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Alternative synthetic approaches to biologically active indeno[1,2-*c*]isoquinoline-5,11-diones.

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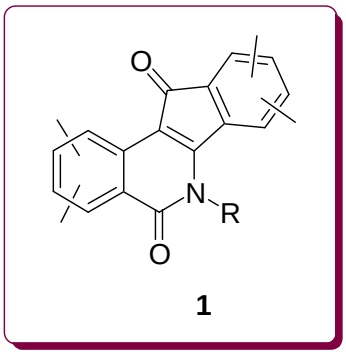
Abstract: Indenoisoquinolinediones, as exemplified by lead compounds indotecan and indimitecan, are a class of non-camptothecin topoisomerase I poisons that display marked cytotoxic properties and for some of them antitumor activities in xenograft models. We have developed two alternative and dramatically different synthetic approaches to a variety of highly fused and diversely substituted models that differ from the elaboration of key precursors, *i.e.* arylated 2,3-dihydroisoquinolones. The first one is based upon a Suzuki-Miyaura cross-coupling reaction involving enol phosphates combined with a ring-closing metathesis (RCM) reaction to ensure the creation of the six-membered lactam unit. The second approach hinges upon the photoinduced electrocyclization of the 6π electron aromatic enamides. The presence of phenolic methoxy groups precluded an additional mandatory and problematic oxidation step to generate the unsaturated lactam ring. Intramolecular carbocationic annulation reaction and ultimate oxidation of the latent hydroxyl functionality completed the synthesis of the targeted title compounds.

Keywords: *Indenoisoquinolinediones, enol phosphate, Suzuki-Miyaura coupling, ring-closing metathesis, photocyclization*

Introduction

Indenoisoquinolinediones **1** are a class of non-camptothecin topoisomerase I poisons that display marked cytotoxic properties and for some of them, potent antitumor activities in xenograft models [1].



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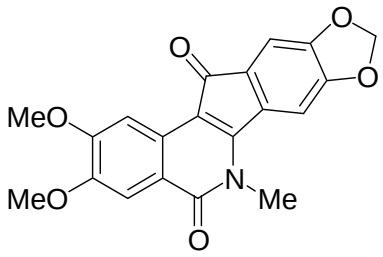
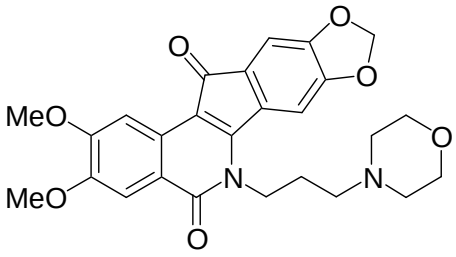
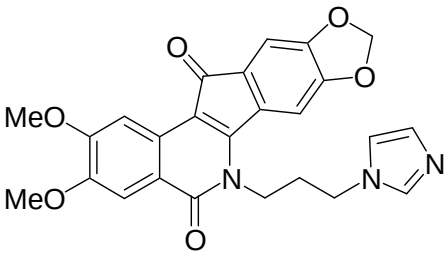
These highly fused compounds which contain a planar tetracyclic heteroring system equipped with multifarious functionalities as exemplified by the lead compound **2** (NCS 314622), indotecan **3** (NCS 724998) and indimitecan **4** (NCS 725776) (Fig. 1) have been demonstrated to inhibit topoisomerase I enzymes by intercalating between the DNA base pairs and to stabilize a ternary complex consisting of the drug molecule. Additionally they produce a unique pattern of DNA cleavage sites relative to camptothecins and therefore may target genes differently, which could result in a different spectrum of anticancer activities [1,2]



2 (NCS 314622)



3 Indotecan (NCS 724998)



4 Indimitecan (NCS 725776)

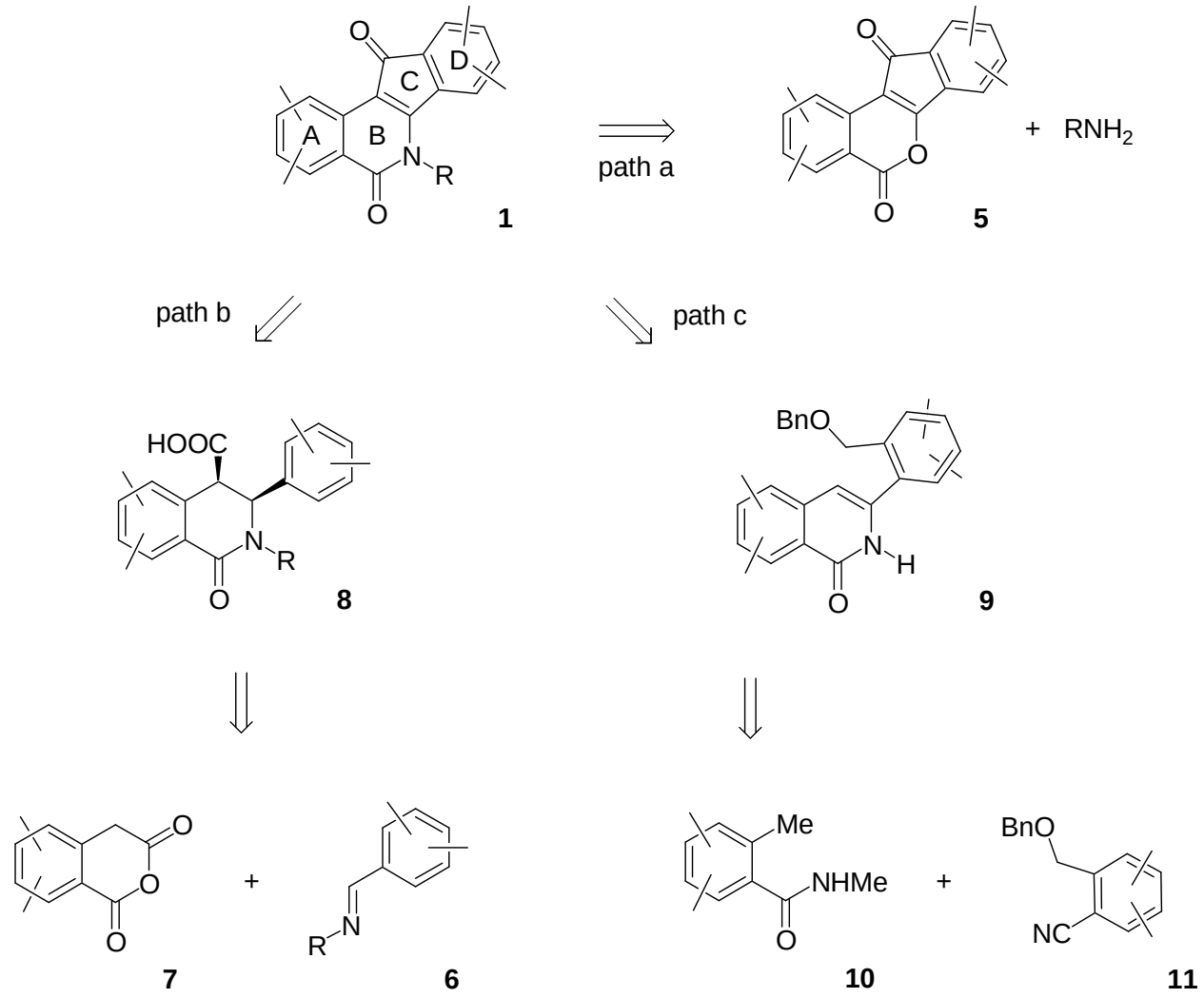
Figure 1.

Synthetic methods for the elaboration of these highly fused lactam compounds can be cursively classified into three main categories (Scheme 1).

The first one hinges upon treatment of the corresponding benzopyran-5,11-diones **5** with primary amines [1c,d,g] (Scheme 1, path a).

The second one is based on the preliminary condensation of Schiff bases **6** with homophthalic anhydrides **7** to afford *cis*-substituted isoquinolones **8** which can be subsequently subjected to an intramolecular $SOCl_2$-induced Friedel-Crafts reaction [1f, 2] (Scheme1, path b).

At last they can be accessed from suitably substituted NH-free 3-arylisoquinolone **9** assembled through a dilithiated toluamide **10** – benzonitrile **11** cyclization process [1e] (Scheme 1, path c).



Scheme 1.

Results and Discussion

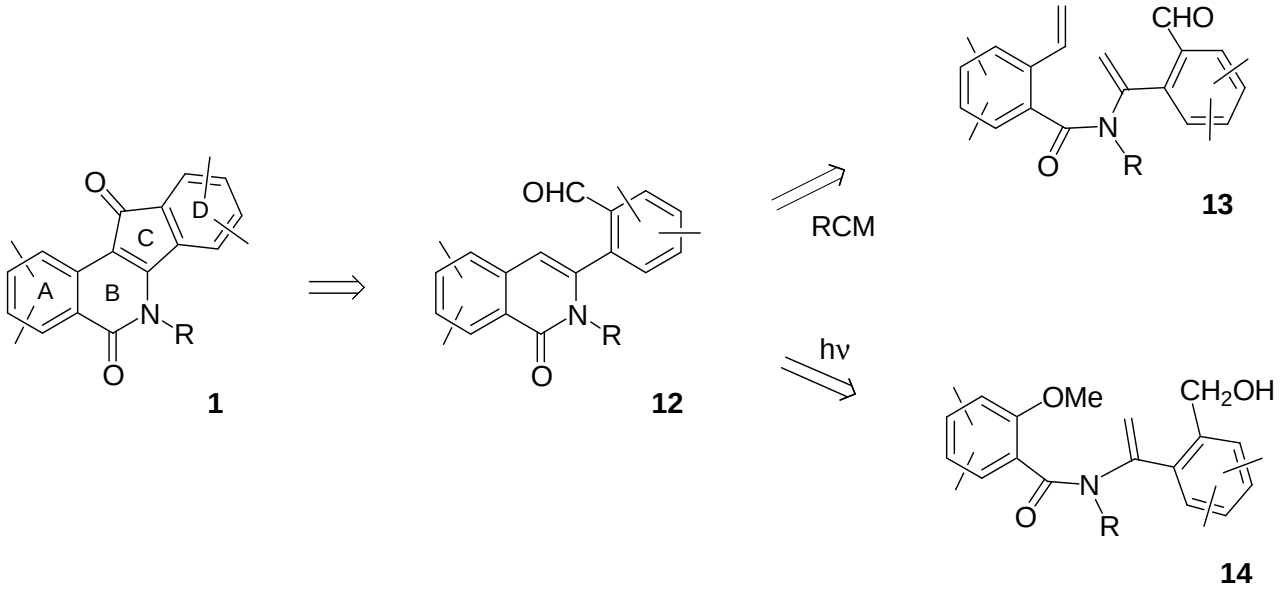
1. Synthetic strategies

We have developed two alternative synthetic approaches to a variety of diversely substituted models that differ from the elaboration of the key precursors **12** (Retrosynthetic Scheme 2).

The first one is based upon the ring-closing metathesis (RCM) of styrenic enamides **13**.

The second approach hinges upon the photoinduced cyclization of aromatic enamides **14**.

Intramolecular carbocationic annulation and ultimate oxidation of the latent hydroxyl functionality should complete the synthesis of titled compounds **1**.



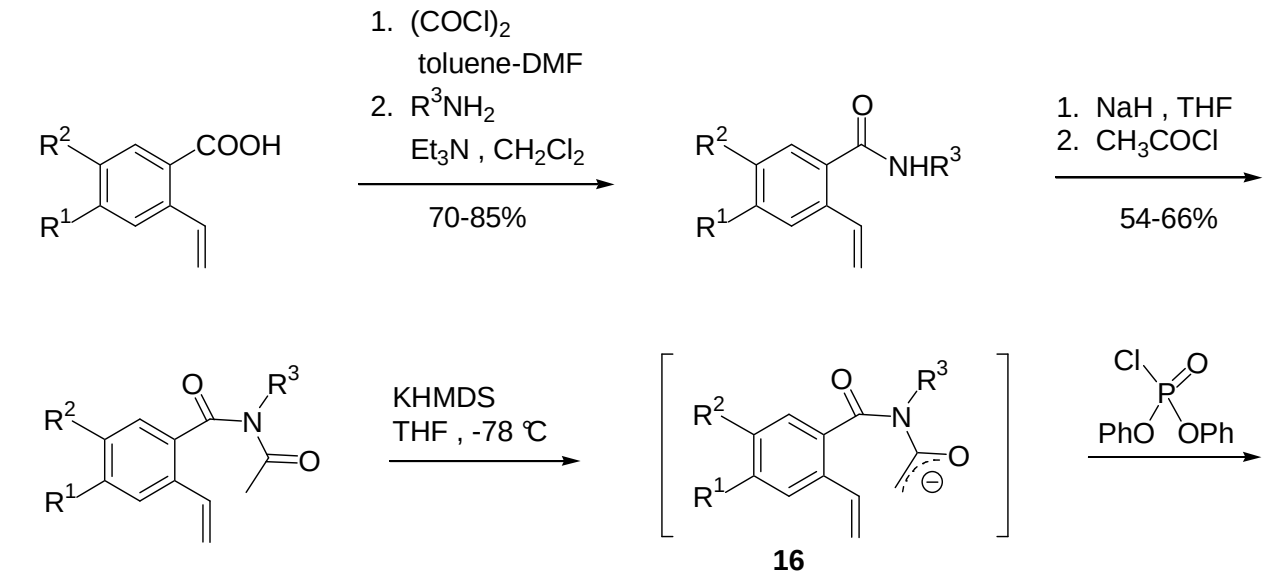
Scheme 2. Retrosynthetic analyses to targeted compounds.

2. The RCM synthetic approach to key models 12a-d (13 → 12)

This new route depicted in Scheme 3 combines:

(i) a ring closing metathesis reaction applied to **13** to secure the creation of the lactam unit that is ring B in titled compound.

(ii) installation of the aromatic unit D by a Suzuki-Miyaura cross coupling reaction involving enol phosphates **15** deriving from enolate **16** and adequately functionalized boronic acids **17**.

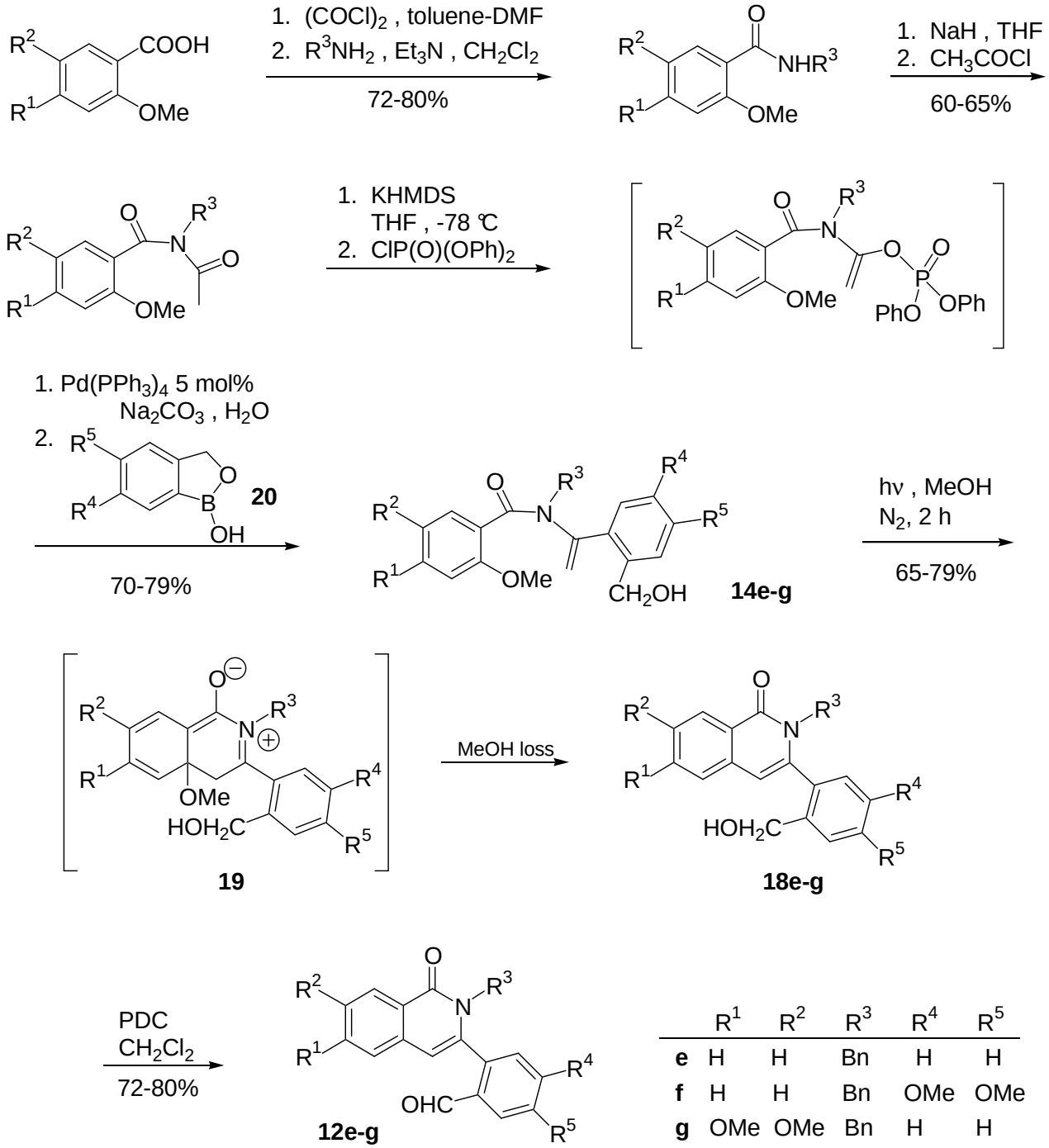


	R^1	R^2	R^3	R^4	R^5
a	H	H	Me	H	H
b	H	H	Me	OMe	H
c	OMe	OMe	Me	H	H
d	H	H	Bn	H	OMe

Scheme 3.

3. The photochemical synthetic approach to key models 12e-g (14 → 12)

The key step is the photoinduced cyclization of the 6π-electron aromatic enamides **14**. The presence of aromatic methoxy groups allows cyclization under mandatory anaerobic conditions and straightforward access to expected oxidized lactamic compounds **18**. This technique precludes an additional oxidation step liable to give access to the desired compounds **18**. Noteworthy MeOH is released upon the photoinduced cyclization reaction (**19** → **18**) carried out in MeOH as solvent. Installation of the hydroxymethyl aromatic unit could be performed as a single one step reaction starting from the cyclic boronic acid derivative **20** (Scheme 4).

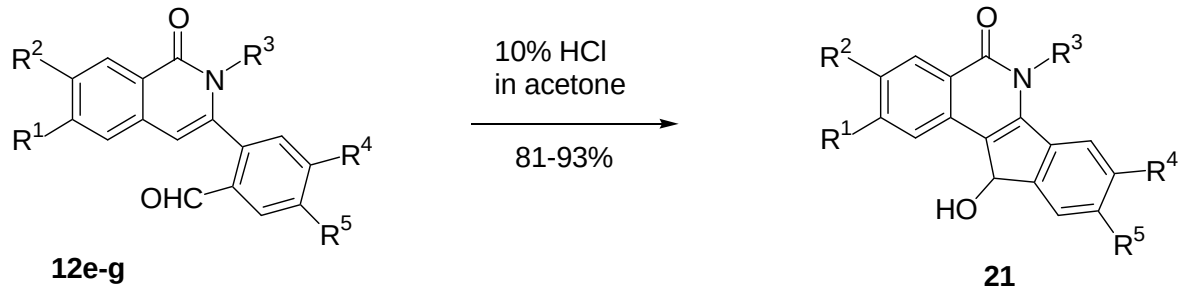


	R^1	R^2	R^3	R^4	R^5
e	H	H	Bn	H	H
f	H	H	Bn	OMe	OMe
g	OMe	OMe	Bn	H	H

Scheme 4.

4. The annulation reaction (creation of the five-membered ketonucleus C). Synthesis of indeno[1,2-c]isoquinolin-5,11-diones **1a-g**

Elaboration of the C ring of the tetracyclic core was secured through a carbocationic intramolecular enamide-aldehyde cyclization process (Scheme 5). It is worth mentioning that hydroxyindenoisoquinolones structurally related to **21** are endowed with profound chemotherapeutic properties [1d,e, 3].



	R^1	R^2	R^3	R^4	R^5
a	H	H	Me	H	H
b	H	H	Me	OMe	H
c	OMe	OMe	Me	H	H
d	H	H	Bn	H	OMe
e	H	H	Bn	H	H
f	H	H	Bn	OMe	OMe
g	OMe	OMe	Bn	H	H

Scheme 5.

Conclusion

In conclusion we have developed two conceptually and complementary synthetic approaches to a variety of indenoisoquiolinediones. The methodologies underpin the synthetic utility of acyclic phosphoryl enamides and enrich the repertoire of the RCM and photoelectrocyclization reactions.

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