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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**).

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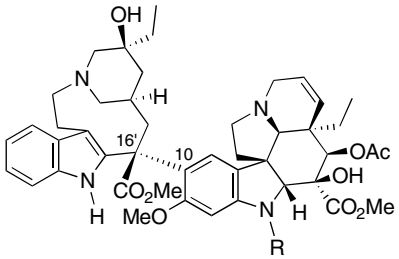
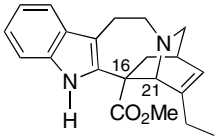
The binary indole–indoline alkaloids (+)-vinblastine (**1**) and (+)-vincristine (**2**) were originally isolated from the Madagascan periwinkle *Cartharanthus roseus* (L.) G. Don. Subsequently, it was shown that these natural products are generated biosynthetically by oxidative coupling of the co-occurring 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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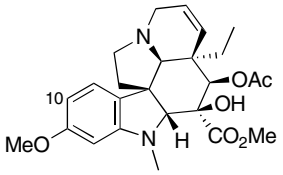

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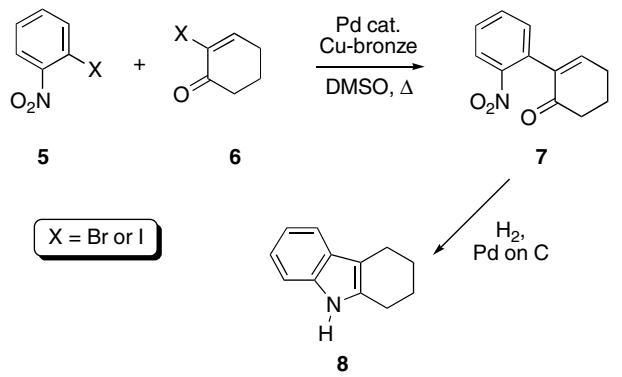
approach to the carbomethoxymethyl-bridged indole–indoline core structures of the title compounds. A major motivation for pursuing the present lines of enquiry was the prospect that biologically active analogs of compounds **1** and **2** could emerge since certain diarylmethanes and benzophenones are 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.

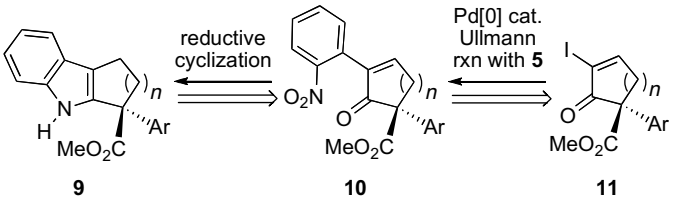
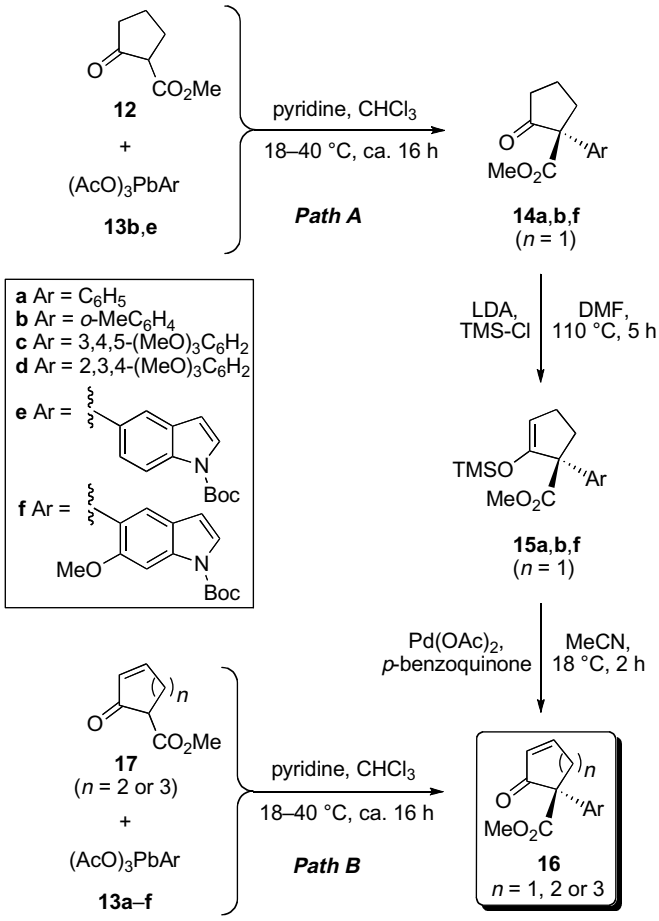


Figure 1.

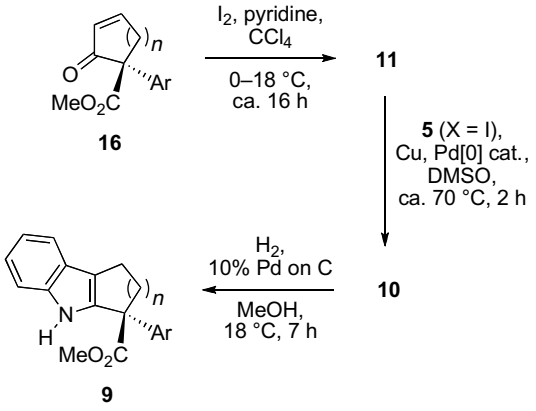


Scheme 2.

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.



Scheme 3.

Table 2
Details of the conversions depicted in Scheme 3

Starting material	Iodination product	Yield (%)	Ullmann product	Yield (%)	Indolic product	Yield (%)
16a ($n = 1$)	**11a** ($n = 1$)	60	**10a** ($n = 1$)	60	**9a** ($n = 1$)	97
16b ($n = 1$)	**11b** ($n = 1$)	96	**10b** ($n = 1$)	58	**9b** ($n = 1$)	98
16e ($n = 1$)	**11e** ($n = 1$)	93	**10e** ($n = 1$)	86	**9e** ($n = 1$)	87
16a ($n = 2$)	**11a** ($n = 2$)	60	**10a** ($n = 2$)	58	**9a** ($n = 2$)	95
16b ($n = 2$)	**11b** ($n = 2$)	60	**10b** ($n = 2$)	56	**9b** ($n = 2$)	95
16c ($n = 2$)	**11c** ($n = 2$)	98	**10c** ($n = 2$)	56	**9c** ($n = 2$)	95
16d ($n = 2$)	**11d** ($n = 2$)	75	**10d** ($n = 2$)	56	**9d** ($n = 2$)	67
16e ($n = 2$)	**11e** ($n = 2$)	73	**10e** ($n = 2$)	62	**9e** ($n = 2$)	87
16f ($n = 2$)	**11f** ($n = 2$)	70	**10f** ($n = 2$)	91	**9f** ($n = 2$)	75
16a ($n = 3$)	**11a** ($n = 3$)	58	**10a** ($n = 3$)	68	**9a** ($n = 3$)	71
16b ($n = 3$)	**11b** ($n = 3$)	68	**10b** ($n = 3$)	56	**9b** ($n = 3$)	95
16e ($n = 3$)	**11e** ($n = 3$)	61	**10e** ($n = 3$)	56	**9e** ($n = 3$)	88

($n = 1$) in 42% yield over the three steps involved. In a related manner, methyl 2-oxocyclopentanecarboxylate (**12**) was cross-coupled with the readily prepared *N*-*tert*-butoxycarbonyl-5-indole lead triacetate (**13e**)[11] in the presence of pyridine to give, after silyl enol ether formation and Saegusa-type oxidation, compound **16e** ($n = 1$). In the six-membered ring series, each of the required reaction sequences started with commercially available enone **17** ($n = 2$) that was reacted, via Path B, with the relevant aryl lead triacetate **13a–e** to give products **16a** ($n = 2$) (79%), **16b** ($n = 2$) (76%), **16c** ($n = 2$) (84%), **16d** ($n = 2$) (75%), **16e** ($n = 2$) (71%) and **16f** ($n = 2$) (82%), respectively. In the seven-membered ring series, the reaction sequences began with commercially available 2-cyclohepten-1-one which was deprotonated with LDA and the resulting enolate anion trapped with Mander's reagent (methyl cyanoformate)[13] to give the previously unreported compound **17** ($n = 3$) in 74% yield. Ester **17** ($n = 3$) was then 'cross-coupled' with the relevant aryl lead triacetate **13a, 13b** and **13c** to give products **16a** ($n = 3$) (63%), **16b** ($n = 3$) (70%) and **16e** ($n = 3$) (71%), respectively. Details of the outcomes of the above-mentioned reaction sequences are presented in Table 1.

When each of the 12 compounds represented by the generic structure **16** was subjected to the Johnson-type α-iodination conditions[9] the corresponding α-iodoenones **11** were obtained (Scheme 3) in yields (Table 2) ranging from a low of 58% [for product **11a** ($n = 3$)] to a high of 98% [for product **11c** ($n = 2$)]. Most significantly, the iodination protocol works surprisingly effectively for systems incorporating the *N*-Boc-protected indoles [i.e., compounds **16e** ($n = 2$), **16f** ($n = 2$) and **16e** ($n = 3$)] given that such electron-rich

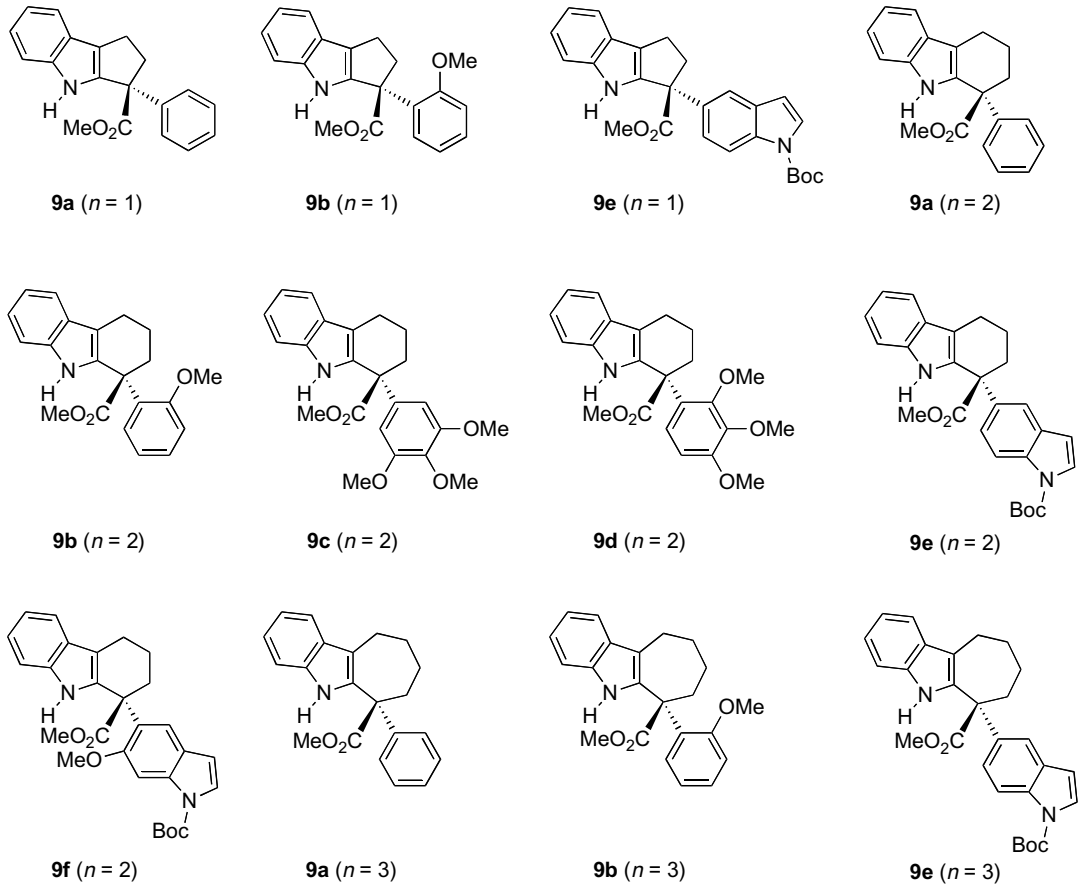
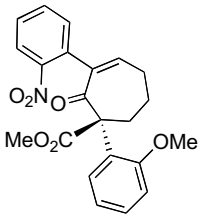


Figure 2.

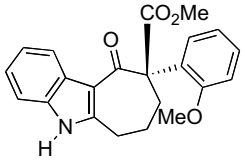
and acid-sensitive moieties might be considered especially prone to electrophilic and protic attack. Equally gratifying was the observation that each of the 12 α-iodoenones **11a–f** (n = 1–3) readily engaged in a Pd[0]-catalyzed Ullmann cross-coupling reaction with *o*-iodonitrobenzene (**5**, X = I) to give the anticipated products **10a–f** (n = 1–3) in yields ranging from a low of 56% [for products such as **10c** (n = 2)] to a high of 91% [for product **10f** (n = 2)].

The reductive cyclizations of compounds of the general form **10** proceeded relatively smoothly when the relevant substrates were exposed to dihydrogen in the presence of 10% Pd on C. In this manner, the target compounds **9** were produced in yields ranging from 67% to 98%. The full range of analogs of the indole–indoline core of the natural products **1** and **2** generated using the present protocols is shown in Figure 2. The spectral data derived from these compounds were in complete accord with the assigned structures.[14]

The results described serve to highlight the utility of the Pinhey arylation and Pd[0]-catalyzed Ullmann cross-coupling reactions in the synthesis of rather densely functionalized indoles, a situation that augers well for the application of such protocols in the rapid construction of a wide range of analogs of the title natural products. In this connection, it was also interesting to observe that reductive cyclization of the Ullmann cross-coupling product **10b** (n = 3) proceeded smoothly using $TiCl_3$[15] (rather than dihydrogen in the presence of 10% palladium on carbon) to give the novel indole **17** in 68% yield. While the mechanism of this conversion remains uncertain, it should provide a means for the construction of a series of new bis-indoles related to the core of (+)-vinblastine (**1**) and (+)-vincristine (**2**). Work directed toward such ends is now underway in our laboratories and results will be reported in due course.



10b (n = 3)



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Acknowledgments

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14. Spectral data for **9e** (n = 1), **9e** (n = 2) and **9f** (n = 2):
Compound **9e** (n = 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.58–7.54 (complex m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.24–7.09 (complex m, 4H), 6.46 (d, J = 3.7 Hz, 1H), 3.77 (s, 3H), 3.55 (m, 1H), 2.91–2.82 (complex m, 2H), 2.70–2.64 (complex m, 1H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 149.6, 141.2, 137.4, 134.1, 130.8, 127.5, 126.5, 124.2, 122.1, 121.8, 119.8, 119.3, 118.6, 118.1, 115.4, 111.9, 107.3, 83.8, 59.5, 52.7, 44.0, 28.1, 22.8; ν_{max} (neat)/cm^{-1} (NaCl) 3385, 2950, 1733, 1467, 1371, 1257, 731; MS *m/z* (EI) 430 (M^+, 16%), 371 (17), 315 (65), 84 (100); HRMS found: $M^{+\cdot}$, 430.1892. $C_{26}H_{26}N_2O_4$ requires $M^{+\cdot}$, 430.1893.
Compound **9e** (n = 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.03 (d, J = 8.9 Hz, 1H), 7.60–7.58 (complex m, 2H), 7.36 (d, J = 7.8 Hz, 1H), 7.25–7.12 (complex m, 3H), 7.01 (dd, J = 8.9 and 1.8 Hz, 1H), 6.45 (d, J = 3.6 Hz, 1H), 3.83 (s, 3H), 2.81–2.69 (complex m, 4H), 2.21–2.05 (complex m, 1H), 1.86–1.68 (complex m, 1H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 149.7, 138.5, 135.9, 131.3, 130.5, 129.0, 127.0, 126.5, 122.8, 122.1, 119.4, 119.2, 118.6, 115.0, 114.1, 111.0, 107.4, 83.8, 53.3, 52.7, 37.0, 28.1, 21.0, 19.7; ν_{max} (neat)/cm^{-1} (NaCl) 3403, 2935, 1733, 1464, 1371, 1255, 1143, 731; MS *m/z* (EI) 444 (M^+, 88%), 385 (42), 329 (100); HRMS found: $M^{+\cdot}$, 444.2048. $C_{27}H_{28}N_2O_4$ requires $M^{+\cdot}$, 444.2049.
Compound **9f** (n = 2): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.80 (s, 1H), 7.60 (d, J = 7.4 Hz, 1H), 7.48 (d, J = 3.7 Hz, 1H), 7.33 (d, J = 7.4 Hz, 1H), 7.24–7.13 (complex m, 2H), 6.67 (s, 1H), 6.31 (d, J = 3.7 Hz, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 2.80–2.76 (complex m, 3H), 2.25 (complex m, 2H), 1.87 (complex m, 1H), 1.67 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 154.4, 149.8, 135.8, 130.7, 128.9, 127.3, 124.5, 123.3, 122.0, 121.8, 119.2, 118.5, 118.2, 114.3, 111.0, 107.4, 98.3, 83.5, 55.7, 52.4, 51.0, 32.1, 28.1, 21.0, 19.3; ν_{max} (neat)/cm^{-1} 3400, 2945, 1733, 1623, 1535, 1373; MS *m/z* (EI) 474 (M^+, 91%), 415 (53), 374 (100), 359 (100); HRMS found: $M^{+\cdot}$, 474.2145. $C_{28}H_{30}N_2O_5$ requires $M^{+\cdot}$, 474.2155.
15. Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673.