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The synthesis of compounds related to the indole–indoline core of the vinca alkaloids (+)-vinblastine and (+)-vincristine

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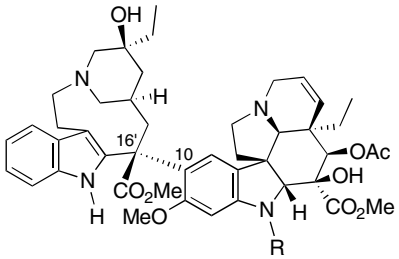
ABSTRACT

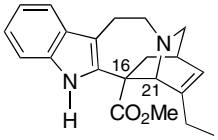
A series of α′-aryl-α′-carbomethoxycycloalk-2-en-1-ones, **16**, has been prepared using the Pinhey arylation methodology for introducing the aromatic residue. Subjection of these compounds to Johnson iodination and Pd[0]-catalyzed Ullmann cross-coupling of the resulting α-iodocycloalkenones **11** with 2-iodonitrobenzene (**5**, X = I) then affords α,α′-diaryl-α′-carbomethoxycycloalk-2-en-1-ones of the general form **10**. Reductive cyclization of this last type of compound gives the corresponding indoles **9a**–**f** (*n* = 1–3), some of which resemble the indole–indoline cores of the clinically important alkaloids (+)-vinblastine (**1**) and (+)-vincristine (**2**).

The binary indole–indoline alkaloids (+)-vinblastine (**1**) and (+)-vincristine (**2**) were originally isolated from the Madagascan periwinkle *Cartharanthus roseus* (L.) G. Don. Subsequently, it was shown that these natural products are generated biosynthetically by oxidative coupling of the co-occurring and structurally simpler metabolites catharanthine (**3**) and (−)-vindoline (**4**).[1] This coupling leads, inter alia, to the establishment of the C10–C16′-bond within compounds **1** and **2**.

The potent tubulin binding properties of (+)-vinblastine (**1**) and (+)-vincristine (**2**) have resulted in their being used clinically for the treatment of a range of cancers including various lymphomas and sarcomas, advanced testicular cancer, breast cancer and acute leukemia.[1] However, their application can be severely limited by damage to the patient's bone marrow or because of neurotoxicological effects.[1] Accordingly, considerable effort has been and continues to be devoted to the identification of analogs, especially structurally simpler ones, that might display improved therapeutic properties.[1,2] Such studies are being facilitated by the recent disclosure of the X-ray crystal structure of a vinblastine–tubulin complex.[3] While the structural complexity of the title compounds has created significant challenges for the synthetic chemist, various spectacular achievements have been recorded in the area,[4] including Fukuyama's first de novo syntheses of these alkaloids which were reported in 2002[4b] and 2004.[4a] Nevertheless, the search continues for new and efficient methods that allow for the assembly of key substructures of compounds **1** and **2**.[5] Without exception, the established routes[4] to the indole–indoline core within these alkaloids have mimicked the proposed biosynthetic pathway for linking the progenitors **3** and **4** to one another.[6] In particular, these processes exploit the nucleophilic character at C10 within the latter compound and the electrophilic properties of C16 that is revealed upon conversion of compound **3** into an azafulvinium ion derivative. On this basis, we now outline a distinctly different



1 R = Me
2 R = CHO



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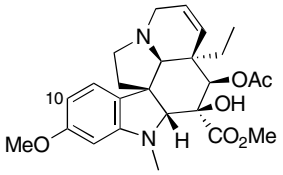

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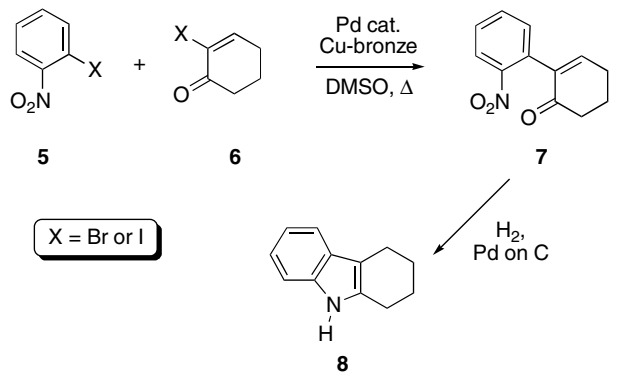
approach to the carbomethoxymethyl-bridged indole–indoline core structures of the title compounds. A major motivation for pursuing the present lines of enquiry was the prospect that biologically active analogs of compounds **1** and **2** could emerge since certain diarylmethanes and benzophenones are known to strongly inhibit tubulin polymerization and thus halt mitosis.[7]

A key element associated with the work described herein was our development, in 2003, of an effective two-step protocol for the synthesis of indoles that starts, as shown in Scheme 1, with the Pd[0]-catalyzed Ullmann cross-coupling of *o*-halonitroarenes (e.g., **5**) and α-iodo- or α-bromo-enones (e.g., **6**) or -enals.[8] This reaction proceeds smoothly using copper in DMSO at temperatures as low as 35 °C and with Pd[0]-catalyst loadings of as little as a few mol %. The ensuing cross-coupling product (e.g., **7**) is then subjected to reductive cyclization, most often using dihydrogen in the presence of palladium on carbon, and thereby affording the target indole (e.g., **8**). The starting α-halo-enone or -enal (e.g., **6**) is generally readily prepared by reaction of the corresponding non-halogented enone or enal with molecular iodine or bromine in the presence of a nucleophilic species such as pyridine according to procedures developed by Johnson and others.[9]

Bearing such results in mind, we sought methods for the construction of α-iodoenones of the general type **11** (Fig. 1) incorporating, at the α′-position, both a carbomethoxy group and various aryl (Ar) units including indoles. If such systems could be constructed it was anticipated that they would participate in Pd[0]-catalyzed Ullmann cross-coupling reactions[8] with *o*-iodonitrobenzene (**5**, X = I) to give products of the general type **10** and these would, in turn, engage in reductive cyclization reactions to deliver the target carbomethoxylated diarylmethanes, including bis-indoles if Ar = indole in structure **9**.

Clearly, the successful implementation of such an approach requires, at the outset, establishing serviceable routes to the non-iodinated equivalents of the enones of the general type **11**. In the event this proved to be a straightforward matter. So, for example, commercially available methyl 2-oxo-1-phenylcyclopentanecarboxylate (**14a**) (Scheme 2) was converted, under conventional conditions, into the corresponding silyl enol ether **15a** ($n = 1$) which was then subjected to a Saegusa-type oxidation[10] with $Pd(OAc)_2$ and *p*-benzoquinone thus affording compound **16a** ($n = 1$) in 70% yield over these two steps. The synthesis of congener **16b** ($n = 1$) required initial preparation of methyl 2-oxo-1-(2′-methoxyphenyl)cyclopentanecarboxylate [**14b** ($n = 1$)] which was achieved by 'cross-coupling' methyl 2-oxocyclopentanecarboxylate (**12**) with *o*-methoxyphenyl lead triacetate (**13b**)[11] (Path A, Scheme 2) in the presence of pyridine using protocols developed by Pinhey and co-workers.[12] Subjection of this 'cross-coupling' product to the same two-step dehydrogenation protocol (Saegusa oxidation) as detailed immediately above then afforded compound **16b**



Scheme 1.

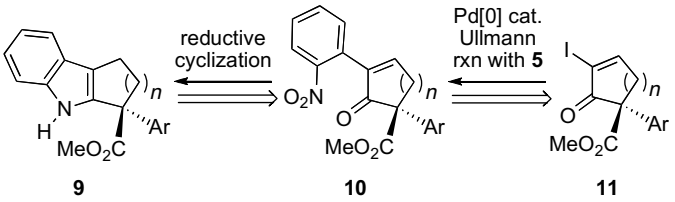
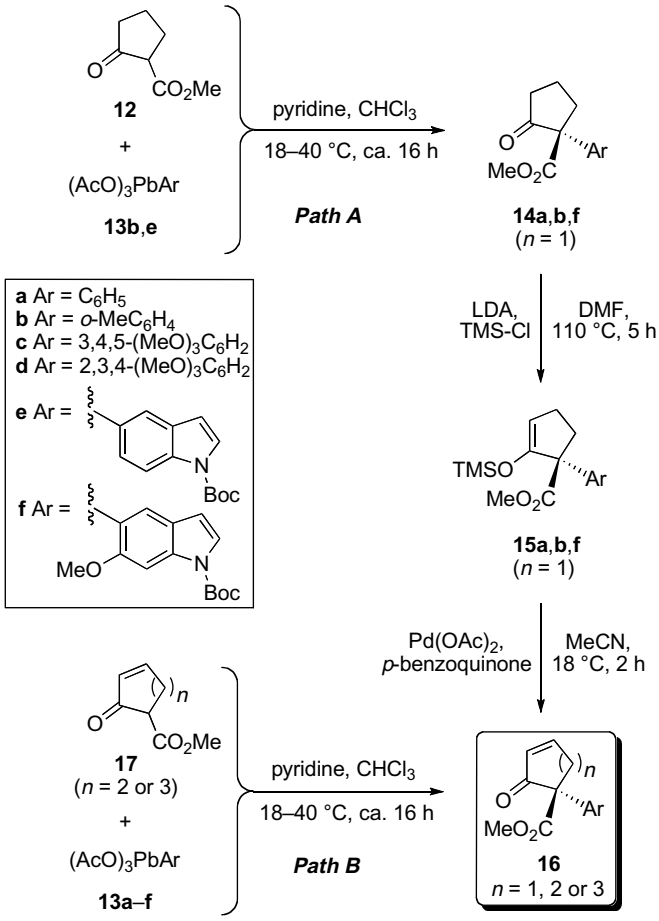


Figure 1.



Scheme 2.

Table 1
Details of the synthetic routes, as depicted in Scheme 2, used to obtain compounds **16a–f** ($n = 1$, 2 or 3)

Cpd	Path	Aryl lead triacetate	Intermediate(s) involved	Number of steps	Yield/step (%)
16a ($n = 1$)	Part of A	NR[a]	**15a** ($n = 1$)	2	72 and 97
16b ($n = 1$)	A	**13b**	**14b** ($n = 1$) and **15b** ($n = 1$)	3	72, 96 and 61
16e ($n = 1$)	A	**13e**	**14e** ($n = 1$) and **15e** ($n = 1$)	3	81, 72 and 60
16a ($n = 2$)	B	**13a**	None	1	79
16b ($n = 2$)	B	**13b**	None	1	76
16c ($n = 2$)	B	**13c**	None	1	84
16d ($n = 2$)	B	**13d**	None	1	75
16e ($n = 2$)	B	**13e**	None	1	71
16f ($n = 2$)	B	**13f**	None	1	82
16a ($n = 3$)	B	**13a**	None	1	63
16b ($n = 3$)	B	**13b**	None	1	70
16e ($n = 3$)	B	**13e**	None	1	71

[a] NR = not required.