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A general approach to the galanthamine ring system

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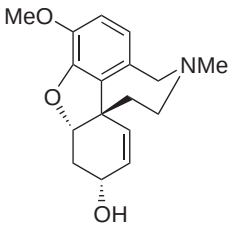
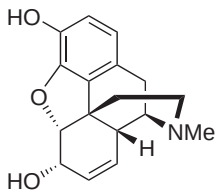
Abstract—An approach to the galanthamine ring system is reported, which utilises an intramolecular Heck reaction to establish the benzofuran ring system present in both galanthamine and morphine.

Galanthamine (**1**) is an alkaloid with a structure related to morphine (**2**). It is isolated from the Cauasian snowdrop, *Galanthaus woronowii*[1] as well as the bulbs of *Amaryllidaceae*. Galanthamine has been shown to exhibit potent acetylcholinesterase inhibitory activity[2] and as such is a primary candidate in the management of Alzheimer's disease. A recent publication by Fels et al.,[3] has prompted us to comment upon our research in this area.



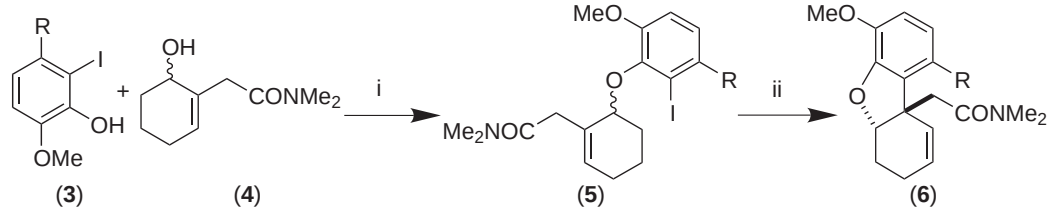
(**1**)



(**2**)

Our approach to both galanthamine and morphine relies on an efficient route to alkenes **6a** and **6b** which were synthesised using Heck methodology (Scheme 1).

We employed a similar synthetic scheme to Fels et al.,[3] utilising a Mitsunobu[4] coupling of phenol **3**;[5] however, we found that using tributylphosphine and the morpholine derivative of DEAD made purification easier. In our case, intramolecular Heck[6] cyclisation proceeded in lower yields with formation of the isomeric alkene (**7**) from palladium(0) mediated isomerisation when potassium carbonate is used as a base. The use of silver(I) salts in Heck reactions prevents double bond isomerisation as described by Overman et al.[7] Indeed, in our case, changing the base to silver(I) carbonate gave exclusively alkene **6** in 75% yield with no evidence of isomeric alkene **7**.



(**3**) (**4**) (**5**) (**6**)

(**3a**) R = CHO, (**3b**) R = -$CH_2CH_2NO_2$
(**5a**) R = CHO, (**5b**) R = -$CH_2CH_2NO_2$
(**6a**) R = CHO, (**6b**) R = -$CH_2CH_2NO_2$

Scheme 1. *Reagents*: (i) azodicarboxylic dimorpholide, Bu_3P, THF, 65%. (ii) $Pd(OAc)_2$, Ag_2CO_3, ethylenebis(diphenylphosphine), DMF, reflux 2 hours, 75%.

Keywords: galanthamine; morphine; Mitsunobu; intramolecular Heck; allylic oxidation.
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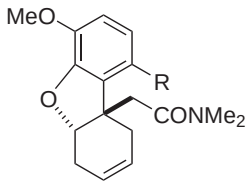


(7)

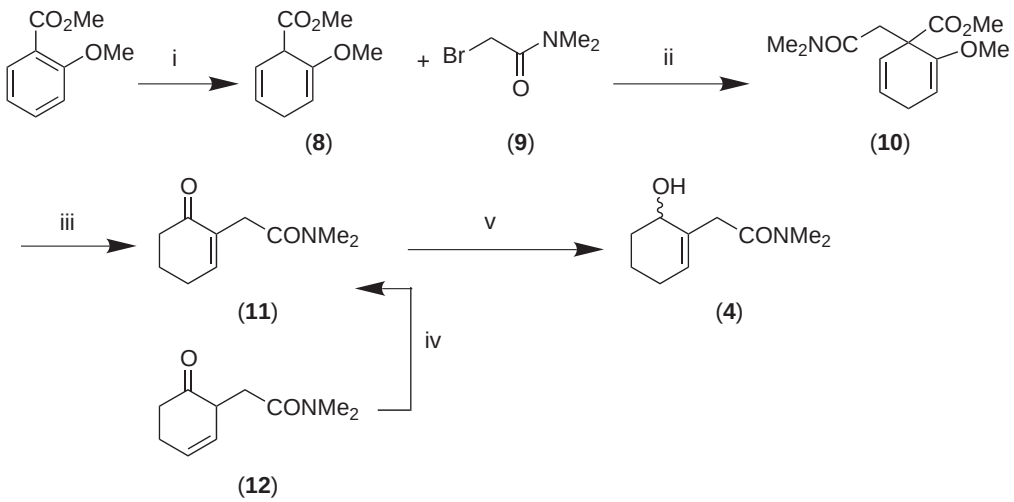
Our allylic alcohol **4** was synthesised by a reliable and highly efficient route utilising Birch[8] reduction chemistry (Scheme 2). Birch reduction of methyl 2-methoxybenzoate under standard conditions gave the cyclohexadiene (**8**) in 83% yield. Deprotonation with LDA, and subsequent quenching with the bromoacetamide (**9**),[9,10] cleanly produced **10** in almost quantitative yield. Saponification of the ester (**10**) and hydrolysis with concentrated hydrochloric acid generated the β-keto acid, which spontaneously decarboxylated to furnish isomeric cyclohexenes **11** and **12**. These were converted into the 2-ene isomer (**11**) by heating in THF and 1 M HCl in an overall yield of 92%. The enone (**11**) was reduced with sodium borohydride, interestingly with no 1,4 reduction occurring, to yield allylic alcohol **4**.

In order to obtain the galanthamine ring system (**14**) the aldehyde (**6a**) was condensed with methylamine, and subsequent sodium borohydride reduction afforded the secondary amine (**13**). The hydrochloride salt of this amine was heated under high vacuum to produce the galanthamine ring system (**14**) in 92% yield (Scheme 3).[11] This is the same intermediate that Fels and coworkers reported and are intending to manipulate at the allylic position. However, we wish to report our findings in this area, as we have found allylic oxidation of **14** to be problematic as shown in Table 1.

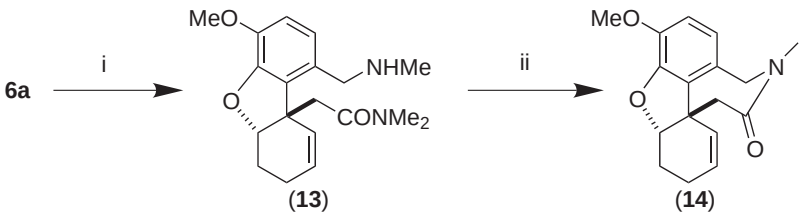
In addition we have also attempted to introduce the desired functionality via various other methods. These include using NBS to produce an allylic bromide which could be manipulated using the procedure of Lallemand et al.[12] However, only a complex mixture was obtained. The use of molecular bromine as an alternative resulted in bromination of the aromatic ring. Epoxidation of **14** and base mediated ring opening was also attempted. Although the epoxide could be produced from 1,1,1-trifluoromethylmethyldioxirane,[13] ring opening could not be effected with a variety of bases.

We are currently investigating a synthetic route to morphine utilising intermediate **6b** in a [3+2] nitrile oxide cycloaddition. The nitroalkane (**6b**) can be smoothly converted with phenylisocyanate in DCM and catalytic triethylamine to the isoxazoline (**17**) in 80% yield.

In summary we have developed a route to the galanthamine ring system by a conceptually similar route to that of Fels et al., and we have shown that manipulation of the allylic position is a far from trivial matter. We are also continuing our research efforts toward



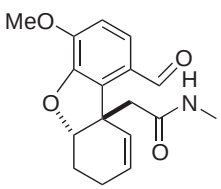
Scheme 2. *Reagents*: (i) K, liq. NH_3, THF, *t*-BuOH; NH_4Cl, 83%. (ii) LDA, THF, **9**, 95%. (iii) NaOH, H_2O; conc. HCl. (iv) 1 M HCl, THF, 92%. (v) $NaBH_4$, MeOH, 75%.



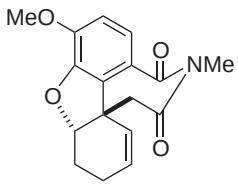
Scheme 3. *Reagents*: (i) $MeNH_2$, EtOH, rt; $NaBH_4$, MeOH, 90%. (ii) HCl, MeOH; vacuum, 120°C, 92%.

Table 1. Results from attempted allylic oxidation of **14**

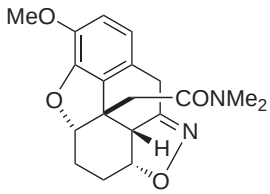
Reagents and conditions	Starting material (%)	Cleaved lactam **15** (%)	Imide **16** (%)	Complex mixture
SeO_2, EtOH, heat	100	–	–	–
SeO_2, *tert*-BuOH, 150°C	100	–	–	–
SeO_2, HCO_2H, dioxane	60	–	–	–
$Cr(CO)_6$, TBHP, MeCN	–	90	–	–
MnO_2, DCM, rt	–	20	70	–
$Pd(OAc)_2$, MnO_2, AcOH, heat	–	70	–	–
CuI, TBHP, benzene, heat	–	80	–	–
CuBr, TBHP, benzene, heat	–	70	–	–
$Pb(OAc)_4$, AcOH, rt	90	–	–	–
CrO_3, *t*-BuOH, rt	–	60	–	–
CrO_3, DMP, −20°C	–	40	50	–
PDC, TBHP, benzene, rt	–	–	–	✓
$[Rh_3O(OAc)_6CH_2O]OAc$, TBHP, AcOH,	100	–	–	–



(**15**)



(**16**)



(**17**)

galanthamine, by utilising an alternative procedure for introduction of the oxygen functionality. In addition research toward morphine is continuing and will be reported at a later date.

Acknowledgements

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