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One-pot C–C/C–O bond formation: synthesis of spirocyclic lactones†

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An efficient and practical method for the synthesis of novel spiro(tri or tetra)cyclic lactones *via* the formation of C–C and C–O bonds in one-pot is presented. The method was successful under Lewis acidic ($FeCl_3$) conditions and enabled the formation of spiro(tri or tetra)cyclic lactones from simple aliphatic exocyclic enoate esters as reacting partners with phenols. Remarkably, the usual self-aromatization of cyclohexanone based enoate esters, under such Lewis acidic conditions is overridden by intermolecular coupling. Significantly, the method was amenable to indanone derived esters as well and furnished novel spiro(tetra or penta)cyclic lactones bearing simple to dense functionalities on the aromatic rings. Notably, these novel spirocyclic systems constitute core structures of natural/unnatural compounds that show good biological properties.

Introduction

Organic chemistry has always dealt with exploring innovative, alternate and new methods for the construction of C–C and/or C-heteroatom bonds. The focus has always been to perform multiple transformations in a single vessel employing one or more catalysts.[1] In this context, domino one-pot methods[2] have acclaimed immense interest as they involve the construction of two or more bonds in a single vessel reducing the chemicals for a sequence of product purifications. It also lowers the loss in yield and thus saves time and resources.

One-pot methods involving Lewis acid mediated domino reactions are highly promoted in the synthetic field. As a part of our ongoing research interest in domino or sequential one-pot transformations, recently, we reported an efficient method for the synthesis of dihydrocoumarins.[3] The process was based on the Lewis acid ($FeCl_3$) promoted dual bond (C–C and C–O) formation in one-pot. Also, our group reported some interesting acid mediated transformations for the synthesis of indanones,[4] indanes[5a] and fused indenoindole tetracyclics.[6] Significantly, in the dihydrocoumarin's report,[3] for the first time, we synthesized the novel spiro(tetra or penta)cyclic compounds starting from tetralone derived enoate ester (Scheme 1). Quite interestingly, this is not usual under either strong acidic or basic conditions, because, tetralone derived systems generally undergo rapid self-aromatization under such harsh acidic conditions. Inspired by the versatility of the method to furnish dihydrocoumarins and the spiro(tetra or penta)cyclic compounds dexterously, it instigated us to apply this method on the aliphatic exocyclic α,β-unsaturated esters, wherein, again, aromatization was a serious concern, particularly, for those derived from cyclohexanone. It was envisioned that one-pot intermolecular Michael addition and intramolecular condensation of the esters with the phenols, would result in the direct construction of the spirocyclic lactones. Although there are a reasonable number of reports on the synthesis of aryl-dihydrocoumarins, from cinnamates/cinnamic acids in conjunction with the external phenols under acidic conditions,[7–9] significantly, to the best of our knowledge there are no reports for direct access to the synthesis of spirocyclic lactones from simple aliphatic exocyclic enoate esters.

Often, it is reported that the spirocyclic compounds have an advantage and the twist around the centrally placed carbon atom discloses some unique properties mostly applicable in the pharmaceuticals. The conformational rigidity of these spirocyclic systems has an added advantage in binding to the protein molecules and as they form the integral part of various naturally occurring compounds having biological significance, their synthesis has been a big source of interest. Some of the spirocyclic compounds are reported to display narcotic, skeletal muscle relaxant, hypotensive and anti-viral properties.[10] Very commonly used antihypertensive, diuretic drug (aldactone) and aldosterone antagonist (eplerenone) comprise the spirocyclic-core responsible for depicting these properties. Significantly, the spiro chiral ligands are also extensively implemented in the asymmetric catalysis for the synthesis of spiro-heterocyclic compounds.[11] Amongst the various spirocyclic systems, the heterocyclic spiro compounds are known to be highly significant for their drug like properties[12] and also for their structural novelty.[13]

The nitrogen containing spirocyclic compounds like the spirolactams[14] and spirooxindols[14g] have been synthesized

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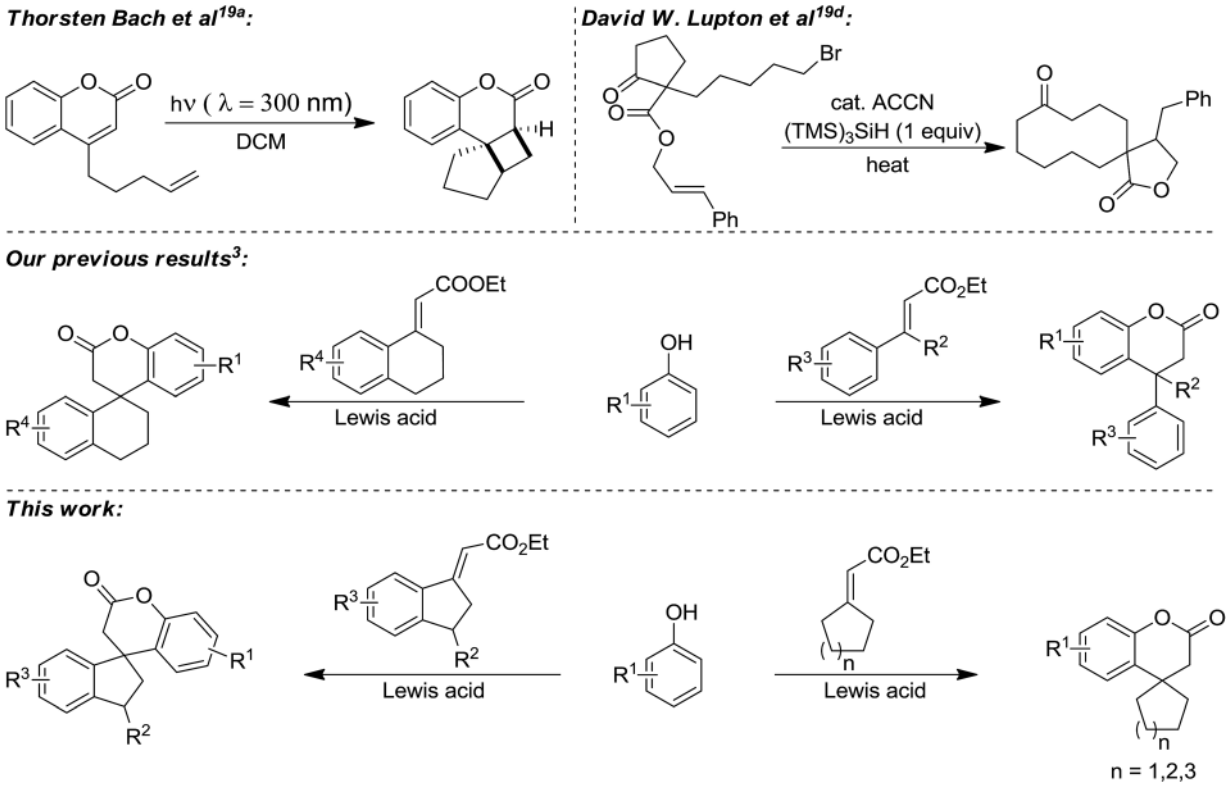


Scheme 1 Present study *vs.* our previous results for the synthesis of spirocyclic lactones.

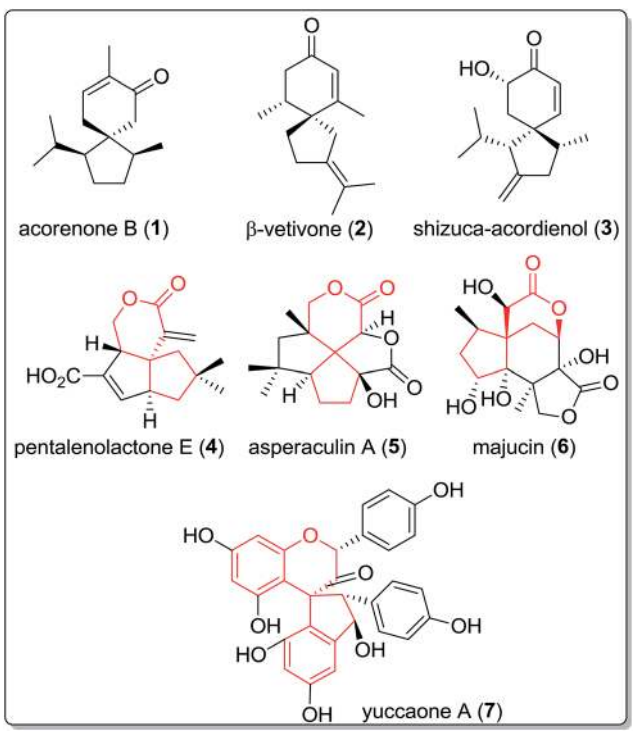
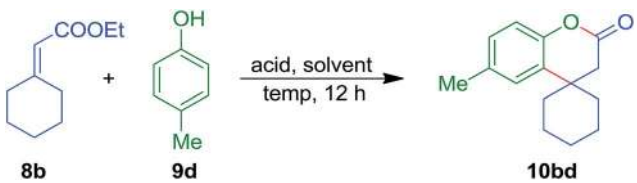


Fig. 1 Natural products containing the spiro-bicyclic lactone core and the major spirotetracyclic core.

Table 1 Optimizations for the formation of spirotricyclic lactone **10bd**



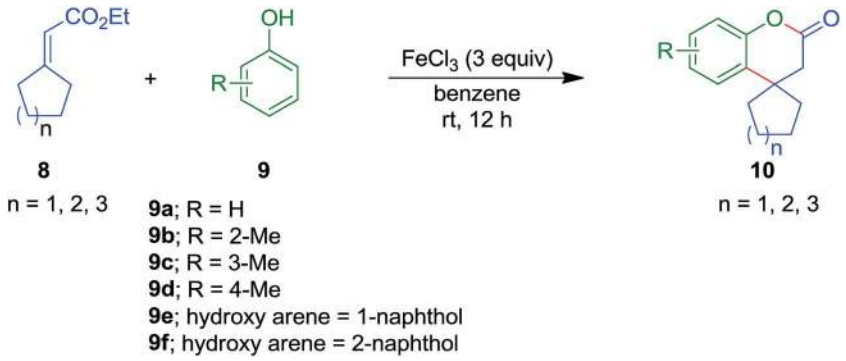
8b **9d** **10bd**

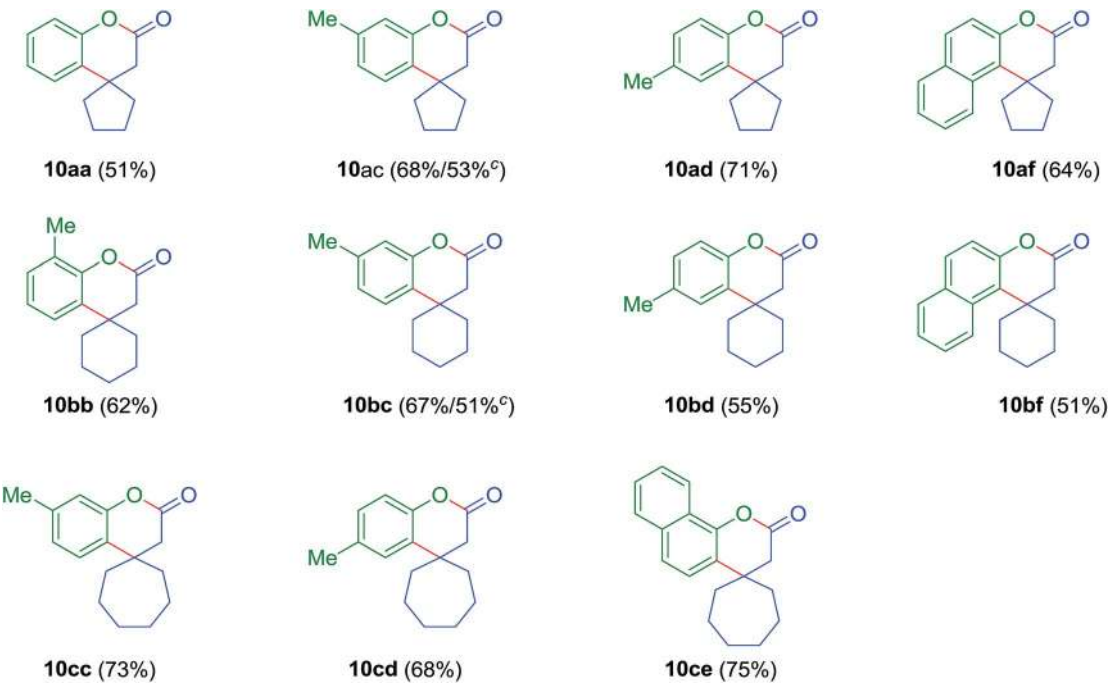
Entry[a]	Acid (equiv.)	Phenol **9d** (equiv.)	Solvent (1.5 mL)	Temp (°C)	Yield of **10bd**[b] (%)
1.	$FeCl_3$ (3)	1.5	DCE	80	0[c]
2.	$FeCl_3$ (3)	1.5	DCE	rt	0[c]
3.	$FeCl_3$ (0.1)	3	DCE	80	0[c]
4.	$FeCl_3$ (0.5)	3	DCE	50	0[c]
5.	$AlCl_3$ (0.5)	3	DCE	50	0[c]
6.	$Sc(OTf)_3$ (0.1)	3	DCE	50	0[c]
7.	$BF_3 \cdot OEt_2$ (0.5)	3	DCE	50	0[c]
8.	$AuCl_3$ (0.1)	3	DCE	50	0[c]
9.	$FeCl_3$ (1)	3	DCE	50	0[c]
10.	$BF_3 \cdot OEt^2$ (3)	3	DCE	50	0[c]
11.	$FeCl_3$ (3)	3	DCE	50	0[d]
12.	$FeCl_3$ (3)	3	DCE	rt	40
13.	$FeCl_3$ (3)	3	Benzene	rt	67
14.	$FeCl_3$ (5)	3	Benzene	rt	60
15.	$FeCl_3$ (3)	3	Toluene	rt	52

[a] All reactions were performed on a 0.5 mmol scale of ester **8b** and 3 equiv. of phenol **9d**. [b] Yields mentioned are of chromatographically purified compounds. [c] Only starting material was isolated. [d] Neither starting material nor the product were seen on TLC.

diversely owing to their restricted conformational flexibility and interesting biological properties. The oxygen containing spirocyclics like the spiro-ketals and spirolactones form an important class of compounds possesing biological significance. The spiroketal ring system is a structural subunit that is often found in many naturally occurring substances of bacterial, insect, marine or plant origin[15] and these assemblies have triggered immense interest in the synthesis owing to their pharmacological benefits.[12a,b] Also, spirolactone based compounds are reported to show antibacterial,[16] birth control,[17] dehydrogenase type 2 inhibition[18] formulations *etc.* Due to these benefits, numerous methods are reported for synthesis of spirolactones. Bach *et al.* reported spirocyclic formation *via* photochemical cycloaddition reactions in the presence of chiral Lewis acid,[19a] and also by acid mediated cyclization of the corresponding synthons.[19b] Very recently, free radical mechanism was used by implementing ACCN as the radical initiator to construct γ-lactones using Beckwith–Dowd ring expansion.[19d] We became very fascinated by the abundance of the spirolactone structure in many of the naturally occurring compounds of which a few are mentioned in Fig. 1. Acorenone B **1**, β-vetivone **2**, shizuca-acordienol **3**, are some of the naturally occurring spirocyclic compounds depicting some unique structural properties.[20] Upon taking a closer look at the compounds **4**, **5** and **6**, they possess the bicyclic spirolactone as a core structure (which is in close resemblance to that present in our designed molecules) and are known to mimic neurotrophin activity useful in treating Alzheimer's disease & Parkinson's disease and show antifungal & antibacterial properties (Fig. 1).[19b] Quite interestingly, our further investigations for compounds with similar structural resemblances, disclosed the natural product[13,19c] yuccaone A **7**, a spirobenzopyran-4-

Table 2 Synthesis of spiro(tri/tetra)cyclic lactones **10** from the exocyclic α,β-unsaturated esters **8**[a,b]





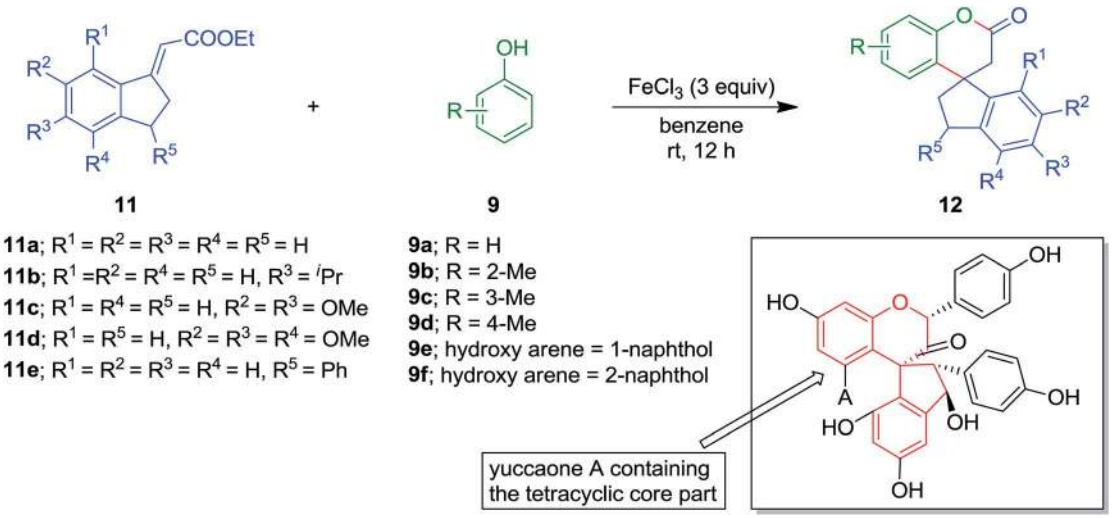
[a] All reactions were carried out on 0.5 mmol scale of **8** and 3 equiv. of **9**, in solvent benzene (1.5 mL). [b] Isolated yields of chromatographically pure products **10**. [c] Reaction was carried out in toluene [(yield of **10ac**; 53%), (yield of **10bc**; 51%)].

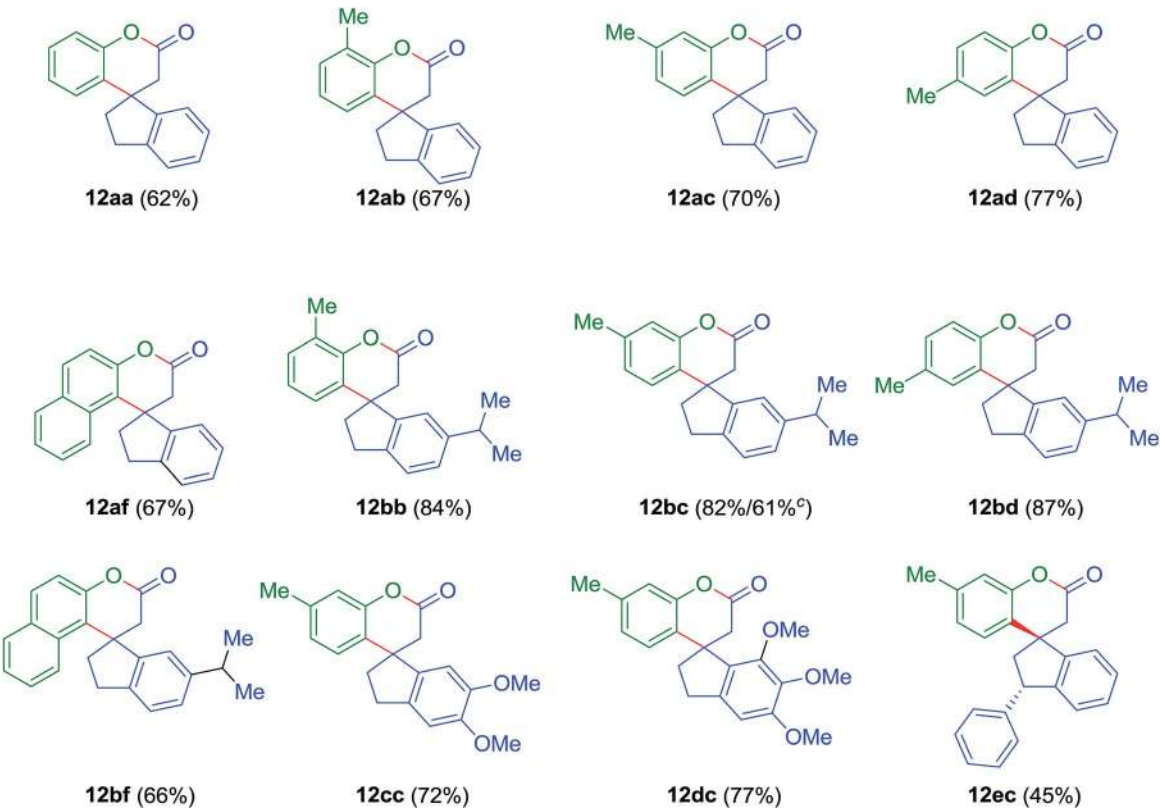
cyclopentan-3-one derivative, and we were highly motivated to design the entire tetracyclic core of the compound as it is one of the very rare naturally occurring phenolic spiro derivative having C-17 core (Fig. 1). Herein, we report an efficient and practical method for the synthesis of novel spiro(tri or tetra) cyclic lactones (Table 2). To our delight, the method was applied to the synthesis of novel spiro(tetra or penta)cyclic systems as well (Table 3). Significantly, this method enabled us to accomplish the entire tetracyclic carbon core of yuccaone A.

Results and discussion

To initiate the study, the requisite cyclic esters **8a-8c** were prepared from the commercially available ketones by implementing the standard Wittig–Horner–Wadsworth–Emmons

Table 3 Synthesis of novel spiro(tetra/penta)cyclic lactones **12** from the indanone based esters **11**[a,b]

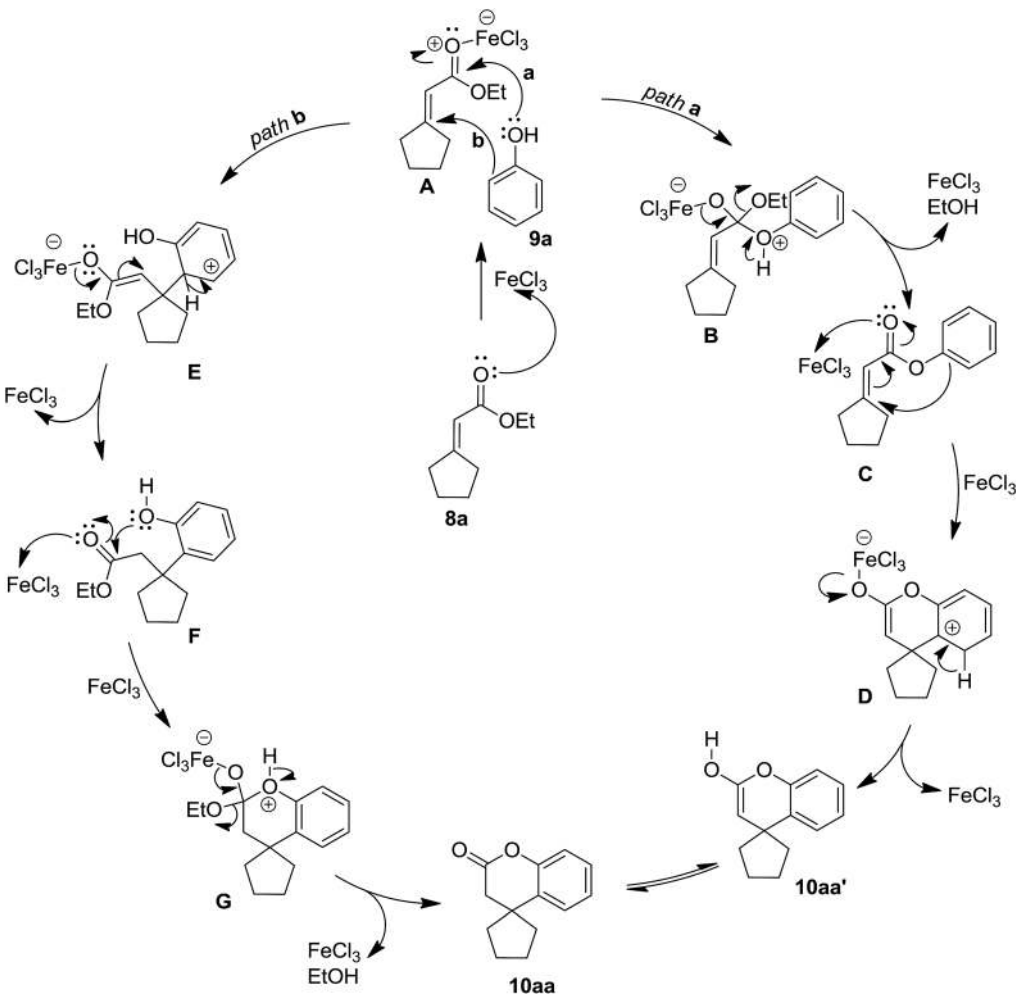




[a] All reactions were carried out on 0.5 mmol scale of **11** and 3 equiv. of **9**, in solvent benzene (1.5 mL). [b] Isolated yields of chromatographically pure products **12**. [c] Reaction was carried out in toluene (yield of **12bc**; 61%).

reaction. Initially, the acid promoted lactonization was explored on cyclohexanone ester **8b** with *para*-cresol **9d** as an external arene, under the conditions that were best suited for the synthesis of dihydrocoumarins reported by our group previously.[3] However, the reaction did not proceed and resulted only in the starting material isolation (Table 1, entries 1 & 2). This directed us to explore the other conditions to optimize the reaction. We began our investigations using catalytic loading of Lewis acid $FeCl_3$ with increased phenol **9d** concentration (3 equiv.), but it did not assist the reaction and led to the recovery of starting materials (Table 1, entries 3 & 4). Other Lewis acids like $AlCl_3$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$ and $AuCl_3$ also did not result in any product formation when used in the catalytic quantities (Table 1, entries 5 to 8). Even the reaction with 1 equiv. of the Lewis acid $FeCl_3$ proved inefficient to initiate the reaction (Table 1, entry 9). Further, we explored the reaction with the increased quantity of the acid. When the reaction was performed with 3 equiv. of acid at 50 °C, $BF_3{\cdot}OEt_2$ showed only starting material (Table 1, entry 10), but quite interestingly, all starting material disappeared in case with $FeCl_3$, however, the product **10bd** was not observed (Table 1, entry 11). Hence, we performed the reaction at room temperature using $FeCl_3$ (3 equiv.) in DCE, the required product **10bd** was obtained in 40% yield (Table 1, entry 12). Delightfully, the yield of tricyclic lactone **10bd** was improved to 67% when benzene was used as the solvent (Table 1, entry 13). However, further increase in $FeCl_3$ to 5 equiv., did not increase the yield of product **10bd** (Table 1, entry 14). We also planned to experiment toluene in place of benzene, and it is worth mentioning that the reaction was successful in toluene as well, albeit, in poor yield (Table 1, entry 15).

Fig. 2 X-ray crystal structure of **12ec**. Ellipsoids are drawn at 50% probability factor.



Scheme 2 Plausible mechanism for the formation of spirocyclic compounds **10**.

Among all the above screened conditions, those mentioned in entry 13 of Table 1 were best with regard to yield of **10bd**. Therefore, to check the scope and limitations of the method, these established conditions were applied to other homologous esters **8** with different phenols **9**. The method was highly amenable on different cyclic enoate esters **8** and furnished the corresponding spiro(tri or tetra)cyclic lactones **10** that are tabulated in Table 2. It is important to mention that the similar methodology when attempted with the ester derived from cyclooctanone failed to furnish the desired product. This might be probably due to the peculiar tub shaped conformational structure of the cyclooctanone moiety which might have hindered the product formation or may facilitate some unwanted reactions/rearrangements under these Lewis acidic conditions.

After successful accomplishment of novel spiro(tri or tetra) cyclic lactones **10aa–10ce**, to further improve the scope of the methodology, we applied it on various indanone based esters **11**. Various indanones were prepared from the corresponding aldehydes using Wittig Horner protocol to give the cinnamates, followed by reduction of the double bond and subsequent acid mediated cyclization to form the indanones, which were subjected to Horner–Wadsworth–Emmons reaction to yield esters **11**. Delightfully, it was found that the method suited to these systems as well and furnished the spiro(tetra or penta)cyclic compounds **12aa–12ec** containing simple to dense functionalities on the aromatic rings. Interestingly, the products **12aa–12ec** were obtained in good to excellent yields, as summarized in Table 3. It is worth mentioning that the reaction of the phenyl substituted indanone **11e**, furnished the spirotetracyclic product **12ec** wherein it is expected that the phenol moiety attacks the double bond from the less hindered exo-face of the ester. Hence, the stereochemistry of **12ec** would be as shown in Table 3. Significantly, all these spriocyclic lactones **12aa–12ec** constitute the major spirotetracyclic carbon core of the natural product yuccaone A.

In addition to the spectroscopic evidence for structural elucidation of the spirocyclic compounds, the complete structure and expected stereochemistry of **12ec** was further confirmed from the single crystal X-ray diffraction analysis (Fig. 2).

A plausible mechanism for the synthesis of spirocyclic compounds is delineated in Scheme 2. The formation of spirocoumarins might be possible in two ways (path a & b). It may be either initial Friedel Crafts acylation followed by intramolecular Michel addition (path a) or Michael addition followed by intramolecular acylation (path b) (Scheme 2). The carbonyl of the enoate may be activated by Lewis acid $FeCl_3$, triggering the attack of phenol at the carbonyl carbon to give **B** (Friedel–Crafts acylation). The adduct **B** would further rearrange to form **C** in which the carbonyl is again activated by the Lewis acid and internal Michael addition at the β-carbon of α,β-unsaturated ester might lead to the **D**, which stabilizes to form the required product **10aa**. On the other hand, in path b, initially $FeCl_3$ mediated Michael addition might lead to **E** which undergoes an intramolecular Friedel–Crafts acylation *via* **F** to form **10aa**.

Conclusions

In summary, we have developed an efficient and practical method for the synthesis of novel spiro(tri or tetra)cyclic lactones *via* the construction of C–C and C–O bonds in one-pot using the Lewis acidic ($FeCl_3$). It enabled the formation of spirocyclic lactones starting from simple aliphatic exocyclic enoate esters as reacting partners to phenols. Significantly, the method was successfully applied to the synthesis of novel spiro(tetra or penta)cyclic lactones bearing simple to dense functionalities on the aromatic rings.

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