Tetrahedron Letters,Vol.30,No.21,pp 2747-2750,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE TOTAL SYNTHESIS OF CHILENINE: NOVEL CONSTRUCTIONS OF CYCLIC ENAMIDES

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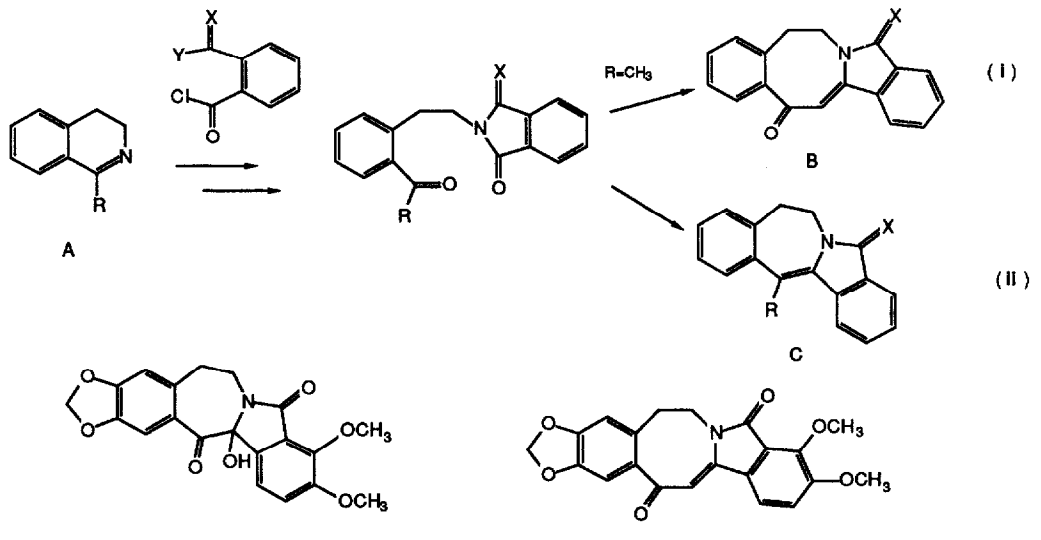
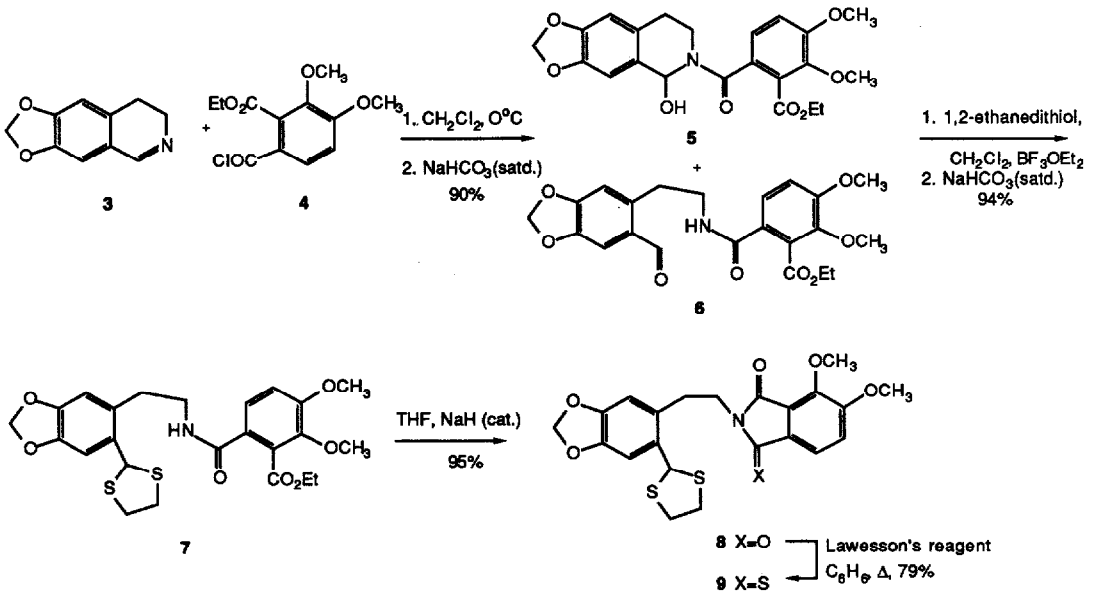
Abstract. Tungsten hexacarbonyl or rhodium(II) acetate mediated reductive coupling of a dithiolane or 2,3-diphenyl-N-aziridinohydrazone respectively with a regioselectively activated unsymmetrical dimethoxyphthalimide provides the key step in a total synthesis of the isoindolobenzazepine alkaloid chilenine (**1**).

Recently, we reported a hydrolytic phthaloylation sequence for the transformation of readily available dihydroisoquinolines (A) to the benzazocine nucleus (B) (cf. eq.(**i**)) and applied this method to a total synthesis of magallanesine(**2**). [1] Extension of such a strategy to the synthesis of a benzazepine ring system (C) (cf. eq.(**ii**)) encouraged us to consider methods for achieving the reductive coupling of a benzaldehyde type carbonyl to an amide like carbonyl group. In this Letter we report a novel carbenoid-monothiophthalimide coupling reaction as a key step in the total synthesis of the highly oxidized isoindolobenzazepine alkaloid chilenine (**1**). [2,3,4]



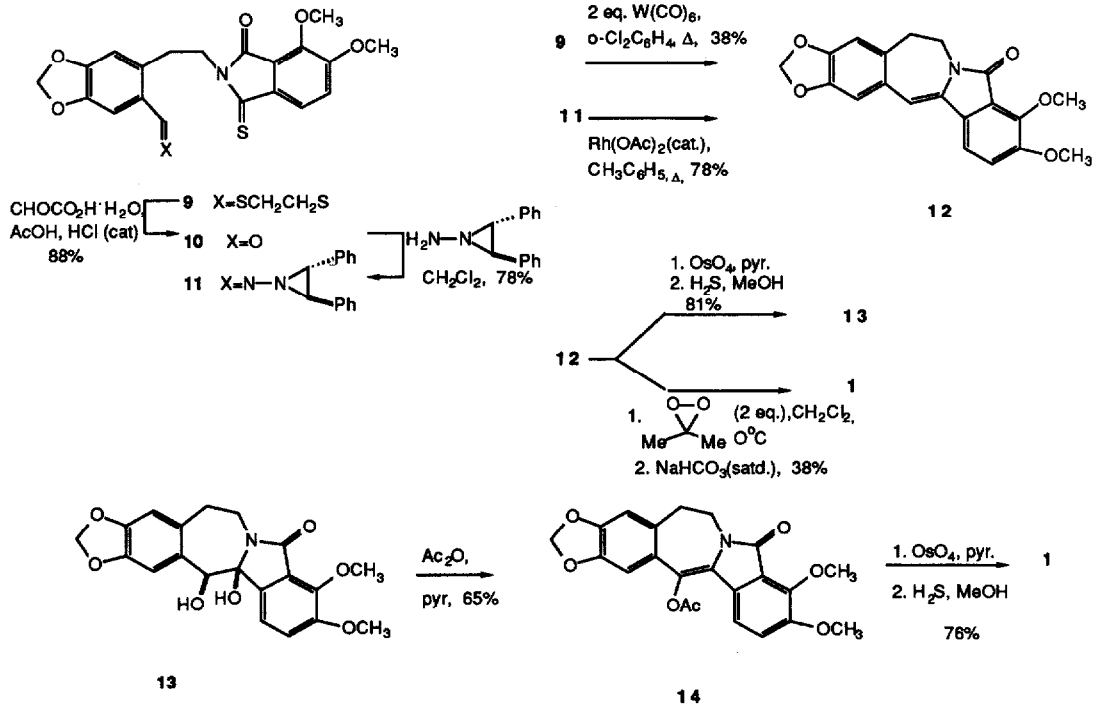
Treatment of β-hydrastine (**3**) [5] with known acid chloride **4** [6] at 0°C followed by addition of saturated aqueous sodium bicarbonate yielded acylated products **5** and **6** as an inseparable mixture in 90% yield. This mixture was allowed to react with ethanedithiol in methylene chloride in the presence of boron trifluoride etherate at O°C to afford a single dithiolane (**7**) in 94% yield. Cyclization of the secondary amidic nitrogen in **7** onto the adjacent carboethoxyl group under base catalysis produced phthalimide **8** in 95% yield. The discovery of the regioselective activation of a related unsymmetrical dimethoxyphthalimide was previously reported in our synthesis of magallanesine.[1] In the case at hand, reaction of **8** with Lawesson's reagent[7] in refluxing benzene provided a 79% yield of monothiophthalimide **9**. That the desired phthalimide carbonyl group had been engaged as its thio analog was demonstrated by subsequent transformation of **9** to chilenine (**1**) (*vide infra*).



Heating **9** in *o*-dichlorobenzene in the presence of two equivalents of tungsten hexacarbonyl effected a reductive cyclization of the dithiolane-monothiophthalimide to provide enamide **12** in 38% yield.[8] Alternatively, transthioacetalization of **9** with glyoxylic acid in acetic acid yielded aldehyde **10** in 88% yield.[9] Treatment of **10** with 1-amino-trans-2,3-diphenylaziridine[10] provided hydrazone **11** in 78% yield. Addition of **11** to a refluxing suspension of rhodium(II) acetate dimer in toluene afforded a 76% yield of enamide **12.**

There remained to be accomplished the oxidative transformation of **12** to chilenine (**1**). An attempt to oxidize **12** with 3-chloroperoxybenzoic acid was complicated by competing carbon-carbon bond cleavage processes.[11] It was proposed that the initially formed epoxide suffered attack by perbenzoate nucleophile to give a perester which underwent subsequent fragmentation. Accordingly, a stepwise approach was initially pursued.

Treatment of enamide (**12**) with osmium tetroxide in pyridine followed by workup with hydrogen sulfide in methanol afforded *cis*-diol **13**[12] in 81% yield. The reaction of **13** with acetic anhydride in pyridine at 60°C yielded enol acetate **14** in 65% yield. Osmylation of **14** produced a 79% yield of chilenine (**1**) which was identical in all respects (^{1}H NMR, IR, MS, mp. 154-156°C) to natural **1**. Alternatively, treatment of **12** with two equivalents of dimethyl dioxirane[13] in methylene chloride at 0°C followed by addition of aqueous sodium bicarbonate directly provided **1** in 38% yield. The outcome of this reaction is apparently due to the non-nucleophilic nature of dimethyl dioxirane as compared to 3-chloroperoxybenzoic acid. Thus, the initially formed epoxide, not being subject to attack by peracid nucleophiles, is able to rearrange to a ketone or enol which can then be oxidized to chilenine (**1**).



In summary, a new strategy for the elaboration of a benzazepine nucleus from a dihydroisoquinoline system has been realized in the context of a total synthesis of chilenine (**1**). In addition, the difficulties associated with transforming enamide **12** to α-keto carbinolamide (**1**) without concomitant carbon-carbon bond cleavage have been overcome. The results of further studies involving new cyclization reactions of various imide and amide derivatives will be reported in due course.

Acknowledgements This research was supported by PHS Grant CA 28824. The authors thank Dr. Martin Maier for significant contributions to the development of the hydrolytic phthaloylation technology employed in this work. A Kent Fellowship (Yale University) to F.G.F. is gratefully acknowledged. We thank John van Duzer (Yale University) for providing a sample of the carboxylic acid corresponding to **4**. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210.

Notes and References

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14. All new compounds were characterized by 1H NMR, IR, MS, HREIMS and/or elemental analysis, and melting point (where appropriate): **8** (186-187°C), **9** (209-211°C), **10** (182-183°C).

(Received in USA 16 February 1989)