Ruthenium-catalysed Atom-transfer Cyclisation of *N*-(Cyclohex-2-enyl)-α-chloro-α-(phenylthio)acetamides. A Formal Total Synthesis of (±)-Haemanthidine and (±)-Pretazettine

Hiroyuki Ishibashi,* Hiroshi Nakatani, Satoshi Iwami, Tatsunori Sato, Nobuyuki Nakamura, and Masazumi Ikeda*

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

The hydroindole (**18**), which previously served as a key intermediate in the total synthesis of (±)-haemanthidine (**2**) and (±)-pretazettine (**1**), has been prepared in a highly stereocontrolled manner by a reaction sequence involving a ruthenium-catalysed atom-transfer cyclisation of an α-chloro sulphide.

Pretazettine (**1**) is one of the most complex molecules of the crinine class of *Amaryllidaceae* alkaloids that contain a *cis*-3a-arylhydroindole ring system as the basic structural element.[1] Its potent antiviral and anticancer properties[1] render this molecule an attractive and challenging synthetic target.[2,3] Haemanthidine (**2**), another member of the same family, is convertible into (**1**) in a single step by treatment with methyl iodide followed by a workup under mildly basic conditions,[4] and hence much effort has gone into the synthesis of (**2**) as the pivotal relay to pretazettine (**1**).[2,5] We now report a concise, stereoselective synthesis of the 3-(pivaloyloxy) hydroindole (**18**), a key intermediate in Martin's total synthesis of (**2**) as well as (**1**),[2] using a ruthenium-catalysed atom-transfer cyclisation of α-chloro sulphides as a key step.

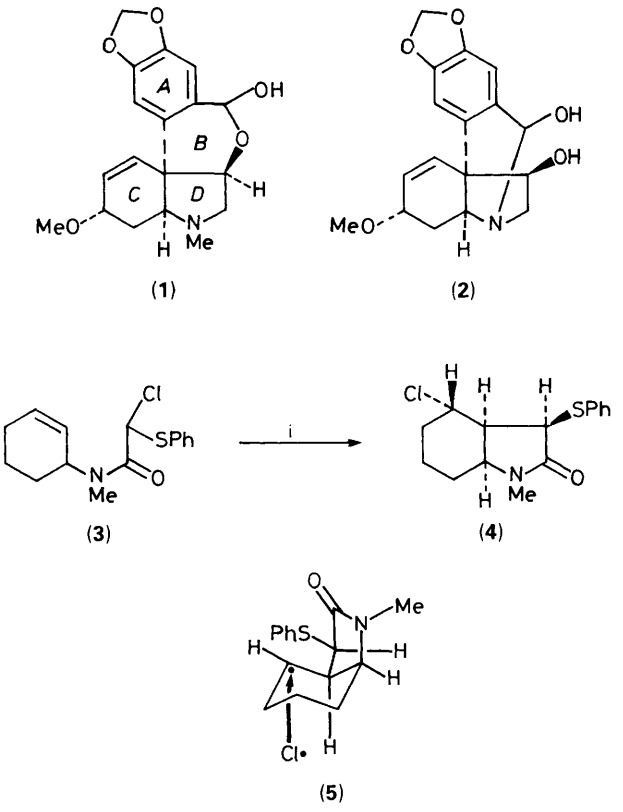
We initiated our investigation by examining the possibility of an alkene cyclisation of the α-chloro sulphide (**3**) under reported atom-transfer conditions.[6] A benzene solution of (**3**) was heated in the presence of 10 mol% of $RuCl_2(PPh_3)_3$ in a sealed tube at 140 °C for 30 min; this gave the lactam (**4**)† in 67% yield. The ^1H NMR spectrum of (**4**)‡ showed its chlorine at C-4 to be equatorial,§ implying that the intramolecular addition of the α-chloro sulphide (**3**) to its alkenic bond proceeded in an *anti*-mode. This result can be explained by assuming the radical intermediate (**5**), in which the chlorine atom attacks the convex face of this *cis*-fused bicyclic system to lead to the *anti*-addition product (**4**).

The key chloro sulphide (**12**) having a methoxy group and relative stereochemistry characteristic of the *C* ring in (**1**) was prepared from the amino alcohol (**9**), which in turn was

† Satisfactory elemental analyses or high resolution mass spectra, and spectroscopic data were obtained for all new compounds.

‡ ^1H NMR *spectral data* ($CDCl_3$, 300 MHz) for the cyclisation products (**4**) and (**13**) are as follows (diagnostic data only). For (**4**): δ 2.38 (1 H, ddd, *J* 7.8, 5.3, 4.9 Hz, H-3a), 3.66 (1 H, q, *J* 5.3 Hz, H-7a), 3.78 (1 H, d, *J* 4.9 Hz, H-3), 4.00 (1 H, ddd, *J* 8.5, 7.8, 4.0 Hz, H-4). For (**13**): δ 3.69 (1 H, tt, *J* 11.0, 4.0 Hz, H-6), 3.97 (1 H, t, *J* 3.4 Hz, H-7a), 4.13 (1 H, s, H-3), 4.74 (1 H, t, *J* 3.5 Hz, H-4).

§ Stereochemistry of the 3β-phenylthio group of (**4**) was confirmed by direct comparison of its dechlorinated compound [Bu_3SnH, azoisobutyronitrile (AIBN), benzene, reflux] with an authentic sample prepared independently by us. Details will be reported in due course.



Scheme 1. *Reagents and conditions:* i, $RuCl_2(PPh_3)_3$, benzene, 140 °C.

synthesised in a highly stereocontrolled manner from the cyclohexene (**6**) by the method recently developed (Scheme 2).[7]

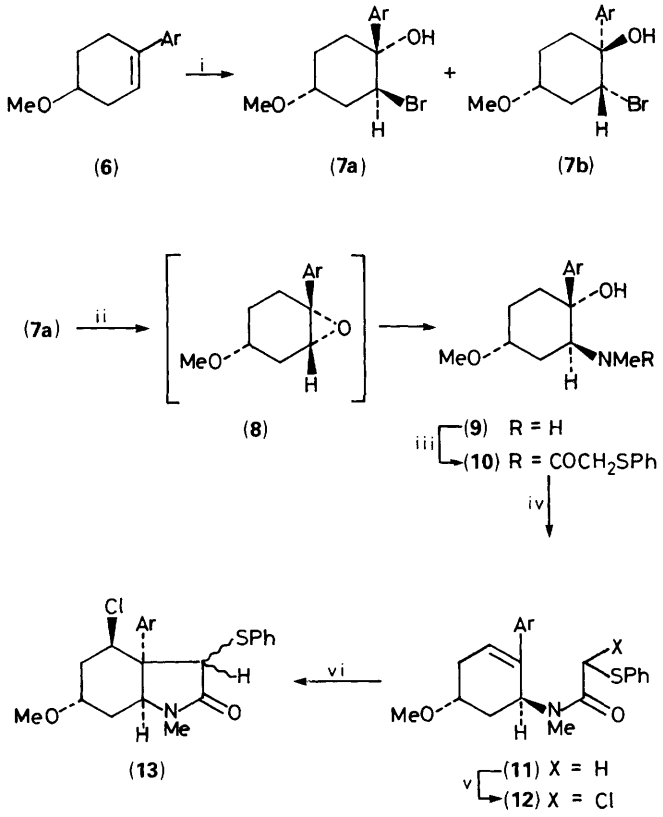
The cyclization of (**12**) was effected by heating in the presence of 20 mol% of $RuCl_2(PPh_3)_3$ at 150 °C for 2.5 h to give the expected lactam (**13**) in 57% yield accompanied by an unidentified product. In contrast to (**4**), the chlorine of (**13**) was found to be axial,¶ which suggested the intramolecular addition of (**12**) occurs in a *syn*-mode. The steric bulk of the angular aryl group is apparently sufficient to direct the chlorine atom to the concave face of the radical intermediate.

Oxidation of (**13**) with *m*-chloroperbenzoic acid followed by sequential treatment of the resultant sulphoxide (**14**) with $(CF_3CO)_2O$ and then with a saturated $NaHCO_3$ solution afforded the dioxo compound (**15**) in 87% yield from (**13**). Heating of (**15**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile at 160 °C in a sealed tube for 3 h furnished the alkene (**16**) in 48% yield.

Reduction of (**16**) with $LiAlH_4$ proceeded in a highly stereoselective manner, where the reducing agent attacks the convex face, giving the 3β-alcohol (**17**)[3a] in 63% isolated yield as a single stereoisomer. No 3α-alcohol was detected (^1H NMR spectroscopy and TLC) in the crude reaction mixture.

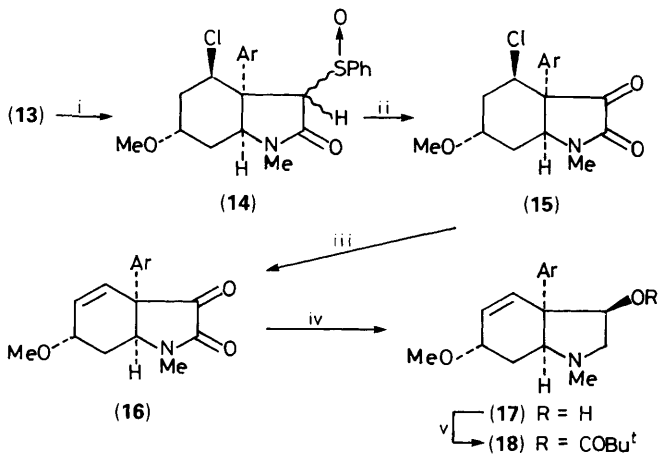
Finally, acylation of (**17**) with pivaloyl chloride afforded, in 83% yield, the ester (**18**), which had spectral characteristics identical to those of previously recorded spectra of compound (**18**). Since compound (**18**) was previously converted in four steps into (±)-haemanthidine (**2**),[2] the present preparation of (**18**) constitutes a formal total synthesis of the two title alkaloids.

¶ The stereochemistry of the phenylthio group is unknown at this stage.



Ar = 3,4,-Methylenedioxyphenyl

Scheme 2. *Reagents and conditions:* i, *N*-bromosuccinimide, H_2O, MeCN, (**7a**) (73%), (**7b**) (18%); ii, $MeNH_2$, MeOH, 100 °C, quant.; iii, $PhSCH_2COCl$, NEt_3, CH_2Cl_2, 80%; iv, *p*-$MeC_6H_4SO_3H$, benzene, reflux, 76%; v, *N*-chlorosuccinimide, CCl_4, quant.; vi, $RuCl_2(PPh_3)_3$, benzene, 150 °C, 57%.



Ar = 3,4-Methylenedioxyphenyl

Scheme 3. *Reagents and conditions:* i, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, quant; ii, $(CF_3CO)_2O$, 2,6-lutidine, CH_2Cl_2, reflux, then sat. $NaHCO_3$, 87%; iii, DBU, MeCN, 160 °C, 48%; iv, $LiAlH_4$, tetrahydrofuran, reflux, 63%; v, Bu^tCOCl, pyridine, 30—40 °C, 83%.

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