Photochemically Induced Synthesis of the Topoisomerase I Inhibitors Indeno[1,2-*c*]isoquinoline-5,11-diones

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Abstract: A convenient synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones has been achieved using combinational photochemical and carbocationic cyclization tactics. The synthetic route involved first the construction of adequately functionalized *N*-styryl benzamides via Suzuki–Miyaura cross-coupling reaction with enol phosphate combined with a six-π-electron photocyclization process. The assembling of the title compounds was readily ensured through sequential carbocationic annulation reaction and ultimate oxidation of a latent hydroxy functionality.

Key words: enols, phosphates, cross-coupling, electrocyclic reactions, lactams

Since the discovery by the National Cancer Institute that NSC 314622,[1] a representative example of the class of indenoisoquinolines **1**, displays good inhibition capacities on topoisomerase I but less toxicity than indimitecan and indotecan (Figure 1),[2] several structure–activity relationships and pharmacomodulations have led to the development of constitutionally diverse analogues with improved pharmacological activities.[2a,3] Novel insights have been namely gleaned regarding the contributions of the indenone and isoquinolone rings, of the environmentally diverse aromatic units, and lactam side chain toward biological activity.[4,5] The indenoisoquinolines, which are found to inhibit the religation reaction by intercalating at the DNA cleavage site,[4a] have also garnered interest as they offer certain advantages over camptothecins, including the greater chemical stability of the compounds themselves and of the drug–enzyme–DNA cleavage complexes.[6] Among the over 400 indenoisoquinolines evaluated two have been selected for preclinical trials.[3h,7] As a consequence the development of synthetic methodologies that may have versatility for the construction of multifarious substituted and unsubstituted indenoisoquinolines continues unabated, and alternative methods are currently the object of synthetic endeavor.[8] To date the most convenient routes to these highly fused compounds containing a planar tetracyclic hetero ring system are based upon the condensation of benzo[*d*]indeno[1,2-*b*]pyrandiones with primary amines[3b,c,f,g] or upon condensation of Schiff bases with homophthalic anhydrides followed by $SOCl_2$-induced Friedel–Crafts reaction,[3e,10] the later tolerating the presence of substituents on the differentiated aromatic rings.

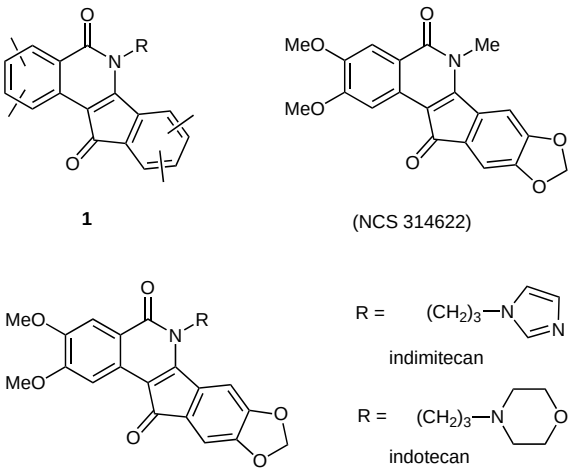

Figure 1 Structures of indenoisoquinolinedione topo I inhibitors

They can also been accessed from suitably substituted arylated isoquinolones assembled by ring-closing-metathesis reaction of polyenic benzamides[11] or through a dilithiated toluamide–benzonitrile cyclization process.[3d] All these methods generally proceed in satisfactory yields but they suffer from several drawbacks associated with the elaboration of structurally diverse precursors,[3,9] the requirement of mandatory stereodefined intermediates,[10] a point at issue,[12] and with the presence of competing metalation sites.[3d]

In this paper we wish to delineate an alternative and tactically new synthetic approach to these highly condensed indenoisoquinolinediones **1a**–**c**. This new route, which is depicted in retrosynthetic Scheme 1, hinges upon the photoinduced electrocyclic ring closure of aromatic enamides **2a**–**c** as the key step to secure the creation of the lactam unit, that is, ring B in titled compounds **1a**–**c**. The use of enamides to form isoquinoline alkaloids photochemically was pioneered by G. R. Lenz and I. Ninomiya and has proved to be very fruitful later.[13] The photocyclization process does not require any specific structural adjustments, often occurs without additional reagents and then is particularly interesting in the context of green chemistry.

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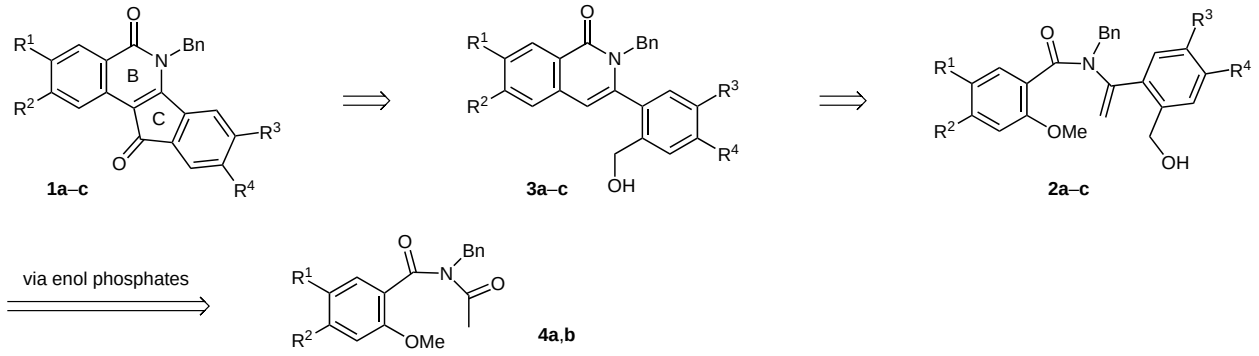
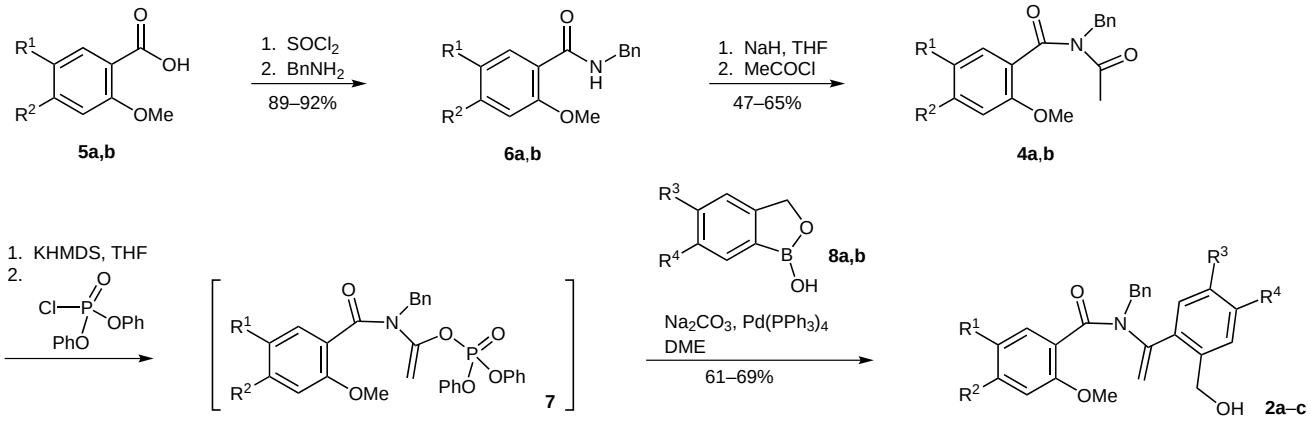


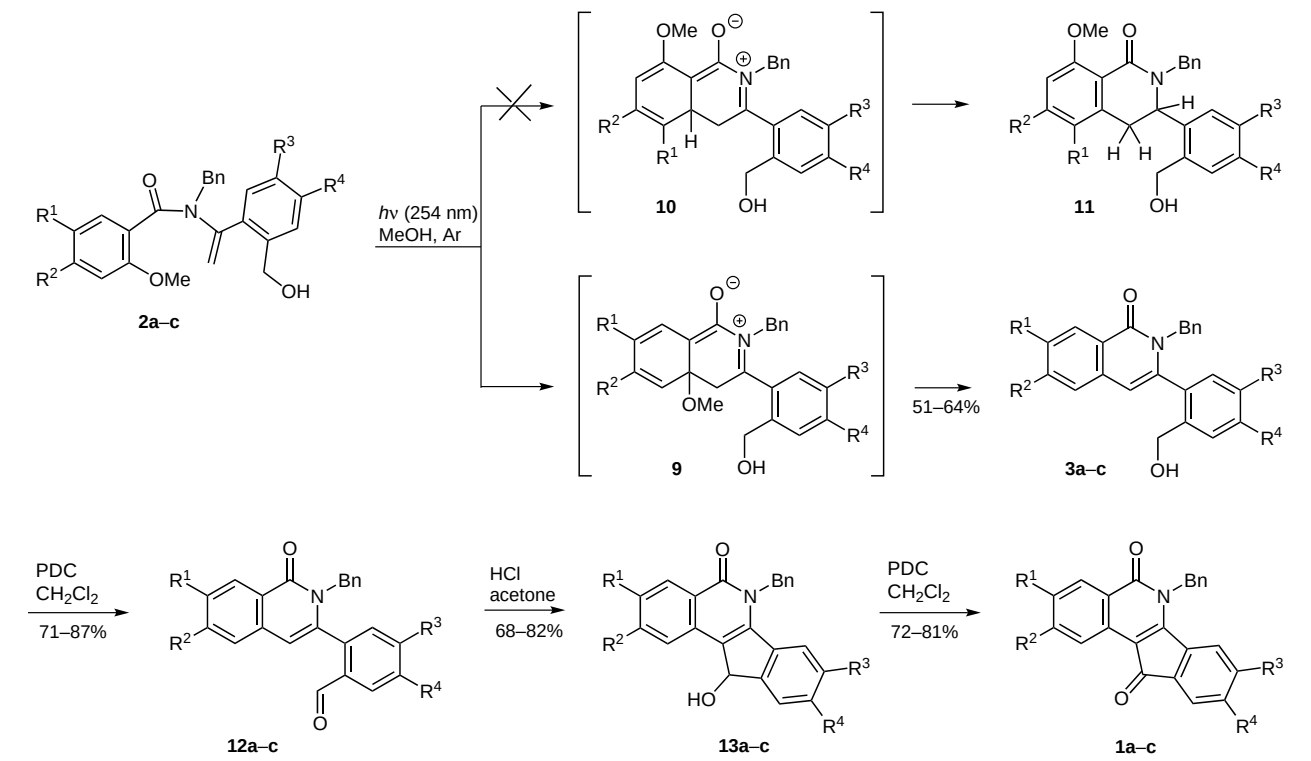
Scheme 1 Retrosynthetic analysis

Subsequent chemical manipulation of the latent benzylic hydroxy functionality of photochemical adducts **3a**–**c** should ensure the ultimate creation of the five-membered oxonucleus C. Beforehand installation of the functionalized styrene unit in **2a**–**c**, one of the major synthetically challenging task would be performed on reliance with Suzuki–Miyaura cross-coupling reaction involving enol phosphates deriving from the parent *N*-acetylbenzamides **4a**,**b**.

The first facet of the synthesis which is outlined in Scheme 2 was then the elaboration of the aromatic enamides **2a**–**c**. Initially the benzoic acids **5a**,**b** were efficiently converted into the free-NH benzamides **6a**,**b** via their acid chlorides. Subsequent deprotonation and capture of the transient amide salt with acetyl chloride delivered very satisfactory yields of the *N*-acetyl-*o*-methoxybenzamides derivatives **4a**,**b**. At this stage we surmised that these quite structurally simple compounds would possess the appropriate functionalities required for installation of a tailor-made styrene unit through a palladium cross-coupling reaction. It has been demonstrated that enol phosphates, deriving from *N*-alkylamides, are effective substrates for cross-coupling reactions and provided that the model compounds are further equipped with electron-withdrawing groups on nitrogen atoms.[14] The N,N-diacylated compounds **4a**–**c** fulfill these structural requirements. They were then exposed to KHMDS in THF at –78 °C, and the resulting potassium enolate was intercepted with diphenyl chlorophosphate to give rise to transient sensitive vinyl phosphate **7**.[14c] Subsequent Suzuki–Miyaura cross-coupling of **7** with adequately substituted oxaborole **8a**,**b**[15] under anhydrous conditions allowed the installation of the styrene unit with the concomitant connection of the mandatory hydroxymethyl appendage. The ring-opening of cyclic boronic acids[16] with enol phosphates is unprecedented and should be of interest for alternative synthetic planning. Compounds **2a**–**c**, candidates for the planned photoinduced electron cyclization process were obtained in quite satisfactory yields (Table 1).[17] The presence of the phenolic methoxy group in the starting compounds **2a**–**c** deserves some comments. It originated from the following premises: (i) upon photolysis the methoxy group forces the hexatriene–cyclohexadiene ring-closure to be regiospecific[18] and favors intermediate **9** vs. **10** (Scheme 3); (ii) initial electrocyclic ring closure is followed by a suprafacial [1,5] shift of the methoxy group. This migration is immediately accompanied by loss of a methanol molecule to provide a straightforward access to the dehydrolactams **3a**–**c**. As a consequence this photocyclization process can be performed with unsymmetrically substituted opened models, for example, compound **2c**; (iii) the photochemical process can then be cleanly performed under anaerobic conditions then ruling out undesirable photo-oxidation of sensitive functionalities and by-passing the formation of dihydrolactams structurally related to **11** which would impose an additional oxidation step, a subject of controversy.[12a] A carefully degassed methanolic solution of enamides **2a**–**c** ($2 \cdot 10^{-3}$ M) was then placed in a quartz vessel and irradiated in a Rayonet RPR photoreactor equipped with 254 nm lamps for one hour. Gratifyingly, removal of the solvent and flash column chromatography delivered very satisfactory yields of a single compound which was identified as the demethoxylated isoquinolone **3a**–**c**.[19] Interestingly, the benzylic hydroxymethyl group was spared upon the photostimulated annulation process, and no trace of the dihydrolactam **11** could be detected in the residual photoproduct. Subsequent PDC oxidation of the hydroxy benzylic function proceeded uneventfully to provide excellent yields of the aromatic carboxaldehyde derivatives **12a**–**c** (Scheme 3, Table 1). All attempts to access the targeted models **12a**–**c** through a reverse sequence, that is, oxidation of the opened models **2a**–**c** prior to photocyclization, met with no success probably due to the sensitivity of the carboxaldehyde function under the defined photolytic conditions. With compounds **12a**–**c** in hand we were only two steps away from the targeted title compounds. The creation of the five-membered unit C embedded in the tetracyclic framework was secured through an intramolecular acid-mediated carbocationic enelactam–carboxaldehyde cyclization to provide the hydroxylated cyclization adducts **13a**–**c**, a class of compounds endowed with promising chemotherapeutic properties.[20] Lastly, standard oxidation of the (bi)benzylic hydroxy group of **13a**–**c** delivered very satisfactory yields of the targeted indenoisoquinolinediones **1a**–**c** (Scheme 3, Table 1).[21]



Scheme 2 Synthesis of starting aromatic enamides **2a–c**



Scheme 3 Photocyclization of enamides **2a–c** and synthesis of indeno[1,2-*c*]isoquinoline-5,11-diones **1a–c**

In conclusion we have devised a tactically new synthetic approach to a variety of indenoisoquinolinediones. This new route which offers special advantages including high regioselectivity, procedural simplicity, and mildness of reaction conditions, hinges upon the photoinduced construction of the isoquinolinone template from tailor-made *N*-styrylbenzamides as the key step. We believe that this work provides a strong incentive for the elaboration of structurally modified alkaloids as well as their biogenetically related congeners.

Table 1 Isoquinoline Derivatives Synthesized

Enamide	R^1	R^2	Boronic acid	R^3	R^4	Yield of isoquinoline derivatives (%)				
4a	H	H	**8a**	H	H	**2a** 61	**3a** 54	**12a** 87	**13a** 82	**1a** 81
4a	H	H	**8b**	OMe	OMe	**2b** 69	**3b** 51	**12b** 86	**13b** 68	**1b** 72
4b	OMe	OMe	**8a**	H	H	**2c** 64	**3c** 64	**12c** 71	**13c** 70	**1c** 77

Acknowledgment

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(17) ***N*-Benzyl-*N*-[1-(2-hydroxymethylphenyl)vinyl]-2-methoxybenzamide (2a):** pale yellow solid; mp 147–148 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 1.82 (br s, 1 H), 3.21 (s, 3 H), 4.33 (d, *J* = 11.7 Hz, 1 H), 4.73 (br s, 1 H), 5.16 (br s, 2 H), 6.30 (br s, 1 H), 6.64 (br s, 1 H), 6.82–7.34 (m, 10 H), 7.36–7.64 (m, 3 H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 52.6, 54.8, 62.3, 110.8, 112.3, 120.2, 121.4, 125.3, 127.4 (2 × CH), 128.5 (2 × CH), 128.7, 129.7, 129.9, 130.1, 132.6, 133.1, 137.4, 139.7, 140.5, 155.9, 169.5 ppm. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.02; H, 5.94; N, 3.97 .

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(19) **2-Benzyl-3-(2-hydroxymethylphenyl)-2*H*-isoquinolin-1-one (3a)**: yellow crystals; mp 102–103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (br s, 1 H), 4.00 (d, *J* = 13.3 Hz, 1

H), 4.30 (d, *J* = 13.3 Hz, 1 H), 4.94 (d, *J* = 14.8 Hz, 1 H), 5.45 (d, *J* = 14.8 Hz, 1 H), 6.39 (s, 1 H), 6.83 (d, *J* = 6.6 Hz, 2 H), 7.12–7.22 (m, 4 H), 7.32 (t, *J* = 7.3 Hz, 1 H), 7.42–7.61 (m, 4 H), 7.70 (t, *J* = 7.5 Hz, 1 H), 8.55 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.2, 62.3, 108.1, 125.3, 125.9, 126.9, 127.1, 127.2, 127.6 (2 × CH), 127.7, 128.3, 128.4 (2 × CH), 129.6, 129.7, 132.6, 133.4, 136.2, 137.5, 140.0, 141.1, 163.3 ppm. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.72; H, 5.84; N, 3.85.

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(21) For compound **1a** (mp 211–212 °C; lit. 202–205 °C), see: Wawzonek, S. *Org. Prep. Proced. Int.* **1982**, *14*, 16.