CO_3, EtOH, rt, 14 h, 80%; (iii) SiO_2, EtOAc, reflux, 6 h, 75%.

Oxime **16** proved to be more stable but treatment with K_2CO_3 in ethanol, or heating in a slurry of silica gel, gave oxazine **21** in good yield. It should be noted that these cyclisation conditions are extremely mild compared to published examples, which employed strong bases.[3,10]

Given the success with oxazine formation we hoped to combine the oximination and cyclisation to achieve a one-pot approach to oxazines (Scheme 4).



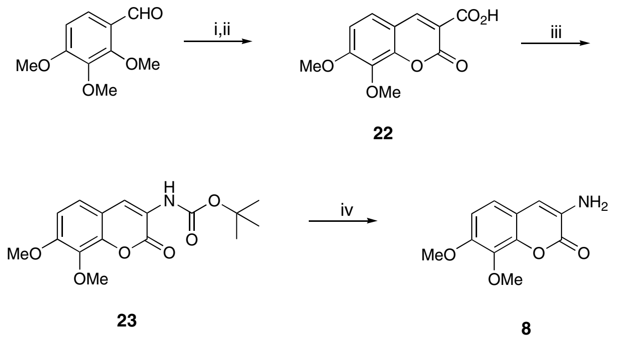
(i) $H_2NOH.HCl$, 1.1 eq. K_2CO_3, DMF	14%
(ii) $H_2NOH.HCl$, 1.1 eq K_2CO_3, EtOH	64%
(iii) H_2NOTBS, EtOH then TBAF	60%

Scheme 4.

This tandem approach was successful with oxazine **21** being obtained from keto-epoxide **15** in up to 64% yield on a 0.1 mmol scale. However, the efficiency diminished on scale up and at present the two step procedure is generally preferred.

At this point, the success of the model studies provided encouragement to prepare analogues more closely related to the trichodermamides. To achieve this, the novel amino-coumarin **8** was first prepared (Scheme 5).

Thus, following a literature protocol,[19] 2,3,4-trimethoxybenzaldehyde was converted into coumarin **22**.

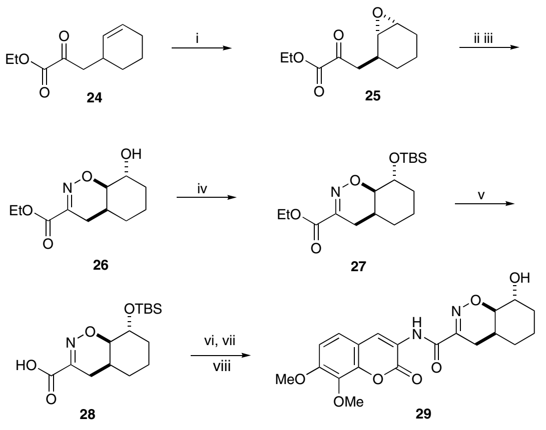


Scheme 5. Reagents and conditions: (i) Meldrum's acid, ZnO, 80 °C, 4.5 h, 83%; (ii) concd HCl, 0 °C, 20 min, 76%; (iii) DPPA, Et_3N, toluene, reflux, 1.25 h, *t*-BuOH, reflux, 1.25 h, 43%; (iv) 10% HCl (aq), MeOH, reflux, 45 min, 76%.

Reaction of coumarin **22** with diphenylphosphoryl azide (DPPA) followed by trapping the isocyanate intermediate with *t*-BuOH gave carbamate **23** in modest yields.[20,21] Deprotection of compound **23** with acid then produced the required amino-coumarin **8** in 76% yield (mp 177–180 °C; 21% overall yield from 2,3,4-trimethoxybenzaldehyde).

Finally, we combined the oxazine and amino-coumarin methodology to prepare analogues of trichodermamide (Scheme 6). The known α-keto-ester **24**[22] was epoxidised with DMDO in a non-stereoselective manner to produce a separable mixture of epoxides (88%, cis:trans = 1.7:1 by ^{1}H NMR spectroscopy). The trans-isomer **25** was oximinated and silica-mediated cyclisation gave the bicyclic oxazine **26** in 72% over two steps.[23]

In order to facilitate the final amide coupling, alcohol **26** was converted into silyl ether **27**, which in turn was saponified using TMSOK[24] in quantitative yield. Based on model studies we established that the direct coupling of acid **28** with amino-coumarin **8** was not viable even under forcing conditions, presumably due to the low reactivity of the amine. We therefore converted acid **28** into the corresponding acid chloride using the mild chloro-enamine reagent developed by Ghosez et al.[25] Amino-coumarin **8** was then deprotonated using *n*-butyllithium and the lithioamide added directly to the freshly prepared acid chloride. Desilylation of the product gave the requisite amide **29**, which was fully characterised, in an unoptimised yield of 18% over the three steps.



Scheme 6. Reagents and conditions: (i) DMDO, Me_2CO, rt, 1 h 88% (1.7:1 dr); chromatography gave **25** (16%) and cis-isomer (44%); (ii) $H_2NOH{\cdot}HCl$, NaOAc, $MeCN/H_2O$, rt, 12 h; (iii) SiO_2, EtOAc, rt, 8 h, 72% (two steps); (iv) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 88%; (v) TMSOK, THF, rt, 1 h then 10% HCl, quant.; (vi) $Me_2C{=}C(Cl)NMe_2$, THF, rt, 2 h, (vii) **8**/*n*-BuLi, THF, 0 °C to rt, 5.5 h, 25%; (vii) TBAF, THF, rt, 6 h, 72%.

In summary, we have developed a mild and straightforward method for the preparation of 4*H*-5,6-dihydro-1,2-oxazines from keto-epoxides via cyclisation of the intermediate oximes, and a preparative route to amino-coumarin **8**; these procedures were then employed to prepare the novel trichodermamide analogue **29**. It should also be noted that the current procedure is successful at the α-keto-ester oxidation level delivering the required carboxylate-substituted oxazines, in contrast to the alternative approach, which produces hydroxymethyl-substituted oxazines.[3]

We are currently optimising the above methodology with a view to completing the total synthesis of the trichodermamide and aspergillazine natural products.

Acknowledgements

We thank the University of York for studentship support (JRD), Elsevier for postdoctoral funding (MGE) and Dr. T. Dransfield (University of York) for assistance with mass spectrometry.

References and notes

1. Garo, E.; Starks, C. M.; Jensen, P. R.; Fenical, W.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2003**, *66*, 423–426; Trichodermamide A is identical to the previously reported penicillazine although the structure of the latter was misassigned: Lin, Y.; Shao, Z.; Jiang, G.; Zhou, S.; Cai, J.; Vrijmoed, L. L. P.; Jones, E. B. G. *Tetrahedron* **2000**, *56*, 9607–9609.
2. Capon, R. J.; Ratnayake, R.; Stewart, M.; Lacey, E.; Tennant, S.; Gill, J. H. *Org. Biomol. Chem.* **2005**, *3*, 123–129.
3. Wan, X.; Doridot, G.; Joullié, M. M. *Org. Lett.* **2007**, *9*, 977–980.
4. Davies, D. E.; Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1275–1281.
5. Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 595–598.
6. Zakarian, A.; Lu, C.-D. *J. Am. Chem. Soc.* **2006**, *128*, 5356–5357, it should be noted that these authors commented on the suitability of the oxaza-Cope rearrangement for the preparation of trichodermamide-like structures.
7. Dondas, H. A.; Grigg, R.; Hadjisoteriou, M.; Markandu, J.; Kennewell, P.; Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 1119–1128.
8. Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1537–1538.

9. Ellames, G. J.; Hewkin, C. T.; Jackson, R. F. W.; Smith, D. I.; Standen, S. P. *Tetrahedron Lett.* **1989**, *30*, 3471–3472.
10. (a) Al-Qawasmeh, R. A.; Al-Tel, T. H.; Abdel-Jalil, R. J.; Voelter, W. *Chem. Lett.* **1999**, 541–542; See also: (b) Dang, T. T.; Albrecht, U.; Gerwein, K.; Siebert, M.; Langer, P. *J. Org. Chem.* **2006**, *71*, 2293–2301.
11. Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736–1738.
12. All novel products were fully charactersied by NMR and IR spectroscopy, as well as HRMS or elemental analysis.
13. Cribiù, R.; Allevi, P.; Anastasia, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3059–3069, the use of caesium carbonate proved much superior to the published procedure for the preparation of **12** from the corresponding bromohydrin using NaOH; (see: Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano, E. *Tetrahedron* **1999**, *55*, 5853–5866).
14. Corey, E. J.; Dittami, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 256–257.
15. Macritchie, J. A.; Silcock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895–3902.
16. Markandu, J.; Dondas, H. A.; Frederickson, M.; Grigg, R. *Tetrahedron* **1997**, *53*, 13165–13176.
17. Attempts to determine the oxime geometry by NOE (as per Imoto, H.; Imamiya, E.; Momose, Y.; Sugiyama, Y.; Kimura, H.; Sohda, T. *Chem. Pharm. Bull.* **2002**, *50*, 1349–1357) were unsuccessful.
18. The known acid (Berryhill, S. R.; Price, T.; Rosenblum, M. *J. Org. Chem.* **1983**, *48*, 158–162) was converted into amide **17** using aniline and 2-propanephosphonic anhydride; (T3P Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133–134).
19. Rouessac, F.; Leclerc, A. *Synth. Commun.* **1993**, *23*, 2709–2715.
20. Bonsignore, L.; Loy, G. *J. Heterocycl. Chem.* **1998**, *35*, 117–119.
21. Attempts to trap the isocyanate with water and produce amine **8** directly gave only intractable mixtures.
22. Bien, S.; Segal, Y. *J. Org. Chem.* **1977**, *42*, 1685–1688, we employed a more efficient route to compound **24** involving addition of (cyclohexenyl)methylmagnesium bromide to diethyl oxalate (see Ref. 15).
23. *Representative experimental—preparation of oxazine* **26**: A solution of hydroxylamine hydrochloride (42 mg, 0.60 mmol, 1.25 equiv) and sodium acetate (49 mg, 0.60 mmol, 1.25 equiv) in water (1 mL) was prepared and added via a pipette to a stirred solution of epoxyketone **25** (102 mg, 0.48 mmol, 1.0 equiv) in MeCN (3 mL) at rt. The resulting colourless solution was stirred at rt for 12 h and then carefully concentrated to remove the acetonitrile present. The remainder was partitioned between EtOAc (20 mL) and water (10 mL), the layers separated and the aqueous further extracted with EtOAc (2 × 10 mL). The combined organic extracts were then washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in EtOAc (10 mL) and SiO_2 (5 g) added in a single portion. The slurry was stirred vigorously at rt for 4 h before the addition of an extra 5 g of SiO_2 and 10 mL of EtOAc. After 8 h of stirring at rt the reaction was judged to be complete by TLC. The mixture was filtered to remove SiO_2, the solids washed with EtOAc (50 mL) and the filtrate concentrated in vacuo. The crude material was pre-adsorbed onto SiO_2 and purified by flash column chromatography (SiO_2, 30 g, 7 cm × 35 mm ∅, 1:1 petrol/EtOAc) to afford oxazine **26** (78 mg, 72%, over two steps) as a colourless oil; R_f 0.29 (1:1, petrol/EtOAc); ν_{max}(film)/cm^{-1} 3425 (OH), 1721 (C=O), 1597 (C=N); δ_H (400 MHz; $CDCl_3$) 4.29 (2H, q, *J* 7.5, OCH_2), 3.89–3.93 (2H, m, C*H*OH and C*H*O–N=C), 2.44 (1H, dd, *J* 19.0, 7.0, C$\mathit{H}_a$$H_b$C=N–O), 2.37 (1H, br s, O*H*), 2.30–2.36 (1H, m, C*H*CH_2C=N–O), 2.22, (1H, dd, *J* 19.0, 6.0, $CH_a\mathit{H}_b$C=N–O), 1.83–1.91 (m, 1H, CH(OH)-$C\mathit{H}_aH_bCH_2$), 1.64 (1H, m, CH(OH)$CH_2C\mathit{H}_aH_bCH_2$), 1.38–1.59 (4H, m, $C\mathit{H}_2CHCH_2$C=N–O, CH(OH)CH_2-$CH_a\mathit{H}_bCH_2$ and CH(OH)$CH_a\mathit{H}_bCH_2$), 1.34 (3H, t, *J* 7.5, $OCH_2C\mathit{H}_3$); δ_C (100 MHz; $CDCl_3$) 163.4 (C=O), 149.2 (C=N), 78.5 (H*C*O–N=C), 66.0 (H*C*OH), 61.9 (O$\mathit{C}H_2CH_3$), 29.4 (CH(OH)$\mathit{C}H_2CH_2CH_2$CH), 27.1 (CH(OH)$CH_2CH_2\mathit{C}H_2$CH), 25.3 (H*C*CH_2C=N–O), 24.1 ($H_2\mathit{C}$C=N–O), 18.5 (CH(OH)$CH_2\mathit{C}H_2CH_2$CH), 14.0 ($OCH_2\mathit{C}H_3$); *m*/*z* (ESI): 228 ($[MH]^+$, 100) [HRMS (ESI): Calcd for $C_{11}H_{18}NO_4$ $[MH]^+$, 228.1230; found, 228.1241 (4.7 ppm error)].
24. Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.
25. Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *Chem. Commun.* **1979**, 1180–1181; Haveaux, B.; Dekoker, A.; Rens, M.; Sidani, A. R.; Toye, J.; Ghosez, L. *Org. Synth.* **1980**, *59*, 26–34.