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Cation Triggered Domino Aza-Piancatelli Rearrangement/Friedel–Crafts Alkylation of Indole-Tethered Furfuyl Alcohols to Access Cycloocta[*b*]indole Core of Alkaloids

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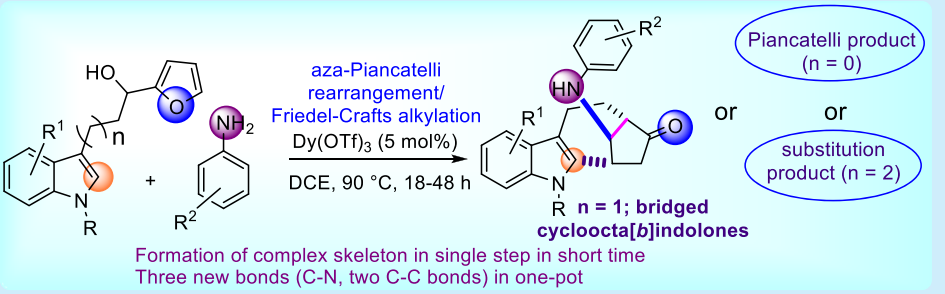

ABSTRACT: A domino approach to bridged cycloocta[*b*]indolone through a cascade of aza-Piancatelli rearrangement/Friedel–Crafts alkylation is developed. This transformation has been realized by reaction of an indole-tethered 2-furylcarbinol and substituted aniline in the presence of a Lewis acid to initiate aza-Piancatelli rearrangement followed by an in situ intramolecular Friedel–Crafts alkylation to access bridged tetracyclic frameworks in one pot.

Catalytic domino reactions represent important advances in synthetic organic chemistry by providing atom- and step-economical method for the construction of complex frameworks. Synthetic organic chemists always pursue new catalytic transformations to construct complex moieties preferably in a single pot. In this regard, great efforts have been made to develop efficient single step transformations which results in the formation of multiple bonds and stereocenters with selectivity.[1]

The cycloocta[*b*]indole core is a common scaffold in many bioactive alkaloids like macroline, lochnerine, sarpagine, ajmaline, macrocapramine, and dispegatrine with a broad spectrum of activities like antiamoebic, antiplasmodic, antihypertensive, anticancer, and antibiotic properties (Figure 1).[2] A recent study by Waldmann et al. showed analogues of cycloocta[*b*]indole frameworks as promising targets for the development of novel class of potent and selective *Mycobacterium* protein tyrosine phosphatase B (MptpB) inhibitors against *Mycobacterium tuberculosis*.[3] In addition, Waldmann et al. have presented an analysis of selected pseudo-natural product (NP) libraries using chemoinformatic tools that provide access to unprecedented pseudo-NPs to offer opportunities for the discovery of bioactive small-molecule scaffolds.[4] Reports of synthetic approaches to construct sarpagine and macroline group of alkaloids consist of multiple steps.[3,5] Few reports are available for the construction of indoles fused to 8-membered rings through cascade or sequential reactions.[6] The scaffold poses a challenge to synthetic organic and medicinal chemists to construct the functionalized cycloocta[*b*]indole core efficiently using one-pot reaction sequences.

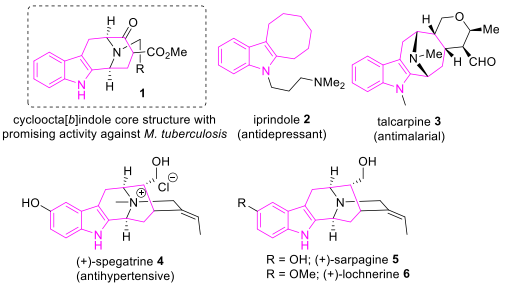

Figure 1. Representative naturally occurring bioactive cycloocta[*b*]-indole alkaloids.

2-Furylcarbinols have emerged as important building blocks for the construction of cyclic systems. Under Lewis acid or Brønsted acid catalysis, the furylcarbinols converts into a highly reactive electron-deficient furfuryl cation intermediate, pre-

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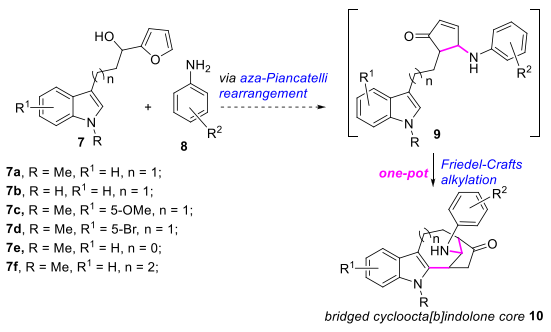
cursor to a variety of cyclic systems.[7] Piancatelli reaction is one of the most efficient method for the conversion of 2-furylcarbinol to 4-hydroxy-2-cyclopentenones which served as valuable building block for a variety of biologically important molecules.[8] This reaction was scarcely used for more than 30 years but of late has been the focus of interest and has been explored to construct a variety of skeletons in the past few years. Developments have been achieved in reaction conditions, catalytic systems, and use of different nucleophiles in the process.[9,10] In addition, cascade and sequential reactions involving Piancatelli rearrangement have also been reported.[11] We have earlier reported a domino aza-Piancatelli rearrangement/aza-Michael reaction where 2-furfurylcarbinol reacted with 2-aminobenzamide to give 1,4-benzodiazepin-5-one in one pot.[12] Recently, Leboeuf and co-workers reported synthesis of bridged tetrahydrobenzo[*b*]azepines via Piancatelli cyclization/Michael addition in sequence.[13] Our continued interest in the development of novel cascade strategies for the synthesis of biologically relavent molecules has resulted in the design and synthesis of bridged nitrogen rich tetracyclic frameworks. Here in, we report for the first time, a simple and efficient approach for the construction of bridged cycloocta-[*b*]indolone, an aza tetracyclic core using a novel domino strategy based on aza-Piancatelli rearrangement coupled with Friedel–Crafts alkylation in single pot.

We anticipated that indole-tethered 2-furylcarbinol **7** in the presence of aniline **8** could serve as a substrate for aza-Piancatelli rearrangement and form 4-arylamino cyclopentenone **9**, which in turn could undergo a Friedel–Crafts alkylation from C-2 position of indole moiety to give bridged cycloocta[*b*]indolone derivative **10** (Scheme 1).

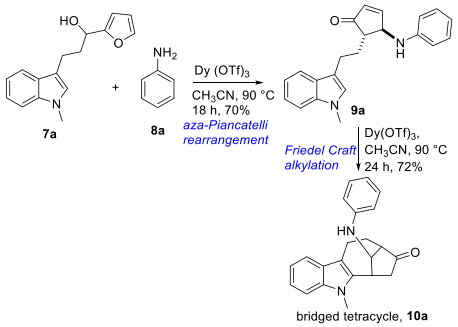
Scheme 1. Proposed Strategy for Bridged Tetracyclic Cycloocta[*b*]indolone core



To test our hypothesis, indole-tethered furfuryl alcohol **7a** was prepared from 3-indole propanoic acid (see Supporting Information).[14,15] To check the feasibility of the bridged cycloocta[*b*]indolone formation, we initially carried out an aza-Piancatelli rearrangement of furfuryl alcohol **7a** with aniline **8a** using $Dy(OTf)_3$ in acetonitrile at 90 °C (Scheme 2). We obtained the corresponding rearrangement product **9a**, in 70% yield, after purification. This product was treated with $Dy(OTf)_3$ in acetonitrile at 90 °C (with the assumption that the cyclopentenone **9a** will undergo intramolecular Friedel–Crafts reaction at C2 position of indole moiety), where the proposed cycloocta[*b*]indolone derivative **10a** was obtained in 72% yield.

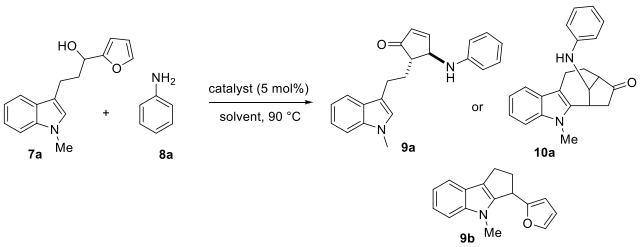
After confirmation of the bridged cycloocta[*b*]indolone compound **10a**, we focused on optimization of reaction conditions to get the target molecule in one pot. We assumed

Scheme 2. Synthesis of Cycloocta[*b*]indolone Tetracycle in Sequence



that proper selection of Lewis or Brønsted acid and solvent may lead to the conversion of the aza-Piancatelli product **9a** to bridged tetracyclic derivative **10a** via an in situ intramolecular Friedel–Crafts reaction in one pot (Table 1). Our initial experiment was performed with 2-furylcarbinol **7a** and aniline

Table 1. Optimization of the Reaction Conditions[a]



				yield[b] (%)		
entry	catalyst	solvent	time (h)	**9a**	**10a**	**9b**
1	$Dy(OTf)_3$	CH_3CN	24	70	<5	10
2	$Dy(OTf)_3$	CH_3CN	48	10	60	10
3	$Sc(OTf)_3$	CH_3CN	48	05	50	10
4[c]	$ZnCl_2$	CH_3CN	48	20	<5	25
5	$Cu(OTf)_2$	CH_3CN	48	15	50	05
6[c]	$Ba(OTf)_2$	CH_3CN	48	30	<5	08
7[d]	$Bi(OTf)_3$	CH_3CN	24	–	–	–
8[e]	$La(OTf)_2$	CH_3CN	24	–	–	–
9[e]	$In(OTf)_3$	CH_3CN	24	–	–	trace
10[e]	$Yb(OTf)_3$	CH_3CN	24	–	–	–
11	$Dy(OTf)_3$, 4 Å MS	CH_3CN	48	10	50	10
12	$Dy(OTf)_3$	DCE	24	30	50	10
13	**$Dy(OTf)_3$**	**DCE**	**36**	**05**	**70**	**10**
14[c]	$Dy(OTf)_3$	toluene	48	50	08	05
15	$Dy(OTf)_3$	dioxane	48	65	05	10
16[c]	$Dy(OTf)_3$	THF	48	30	05	10
17[d]	$Dy(OTf)_3$	HFIP	24	–	–	–
18	TFA	DCE	02	–	–	82
19[f]	$Dy(OTf)_3$	DCE	36	05	68	10
20[g]	$Dy(OTf)_3$	DCE	72	05	50	20
21[h]	$Dy(OTf)_3$	DCE	36	04	65	10
22[i]	$Dy(OTf)_3$	DCE	36	05	66	10

[a]The reactions were performed with **7a** (0.4 mmol), **8a** (0.4 mmol), and catalyst (5 mol %) in solvent (1.5 mL) at 90 °C, unless otherwise noted. [b]Yields of purified products. [c]Starting material was not consumed completely. [d]Starting material was decomposed. [e]Multiple spots observed in TLC. [f]10 mol % of catalyst was used in the reaction. [g]Reaction was performed at 70 °C. [h]Reaction was performed at 120 °C. [i]2,2′-Bipyridine (10 mol %) was used as an additive.

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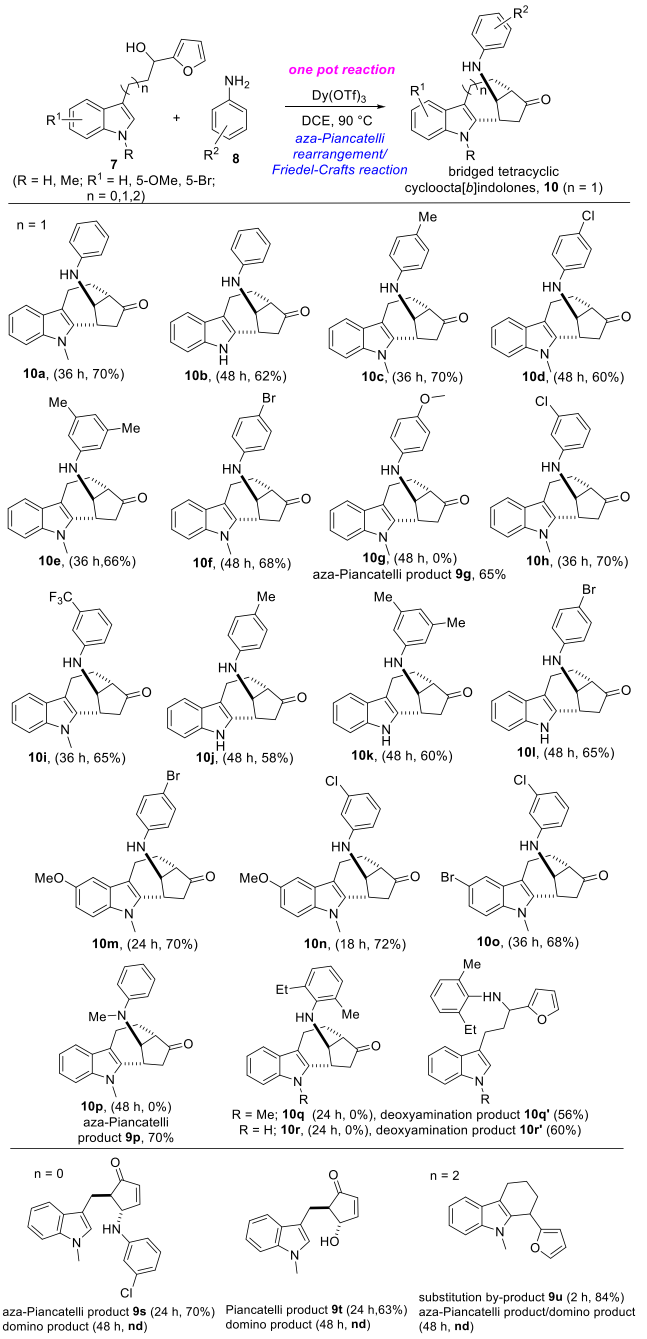
8a in the presence of $Dy(OTf)_3$ in CH_3CN at 90 °C for 24 h. The aza-Piancatelli product **9a** and domino product **10a** were obtained in 70% and <5% yields, respectively (Table 1, entry 1). In this reaction, substitution product of furfuryl cation **9b** (10%) was also observed. When the reaction time was increased to 48 h, the domino product **10a** has increased to 60% (Table 1, entry 2). Various Lewis acids were screened to choose the best suited for the reaction (Table 1, entries 3−10). The Lewis acids $Sc(OTf)_3$and $Cu(OTf)_2$ were found to be comparatively good catalysts for the reaction (Table 1, entries 3 and 5) whereas the reaction was found to be slow with $ZnCl_2$ and $Ba(OTf)_2$ (Table 1, entries 4 and 6). The formation of substitution product **9b** was observed in the reactions. Other Lewis acids were not found to be suitable for the domino reaction (Table 1, entries 7−10). The $Dy(OTf)_3$ was found to be the better catalyst for the domino aza-Piancatelli−Friedel−Crafts alkylation to get the required bridged tetracycle (Table 1, entry 2). When the reaction was performed in the presence of molecular sieves, the yield of domino product did not increase further (Table 1, entry 11). Then, we moved to solvent screening where the domino reaction was conducted in solvents such as DCE, toluene, dioxane, THF, and HFIP (Table 1, entries 12−17). It was observed that DCE was found to be the best solvent for the domino reaction (Table 1, entries 12 and 13). When the reaction was conducted in the presence of strong acid such as TFA, the formation of domino product was significantly inhibited and we observed the formation of substitution product of furfuryl cation **9b** alone (Table 1, entry 18). When the catalyst loading was increased to 10 mol %, there was no considerable change in the reaction time and yield (Table 1, entry 19). When the reaction was carried out at 70 °C, reaction became slow and yield was decreased (Table 1, entry 20). There was no improvement in the yield observed by increasing the reaction temperature to 120 °C (Table 1, entry 21). One reaction was performed with ligand 2,2′-bipyridine (10 mol %) as an additive (Table 1, entry 22). No chiral induction was observed as confirmed by HPLC (see the Supporting Information).

We then turned our attention to examine the substrate scope of domino reaction, and the results are summarized in Scheme 3. The furfuryl alcohol with methyl protected indole **7a** was reacted with different substituted anilines and the corresponding domino products were obtained in good yields (60−70%, **10a**, **10c**−**10f**). The structure and configuration of bridged tetracycle **10a** were confirmed by X-ray crystallography (Figure 2, CCDC 1999110). Here, the aza-Piancatelli reaction is *trans*-selective and Friedel−Crafts reaction is diastereoselective and *cis*-fused ring was obtained in **10a**. In the case of *p*-anisidine, the reaction stopped after aza-Piancatelli rearrangement **9g** (65%) where the corresponding domino product **10g** was not obtained even after increasing the reaction time and catalyst. Reaction of 2-furylcarbinol **7a** with *meta*-substituted anilines also gave corresponding domino products **10h** and **10i** in 65−70% yields. We have carried out one reaction using unprotected indole substrate **7b** and aniline **8a**. To our delight, the domino reaction proceeded smoothly to give corresponding domino product **10b** in 62% yield. Similarly, unprotected indole substrate **7b** was also reacted with substituted anilines and the corresponding domino products were obtained in 58−65% yields (**10j**−**10l**). Another two indole-tethered 2-furfuryl alcohols were prepared to see the substituent effect of indole ring on the domino reaction. The furfuryl alcohol **7c** was obtained from 5-methoxyindole, and **7d** was obtained from 5-bromoindole. The substrate **7c** was reacted with 4-bromoaniline and *m*-chloroaniline to give the

Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: **7** (0.75−0.83 mmol), **8** (0.75−0.83 mmol), and $Dy(OTf)_3$ (5 mol %), DCE (3 mL), 90 °C, 18−48 h. [b]Isolated yields after chromatographic purification. nd, not detected.

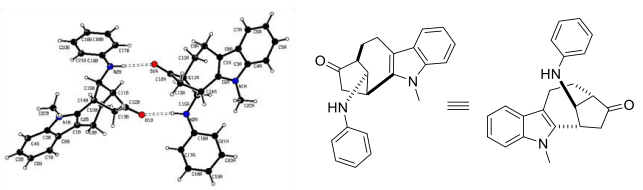


Figure 2. ORTEP diagram of compound **10a**.

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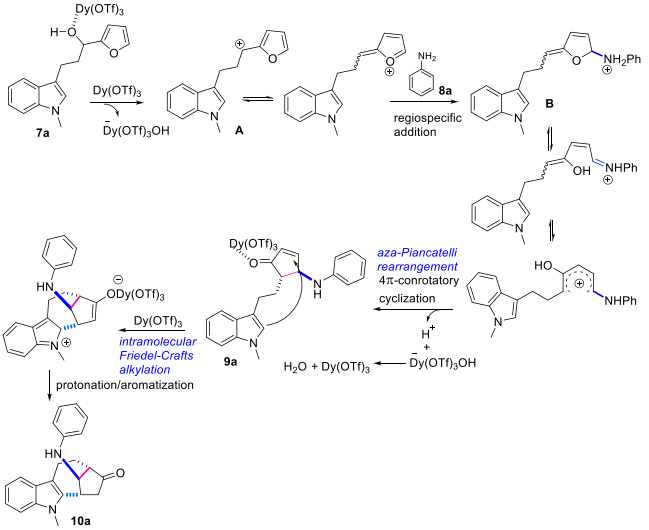
corresponding domino products **10m** and **10n** in good yields, 70 and 72%, respectively. The substrate **7d** was also reacted with *m*-chloroaniline to give the corresponding domino product **10o** smoothly in 68% yield. In the case of *N*-methylaniline, the corresponding aza-Piancatelli product **9p** was obtained in 70% yield and failed to give domino product **10p**. The substrates **7a** and **7b**, when treated with 2-ethyl 6-methylaniline, failed to give corresponding products **10q** and **10r**, respectively. In this case, aniline was added on to furfuryl cation and deoxyamination products (**10q′** and **10r′**) were formed, hence no aza-Piancatelli rearrangement was observed. Then, we turned our attention to see the possibility of making other fused indole tetracycles such as indoles fused to 7- and 9-membered rings using different indole-tethered furfuryl alcohols. The furfuryl alcohol **7e** was prepared from 3-indole acetic acid. Another furfuryl alcohol **7f** was prepared from 3-indole butyric acid (see Supporting Information). When furfuryl alcohol **7e** was treated with *m*-chloroaniline, the corresponding Piancatelli product **9s** was obtained in 70% yield and failed to undergo Friedel−Crafts alkylation to give bridged cyclohepta[*b*]indolone derivative. Another attempt was made, wherein furfuryl alcohol **7e** was reacted with ^{t}BuOH/H_2O in the presence of $Dy(OTf)_3$ to get Piancatelli product **9t** in 63% yield but failed to give cyclohepta[*b*]-indolone derivative. The furfuryl alcohol **7f** was treated with *m*-chloroaniline in the presence of $Dy(OTf)_3$ and the substitution product of furfuryl cation **9u** was formed exclusively in 2 h only and no Piancatelli rearrangement product as well as domino product was detected. This confirms that under Lewis acid conditions indole moiety is more reactive to add on furfuryl cation to form cyclized byproduct **9u**. Hence, the furfuryl cation was not available for aniline to undergo Piancatelli rearrangement.

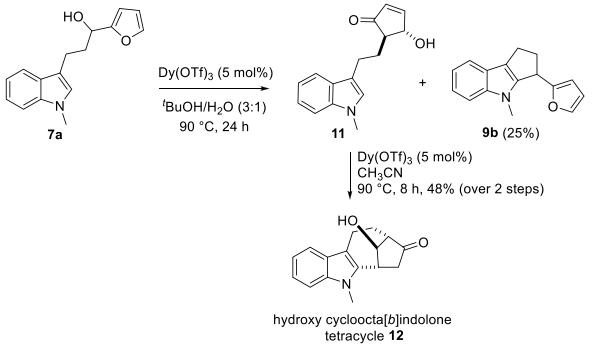
Based on the observations, we propose a plausible reaction pathway of the domino process which is shown in Scheme 4. The furfuyl alcohol **7a** on treatment with Lewis acid converts into reactive furyl cation **A**. Then aniline **8a** attacks on the cation **A** to form intermediate **B** which rearranges to key intermediate trans-cyclopentenone **9a** via aza-Piancatelli rearrangement. Cyclopentenone part of **9a** acts as a Michael acceptor, activated by $Dy(OTf)_3$ and undergoes diastereoselective Friedel−Craft's alkylation from C2 position of indole moiety followed by protonation/aromatization to afford bridged tetracycle **10a**.

Scheme 4. Plausible Reaction Pathway of Domino Aza-Piancatelli/Friedel−Crafts Alkylation



After successfully obtaining a library of domino aza-Piancatelli/FC alkylation products, we turned our attention to see the feasibility of other nucleophile such as H_2O for the domino process (Scheme 5). The furfuryl alcohol **7a** was treated with $Dy(OTf)_3$ in ^{t}BuOH/H_2O (3:1) at 90 °C. The Piancatelli product **11** was obtained along with **9b**. The crude hydroxy cyclopentenone **11** after solvent evaporation, was subjected to Friedel−Crafts alkylation conditions in acetonitrile at 90 °C to get required bridged hydroxy cycloocta[*b*]-indolone tetracycle **12** in 48% yield over two steps.

Scheme 5. Domino Reaction with *O*-Nucleophile



In summary, we have developed a simple and highly efficient domino aza-Piancatelli rearrangement/intramolecular Friedel−Crafts alkylation reaction to access a series of novel complex bridged cycloocta[*b*]indolone derivatives. This domino protocol is found to be general, and the corresponding nitrogen-rich bridged tetracyclic adducts are isolated in good yields. The synthesized products were looked using Tanimoto index and 3D overlap with the Waldmann's pseudo-NP 1 and alkaloids thus giving a clue that these new skeletons could be considered as novel pseudo-NPs for further evaluation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03155.

Experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of related compounds, HPLC and X-ray crystal structure of **10a** (PDF)

Accession Codes

CCDC 1999110 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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