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# Exploiting the palladium[0]-catalysed Ullmann cross-coupling reaction in natural products chemistry: application to a total synthesis of the alkaloid (±)-aspidospermidine

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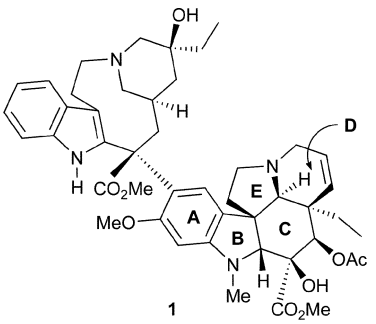
**Azide 14, available through the title cross-coupling process, has been converted, *via* the ring-fused aziridine 15, into the alkaloid aspidospermidine.**

We have recently disclosed a two-step process for the preparation of indoles that involves the initial palladium[0]-catalysed Ullmann cross-coupling of *o*-nitrohalobenzenes with readily available α-halo-enones or -enals.[1] The resulting α-(*o*-nitrophenyl)enones or -enals then engage in a simple reductive cyclisation reaction to deliver the target indoles.[2] We are now seeking to exploit such chemistry in the development of a total synthesis of the structurally complex and clinically significant indole–indoline binary alkaloid vinblastine (**1**),[3] a compound that had eluded *de novo* total synthesis until recently.[4] As part of such endeavours, we have recently shown[5] that the micro-organism *Pseudomonas putida* BGXM1 can convert *m*-ethyltoluene into the metabolite **2**, a compound incorporating key elements associated with the C-ring of compound **1**. Herein we outline complementary work that has culminated in the synthesis of the racemic modification of the alkaloid aspidospermidine (**3**),[6] a compound embodying the ABCDE-ring system associated with vinblastine. This study serves to highlight the synthetic utility of α-(*o*-nitrophenyl)enones available through the title cross-coupling process as well as the likelihood of being able to exploit compound **2** in developing a synthesis of vinblastine.

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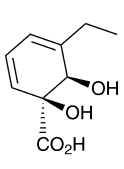


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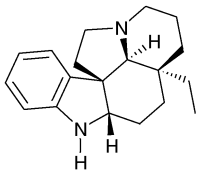


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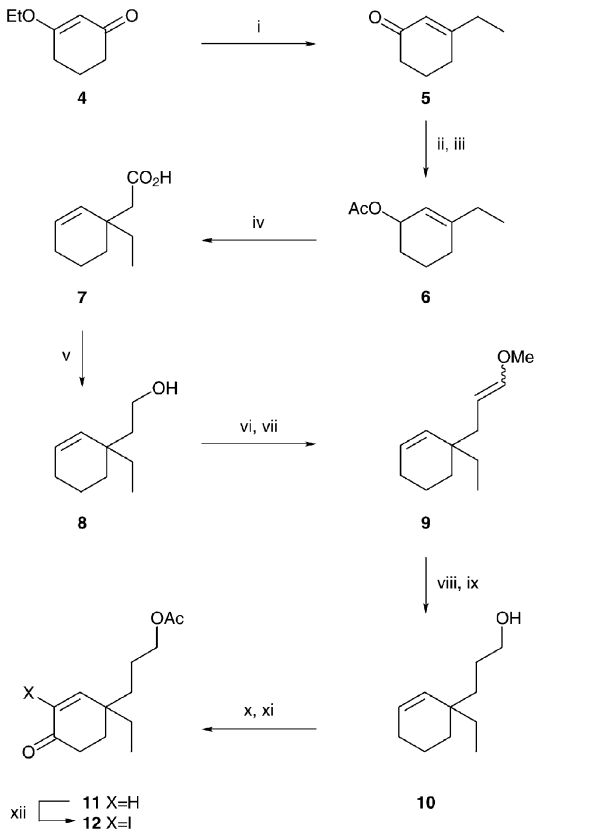
The synthesis of the α-iodocyclohexenone required for the Pd[0]-catalysed Ullmann cross-coupling reaction is shown in Scheme 1. Thus, commercially available 3-ethoxycyclohexenone (**4**) was treated with ethylmagnesium bromide and the resulting tertiary-alcohol subjected to an acidic work-up. In this manner the previously reported enone **5**[7] was obtained in 89% yield. Subjection of the last compound to 1,2-reduction using sodium borohydride gave the expected allylic alcohol which was immediately acetylated under standard conditions to provide




**Scheme 1** *Reagents and conditions*: (i) EtMgBr (2 mol equiv.), THF, 18 °C, 3 h then 10% aq. HCl, 0 °C, 14 h; (ii) $NaBH_4$ (1 mol equiv.), MeOH, 0→18 °C, 3 h; (iii) $Ac_2O$ (2 mol equiv.), DMAP (cat.), pyridine, 0→18 °C, 10 h; (iv) LDA (1.2 mol equiv.), TBDMS–Cl (1.3 mol equiv.), THF, −78→66 °C, 6 h then MeOH, 18 °C, 14 h; (v) $LiAlH_4$ (7 mol equiv.), THF, 0→18 °C, 4 h; (vi) TEMPO (cat.), $PhI(OAc)_2$ (1.1 mol equiv.), $CH_2Cl_2$, 18 °C, 5 h; (vii) $Ph_3P{=}C(H)OMe$ (1.1 mol equiv.), THF, −78→18 °C, 3 h; (viii) 1 : 10 v/v 10% aq. HCl–THF, 0 °C, 3 h; (ix) $NaBH_4$ (1 mol equiv.), MeOH, 0→18 °C, 3 h; (x) $Ac_2O$ (2 mol equiv.), DMAP (cat.), pyridine, 0→18 °C, 10 h; (xi) $Cr(CO)_6$ (0.5 mol equiv.), 70% *t*-BuOOH (3.0 mol equiv.), MeCN, 82 °C, 14 h; (xii) $I_2$ (4 mol equiv.), 1 : 1 v/v $CCl_4$–pyridine, 18 °C, 12 h.

the allylic acetate **6**[8] in 96% yield over the two steps. The ketene acetal obtained by treating compound **6** with LDA then *tert*-butyldimethylsilyl chloride (TBDMS–Cl) engaged in an Ireland–Claisen rearrangement[9] reaction on heating in refluxing THF and, after workup, the cyclohexene acetic acid **7**[10] was obtained (62%). Acid **7** was reduced to the corresponding alcohol **8**[11] (96%) using lithium aluminium hydride (LAH) and the latter then oxidised to the corresponding aldehyde using the protocol of Margarita *et al*.[12] Reaction of this aldehyde with (methoxymethylene)triphenylphosphorane, generated *in situ* by treating the corresponding phosphonium salt with sodium hexamethyldisilazide, afforded a 1 : 1 mixture of the *E*- and *Z*-isomers of the alkenyl ether **9** in 92% over these two steps.

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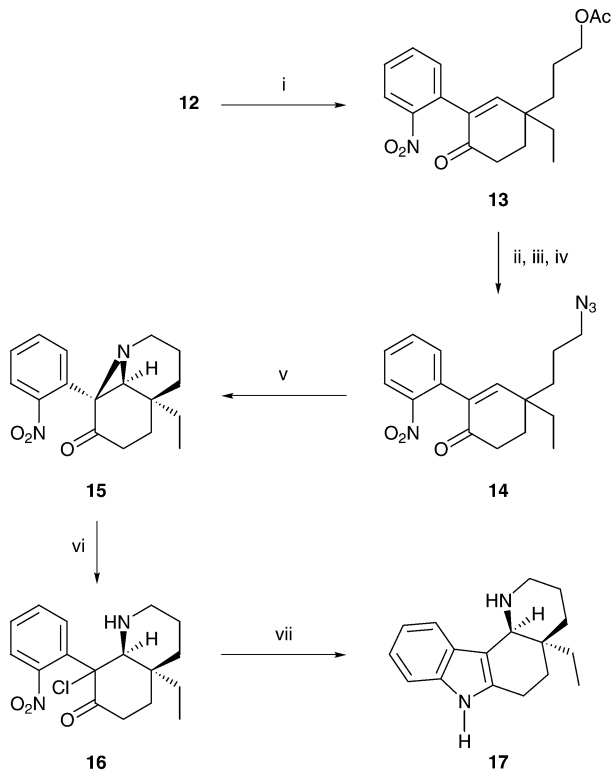
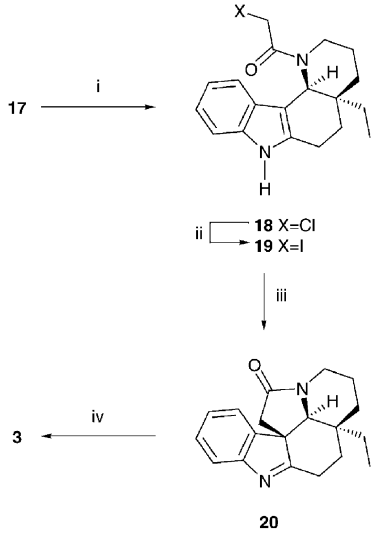
Acid-catalysed hydrolysis of the last compound and reduction of the resulting aldehyde with sodium borohydride then afforded the higher homologue, **10** (84% from **9**), of alcohol **8**. The readily derived acetate was then subjected to allylic oxidation using $Cr(CO)_6$–*t*-BuOOH[13] to give enone **11** (65% from **10**). Subjection of compound **11** to the versatile α-iodination protocol of Johnson and coworkers[14] finally gave the target halide **12** in quantitative yield.

The initial step associated with the second stage (Scheme 2) of our synthesis of aspidospermidine involved the pivotal Pd[0]-catalysed Ullmann cross-coupling of α-iodoenone **12** with *o*-iodonitrobenzene. This was achieved in DMSO at 70 °C using 5 g atom equiv. of copper powder and $Pd_2(dba)_2$ as catalyst. In this manner compound **13** was obtained in 75% yield. In anticipation of carrying out an intramolecular 1,3-dipolar cycloaddition reaction of the type recently reported by Guo and Schultz,[15] acetate **13** was hydrolysed to the corresponding alcohol and the readily derived mesylate reacted with sodium azide in DMF at 67 °C to give compound **14** in 87% yield over these three steps. Heating a benzene solution of azide **14** at *ca.* 75 °C for three days then afforded the ring-fused aziridine **15** in 72% yield. The triazoline arising from 1,3-dipolar cycloaddition of the azide moiety within substrate **14** to the tethered α-(*o*-nitroaryl)enone unit is undoubtedly the immediate precursor to product **15** although it could not be isolated from the reaction mixture.[16] After much experimentation we established that regioselective cleavage of aziridine **15** could be achieved by treating this compound with an ethereal solution of HCl in $CH_2Cl_2$. The resulting and rather unstable hydrochloride salt of α-chloroketone **16**, which was obtained as a single diastereoisomer, was immediately subjected to reduction with titanium trichloride·3THF in the presence of ammonium acetate. In this manner the crystalline indole **17** (mp 172–177 °C; lit.[6g] mp 180–182 °C) was obtained in 46% yield over the two steps. The physical and spectral data derived from this material proved a good match, in all respects, with those reported previously by Wenkert and Hudlicky[6g] who have described a two-step method for the conversion of compound **17** into aspidospermidine (**3**). However, we followed the slightly longer but higher yielding procedure (Scheme 3) described by Toczko and Heathcock[6r] in completing the present synthesis of (±)-aspidospermidine. Thus, reaction of piperidine **17** with α-chloroacetyl chloride afforded the α-chloroamide **18**[6r] (69%) that was, in turn, converted into the corresponding α-iodoamide **19**[6r] under Finkelstein conditions. Treatment of this last compound with silver(I) triflate then gave the lactam **20**[6r] which was reduced with LAH to give (±)-aspidospermidine (**3**) (47% yield from amide **18**). The spectral data derived from this material matched those reported[6m,r] for the natural product.




**Scheme 2** *Reagents and conditions*: (i) *o*-nitroiodobenzene (2 mol equiv.), Cu (5 g atom equiv.), $Pd_2(dba)_3$ (cat.), DMSO, 70 °C, 5 h; (ii) 1 : 4 v/v 1 M aq. $K_2CO_3$–MeOH, 18 °C, 16 h; (iii) MsCl (1.2 mol equiv.), $Et_3N$ (1.2 mol equiv.), $Et_2O$, 0→18 °C, 2 h; (iv) $NaN_3$ (3 mol equiv.), DMF, 67 °C, 3 h; (v) $C_6H_6$, 75 °C, 3 d; (vi) 1 M HCl in $Et_2O$ (2.4 mol equiv.), $CH_2Cl_2$, −15 °C, 1.5 h; (vii) $TiCl_3$·3THF (10 mol equiv.) in 1 : 2 : 2 v/v/v $H_2O$–2.5 M aq. $NH_4OAc$–acetone, 18 °C, 0.33 h.




**Scheme 3** *Reagents and conditions*: (i) α-chloroacetyl chloride (1.1 mol equiv.), $Et_3N$ (1.1 mol equiv.), $CH_2Cl_2$, 0→18 °C, 2 h; (ii) NaI (10 mol equiv.), acetone, 56 °C, 2 h; (iii) AgOTf (2 mol equiv.), THF, 18 °C, 0.5 h; (iv) LAH (4 mol equiv.), THF, 18→66 °C, 2 h.

The *S*-enantiomer of compound **8** is readily available[11] in 96% ee so the present work also constitutes a formal total synthesis of the unnatural or (−)-enantiomer of aspidospermidine. Since *R*-**8** will almost certainly be available by closely related means, the chemistry presented here should also allow access to the naturally occurring enantiomeric forms of various *Aspidosperma* alkaloids.

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16 The triazoline derived from thermolysis of the des-ethyl analogue of compound **14** is an isolable and crystalline species that has been characterised by single-crystal X-ray analysis. Full details will be reported in due course.