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Indium-mediated Domino Lactonisation Approach towards Diastereoselective Synthesis of Pyrazole C-3 Linked Butyrolactones

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Abstract

A facile tandem approach has been established for the convenient diastereoselective synthesis of novel pyrazole and *α*-methylene-*γ*-butyrolactone based molecular hybrids. Indium-mediated Barbier-type allylation reaction was performed followed by *in situ* lactonisation approach. No additive was needed for this transformation and the butyrolactone derivatives were obtained with *syn* stereochemistry in good yields. The current protocol offers several advantages such as one-pot procedure, high diastereoselectivity, broad substrate scope and good yields of the desired products.

Keywords

Pyrazole-3-carbaldehyde; *α*-Methylene-*γ*-butyrolactone; Barbier-type allylation; Diastereoselectivity

Introduction

In the past years, attention of researcher in pyrazole chemistry has remarkably enhanced owing to the discovery of the exciting properties exhibited by a countless figure of pyrazole and its derivatives [1]. Being so synthesized and having pharmacological activity on human life cycle, they are categorized as alkaloids; however they are infrequent in nature. There are renowned natural compounds containing pyrazole nucleus that have several pharmacological and physiological effects (Figure 1) [2-3]. Moreover, pyrazole and its analogs are of significant importance to medicinal chemistry as they are gifted with many pharmacological effects [4-5] such as anti-inflammatory [6], anticancer [7-8], anticonvulsant [9], antimicrobial [10], analgesic [11] and antiviral [12]. Specifically, in recent years, various pyrazole based drugs have been developed; as a prime example, Celebrex [13-14] acts as a nonsteroidal anti-inflammatory agent, Ocinaplon [15] act as an anxiolytic drug, Rimonabant [16] act as an anti-obesity, Sildenafil [17-18] used to treat erectile dysfunction (Figure 2). In 1998 [19], sildenafil drug was permitted for prescription use within the European Union and United States and has turn out to be the most-selling medicine of all time. Accordingly, chemical, pharmaceutical and agrochemical industries have a great attention in their synthesis.

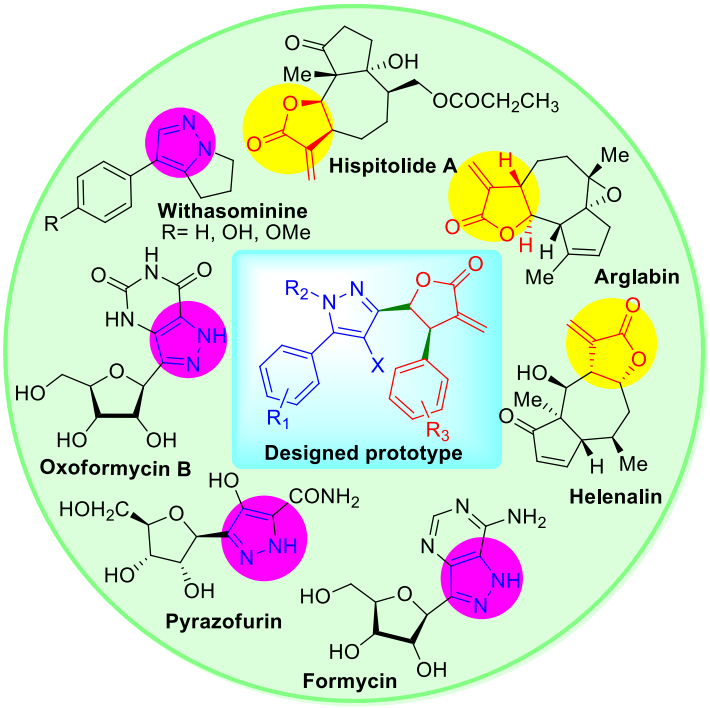


Figure 1. Pyrazole and butyrolactone based natural products

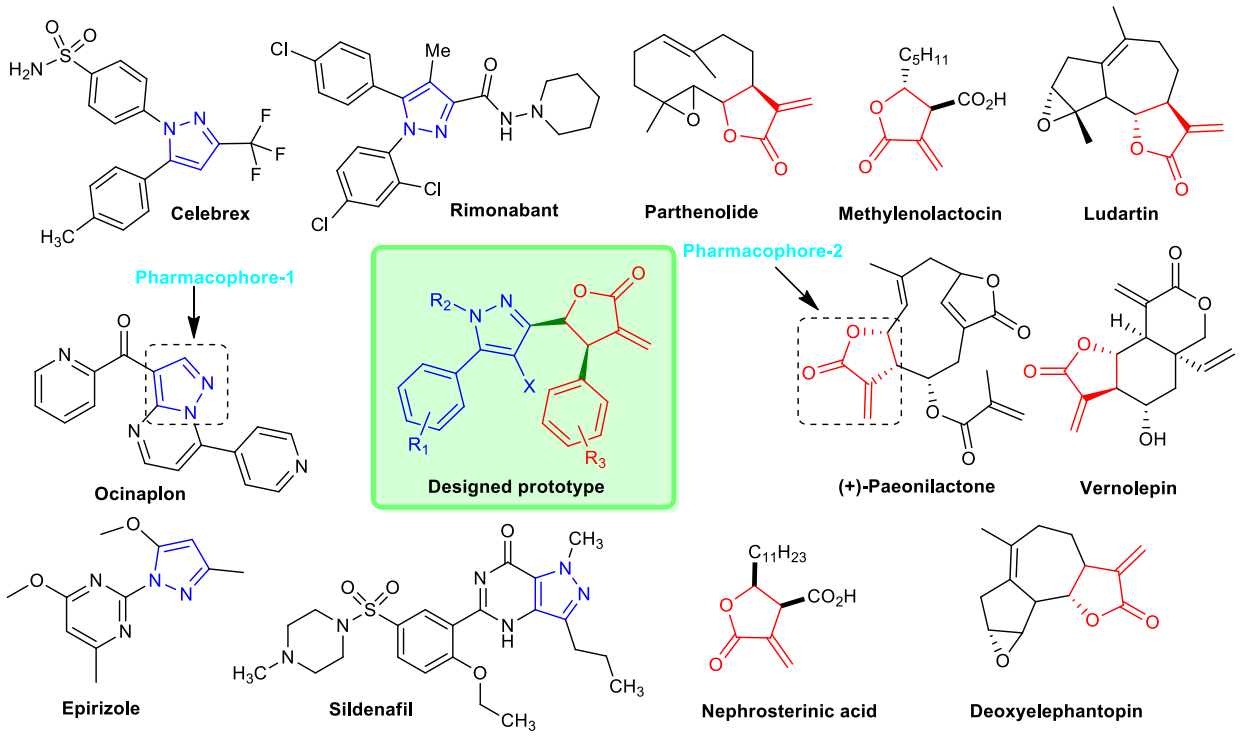


Figure 2. Few example of pyrazole and butyrolactone based drug moieties

Similarly, *α*-Methylene-*γ*-butyrolactone is one of the most abundant core structures found in natural products and displays a vast spectrum of biological properties such as FAS inhibitor, anticancer, antibacterial, anti-inflammatory and antifungal [20-21]. *α*-Methylene-*γ*-butyrolactone scaffolds are well recognized to interact with an extensive range of proteins, receptors with high affinity and act as cellular steroidal inhibitors, DNA polymerase inhibitors, blockers of tumor necrosis factor-*α* production, anticancer agents (breast, lung and liver cancer,) etc [22-25]. One prime example, Arglabin isolated from Artemisia glabella, has been demonstrated to treat liver, lung and breast cancer (Figure 1) [26-27]. These *α*-methylene-*γ*-butyrolactone derivatives show significant biological activity, *α*-exo-methylene skeleton which is an excellent Michael acceptor, which can interact with nucleophilic active sites on enzymes [28]. Figure 2 displayed the few examples of butyrolactone based drugs. On the basis of their exciting profile in the pharmacological field, butyrolactone and its derivatives have been developed by various research group across the globe; however, most of these strategies are multi-step

reactions and require additives (K_2CO_3, TFA, $In(OTf)_3$, $Yb(OTf)_3$, *p*-TSA , HCl, TfOH, NH_4Cl, K_2HPO_4), expensive reagents and long reaction times followed by tedious work up and purification methods [29-35]. Among the developed approaches, Barbier-type allylation strategy remains the key approach towards in the fabrication of these bioactive molecular architectures [36-38]. In order to develop the butyrolactones, allyl bromide substrates obtained from Morita-Baylis-Hilman reaction have been widely utilized for the diversity-oriented construction of this valuable skeleton [39-41].

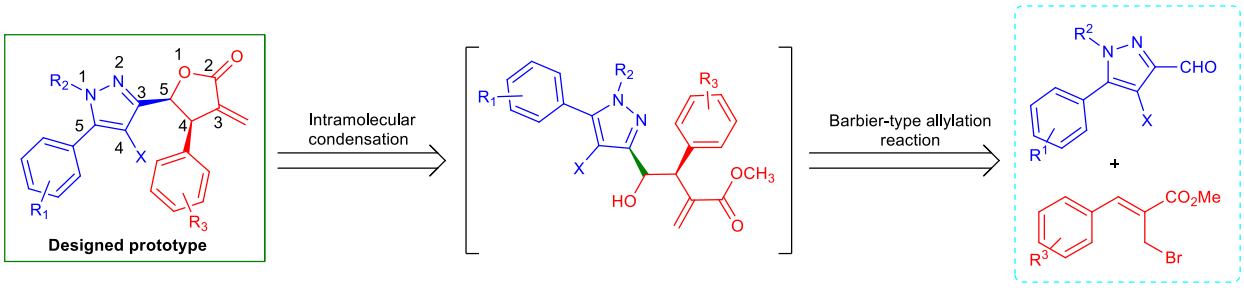


Figure 3. Retrosynthetic approach for the construction of pyrazole and γ-butyrolactone based molecular hybrids

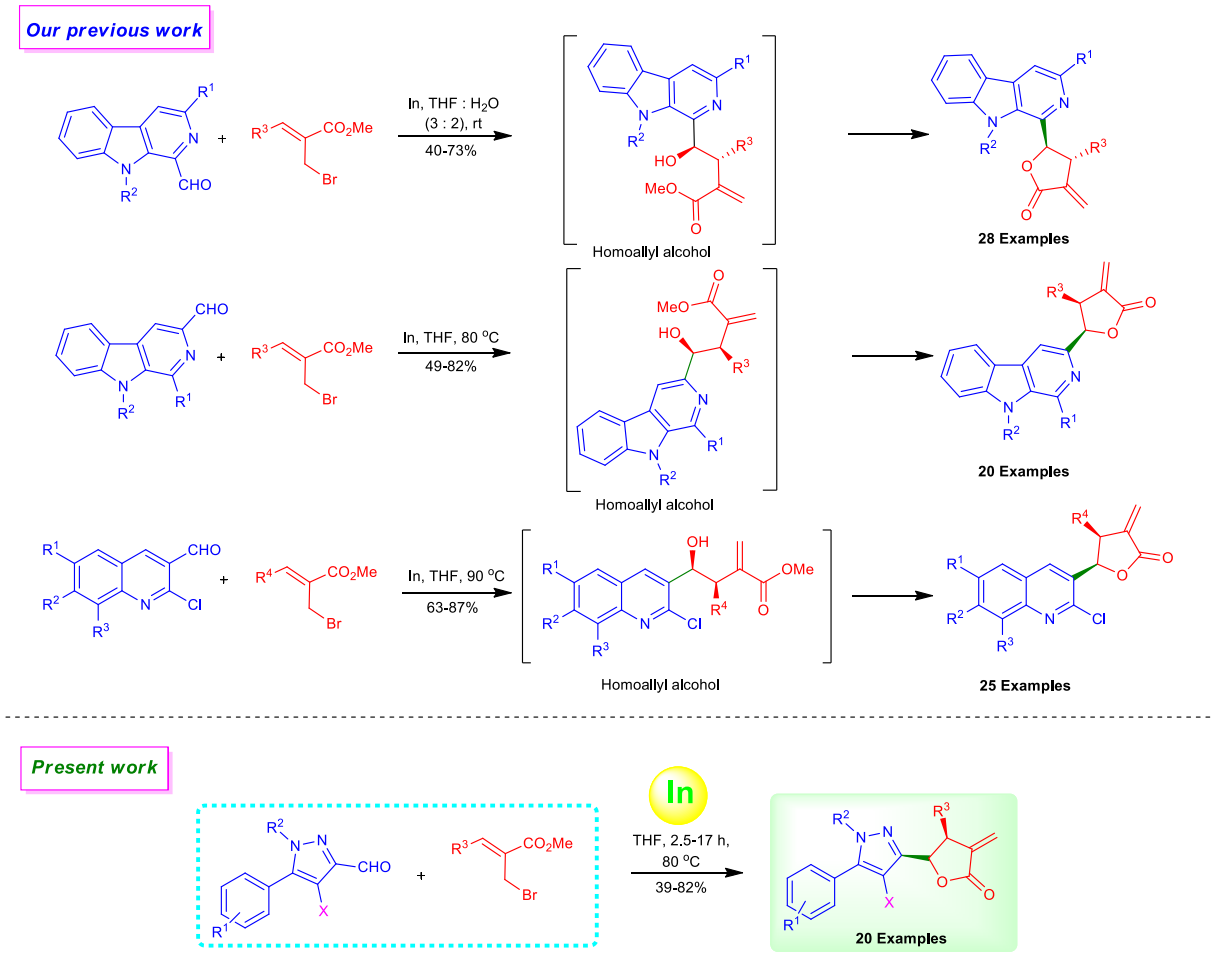


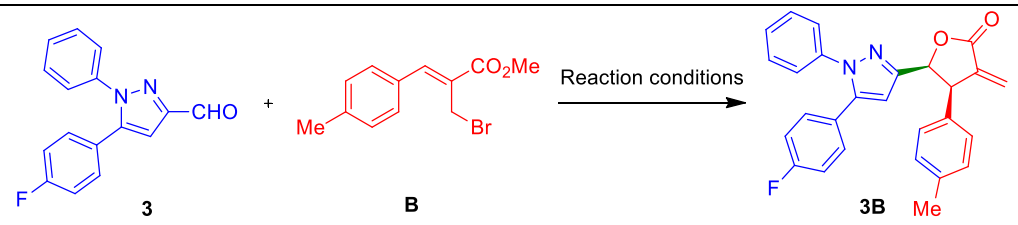
Figure 4. Our previous and present work related to the synthesis of *γ*-butyrolactone moieties

Motivated by the pharmacological potential of the pyrazole and butyrolactone, it was envisaged to associate these interesting moieties in a single molecular framework *via* a one-pot operation. In recent past, our group successfully reported the synthesis of *β*-carboline and quinoline tethered butyrolactone frameworks (Figure 4) [42-44]. Following our previous project, we planned to explore valuable butyrolactone moiety along with the substituted pyrazole framework. In this context, a retrosynthetic investigation was conducted which exposed that the desired prototype **V** may be synthesized *via* Barbier-Type reaction of pyrazole-3-carbaldehyde with allyl bromides followed by *in situ* intramolecular lactonisation using the substrate as presented in Figure 3. In this respect, we have carried out studies with the scope of this approach which is delineated herein.

Results and Discussion

In search of optimal conditions for the Barbier-type allylation reaction of pyrazole carbaldehydes and allyl bromide; we first investigated the reaction of 5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-3-carbaldehyde (**3**) and (*Z*)-methyl 2-(bromomethyl)-3-(*p*-tolyl)acrylate (**B**) in THF with elemental Fe and Bi powder (Entries 1-2, Table 1). Unfortunately, the anticipated product could not be delivered and starting precursors **3** and **B** remained intact even after 16-18 hours of reaction time. After that, tin (Sn, 1.5 equiv. and 2.5 equiv.) powder was tested in THF to execute this allylation reaction (Entries 3-4, Table 1). It was gratifying that a polar product was observed with 1.5 and 2.5 equiv. of Sn after 18-24 h. The spectroscopic analysis affirmed that the isolated product as the desired lactone derivative. The structure shown is (4*R*,5*R*)-5-(5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)-3-methylene-4-(*p*-tolyl)dihydrofuran-2(3*H*)-one (**3B**).

Table 1. Optimisation studies for the synthesis of pyrazole C3 tethered butyrolactone[a]



Entry	Reagent[b] (equiv.)	Solvent[c]	Temp (°C)	Time (h)	Isolated yield (3B)
1[d]	Fe (1.5)	THF	80	16	NR
2[d]	Bi (1.5)	THF	80	18	NR
3[d]	Sn (1.5)	THF	80	18	30%
4[e]	Sn (2.5)	THF	80	24	52%
5[f]	Sn (2.0)	THF:H_2O (3:2)	80	24	61% + **3**
6[e]	Sn (2.5)	THF:H_2O (3:2)	120	24	47%
7	**In (1.0)**	**THF**	**80**	**12**	**73%**

8	In (1.0)	THF:H_2O (3:2)	80	12	traces
9	In (1.0)	THF	rt	12	traces + **3**
10	In (1.0)	THF:H_2O (3:2)	rt	16	traces
11	-	THF	80	24	NR
12	In (1.0)	H_2O	90	24	43% + **3**
13	In (1.0)	MeOH	80	17	traces
14[g]	ZnONPs	THF	80	17	NR
15[g]	$Cu(OTf)_2$	THF	80	17	NR

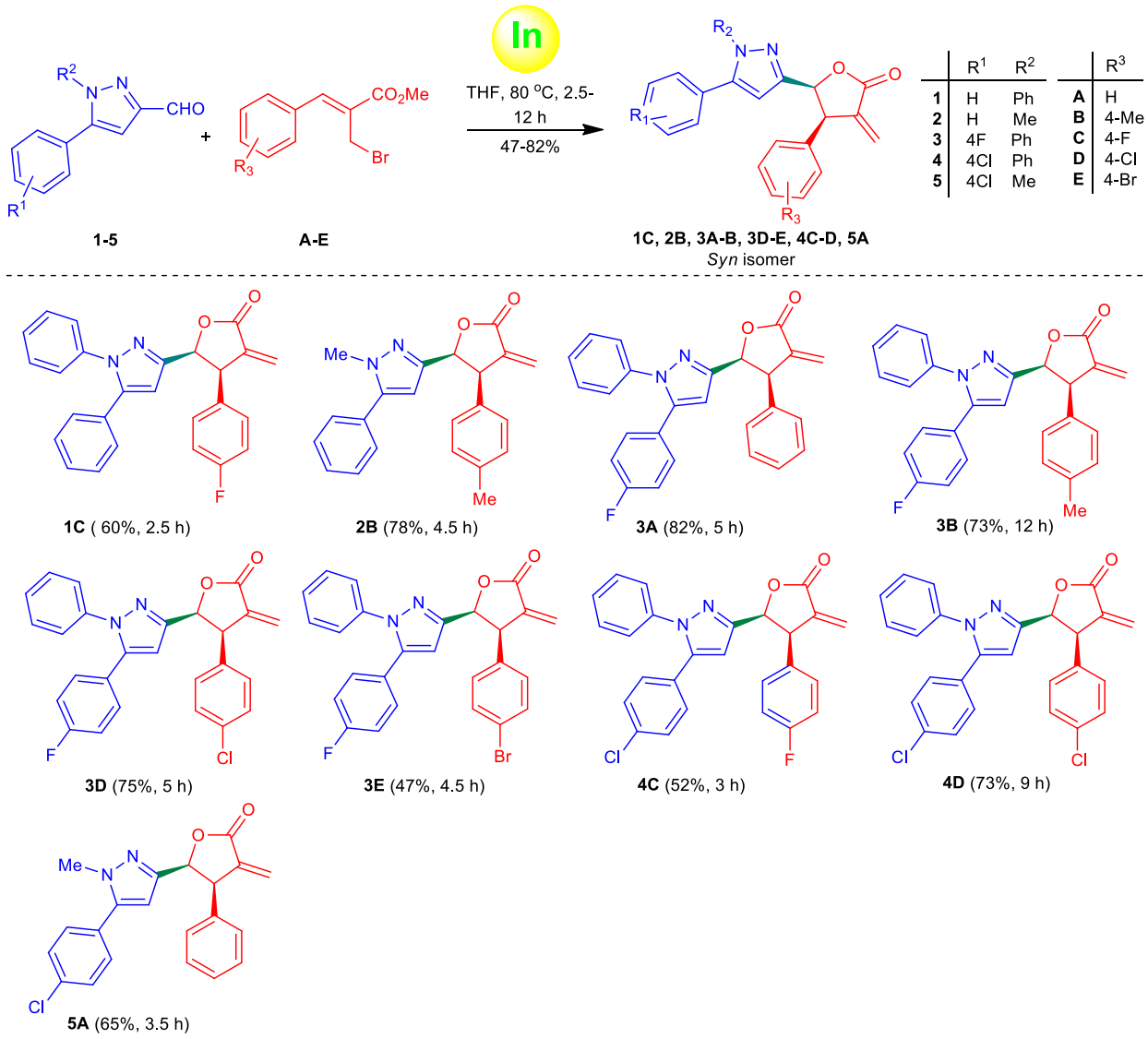
[a]All the optimization reactions were conducted with 0.19 mmol (1.0 equiv.) of **3** and 0.47 mmol (2.5 equiv.) of **B**, in 2 mL of solvent; [b]1.0 equiv. of reagent was used; [c]The optimization reactions were performed with anhydrous solvents except entries 5-6, 8,10 and 12; [d]1.5 equiv. of reagents were utilized; [e]2.5 equiv. of reagents were utilized; [f]2.0 equiv. of reagent was utilized; [g]10 mol% of reagents were used; NR = No reaction and **3** was recovered.

The reaction was observed to be diastereoselective in nature as the single diastereomer was obtained and the stereochemistry of the pyrazole C3 tethered butyrolactone **3B** across C4 and C5 proton of lactone was assigned as a *syn* isomer on the basis of a NOESY (2D NMR) experiment. The literature survey disclosed that THF, H_2O and semi-aqueous reaction medium were the best solvents for this transformation [42-44]. Keeping in mind these facts, we performed an experiment with Sn (2.0 equiv.) in THF:H_2O under heating condition (Entry 5, Table 1) and a slight positive effect was noticed on the yield (61%) of pyrazole linked butyrolactone **3B** though the substrate **3** was not fully consumed even after 24 h.

Thereafter, we enhanced the amount of Sn (2.5 equiv.) and increased temperature of the reaction (120 ^oC) but the yield of the designed product **3B** declined to 47% (Entry 6, Table 1). Next, indium (In) powder was employed for the Barbier-type allylation approach in the presence of anhydrous THF and THF:H_2O as reaction solvent at 80 ^oC (Entries 7-8, Table 1). To our delight, the anticipated framework **3B** was obtained in good yield (73%) with a significant reduction in time (12 h) while the mixture of THF and

H_2O could deliver the product in traces only. To examine the role of temperature, a reaction was examined at rt (room temperature) in the presence of THF and THF:H_2O and with In as a promoter (Entries 9-10, Table 1). Surprisingly, pyrazole C3 substituted butyrolactone **3B** was obtained in traces only. Additionally, a reaction was conducted in the absence of indium and it was observed that only starting materials remained, even after 24 h (Entry 11, Table 1). The optimization studies clearly indicated that the In was mandatory for this one-pot transformation. To find the better reaction conditions, we screened water and methanol as a reaction solvent in combination with indium under heating condition (Entries 12-13, Table 1). Reaction in methanol failed to deliver the desired prototype **3B**; however, the product was obtained in 43% yield in water as a solvent. Moreover, ZnO nanoparticles and $Cu(OTf)_2$ were investigated for the preparation of pyrazole based butyrolactone **3B** (Entries 14-15, Table 1) but the expected results were not obtained. On the basis of screening experiments, it was concluded that 1.0 equiv. of In in THF as a reaction solvent at 80 ^oC was the optimized reaction conditions (Entry 7, Table 1).

Having the established reaction conditions in hand, we tested the scope and generality of the present protocol against the diversified pyrazole-3-carbaldehydes (**1-5**) and substituted allyl bromides **A-E** for the diastereoselective synthesis of butyrolactones. Initially, the 5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-3-carbaldehyde (**3**) was treated with variously substituted allyl bromides **A-B** and **D-E** having electron releasing (CH_3) as well as electron donating (F, Cl and Br) groups under optimum reaction conditions as illustrated in Scheme 1. All of the cinnamyl bromides **A-B** and **D-E** responded positively to afford the pyrazole tethered α-methylene-γ-butyrolactones **3A-B** and **3D** in good to excellent yields (73-82%). Additionally, (*Z*)-methyl-2-(bromomethyl)-3-(4-bromophenyl)acrylate (**E**) delivered the designed product **3E** in acceptable yields (47%). Next, we employed other pyrazole-3-carbaldehydes **1-2** and **4-5** for the development of a library of pyrazole C3 tethered *cis*-butyrolactone derivatives **1C, 2B**, **4C-D** and **5A**. It is satisfactory to note that all the reactants **1-2** and **4-5** were well tolerated and delivered the anticipated prototypes **1C, 2B**, **4C-D**, **5A** in good yields (52-78%) within 2.5-12 hours of reaction time.



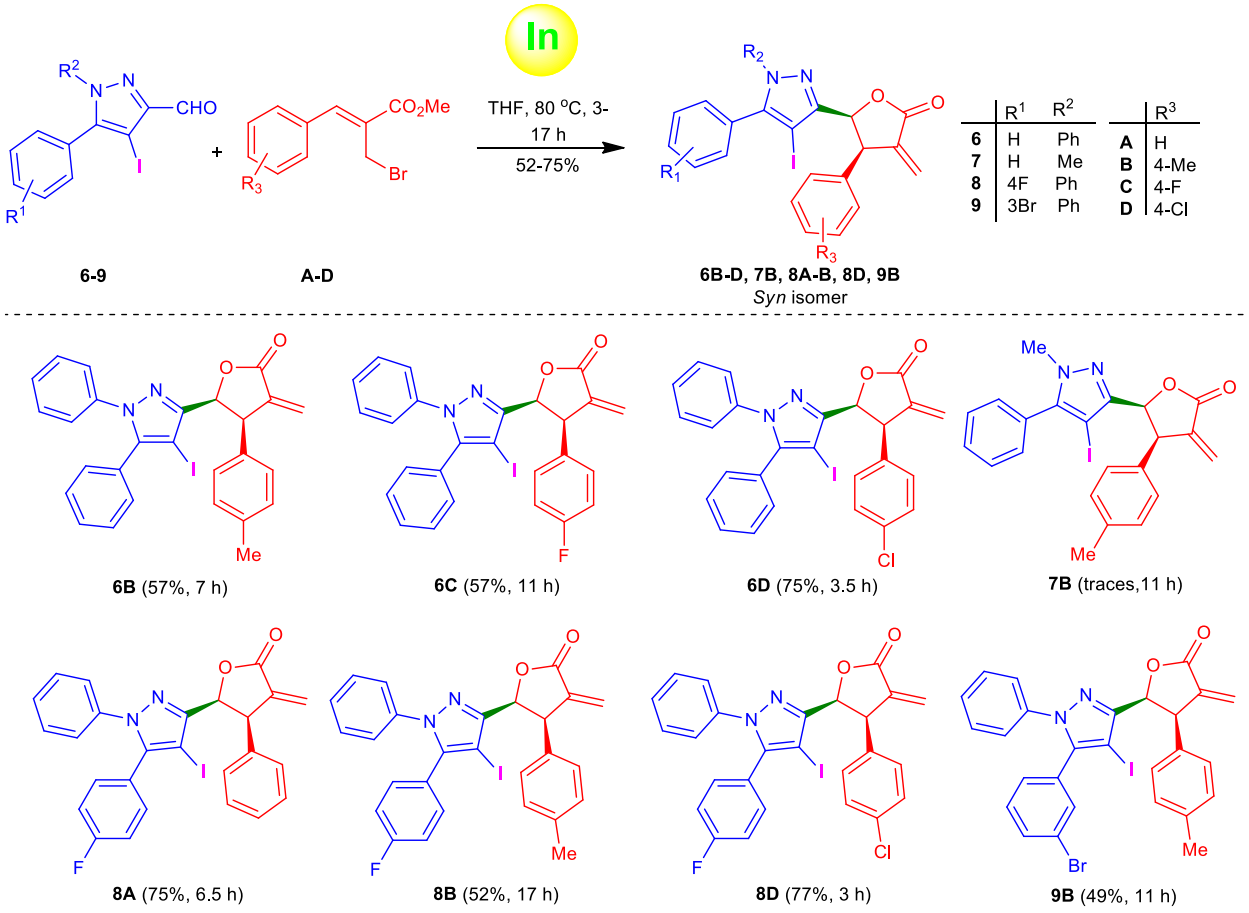
	R^1	R^2
1	H	Ph
2	H	Me
3	4F	Ph
4	4Cl	Ph
5	4Cl	Me

	R^3
A	H
B	4-Me
C	4-F
D	4-Cl
E	4-Br

Scheme 1. Synthesis of pyrazole C3 tethered butyrolactone derivatives

Delighted by these outcomes, it was further envisaged to explore C4 iodo substituted pyrazole-3-carbaldehydes **6-9** [45] to determine any the effect of substitution at the C4 position towards this In-mediated Barbier type allylation reaction as presented in Scheme 2. As expected, the reaction of all the 4-iodopyrazole-3-carbaldehydes **6-9** with the substituted allyl bromides **A-D** delivered the 4-iodopyrazole-3-carbaldehyde tethered *α*-Methylene-*γ*-butyrolactones **6B-D**, **8A-B**, **8D** and **9B** in good yields (52-75%) within 3-17 hours of reaction time. Unfortunately, 4-iodo-1-methyl-5-phenyl-1*H*-pyrazole-3-

carbaldehyde (**7**) and methyl substituted allyl bromide **B** delivered the anticipated product **7B** in traces only under optimized reaction condition.

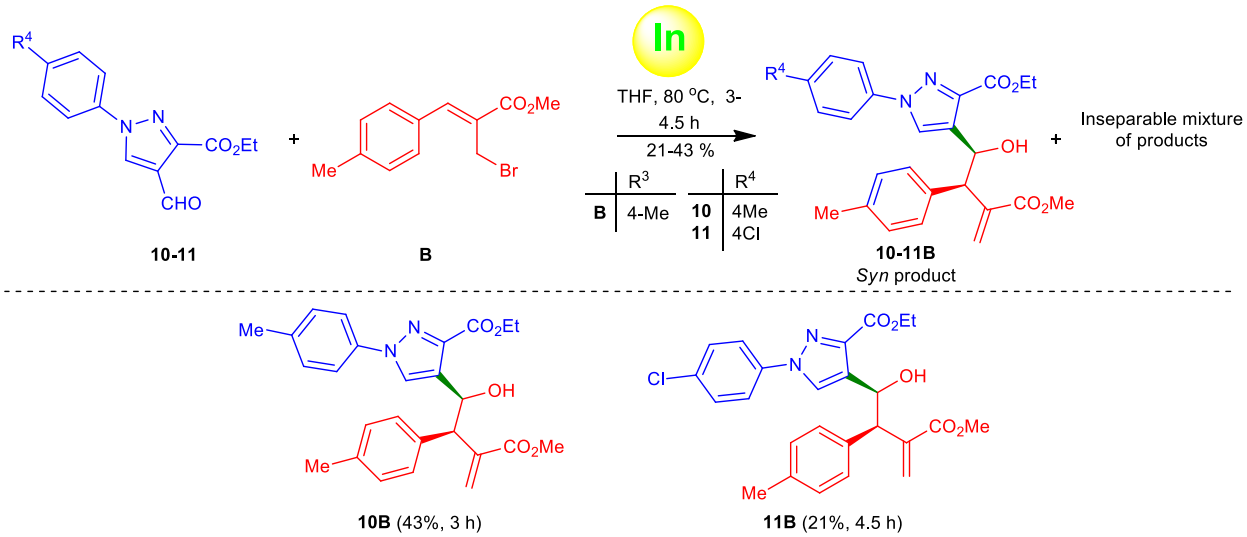


	R^1	R^2
6	H	Ph
7	H	Me
8	4F	Ph
9	3Br	Ph

	R^3
A	H
B	4-Me
C	4-F
D	4-Cl

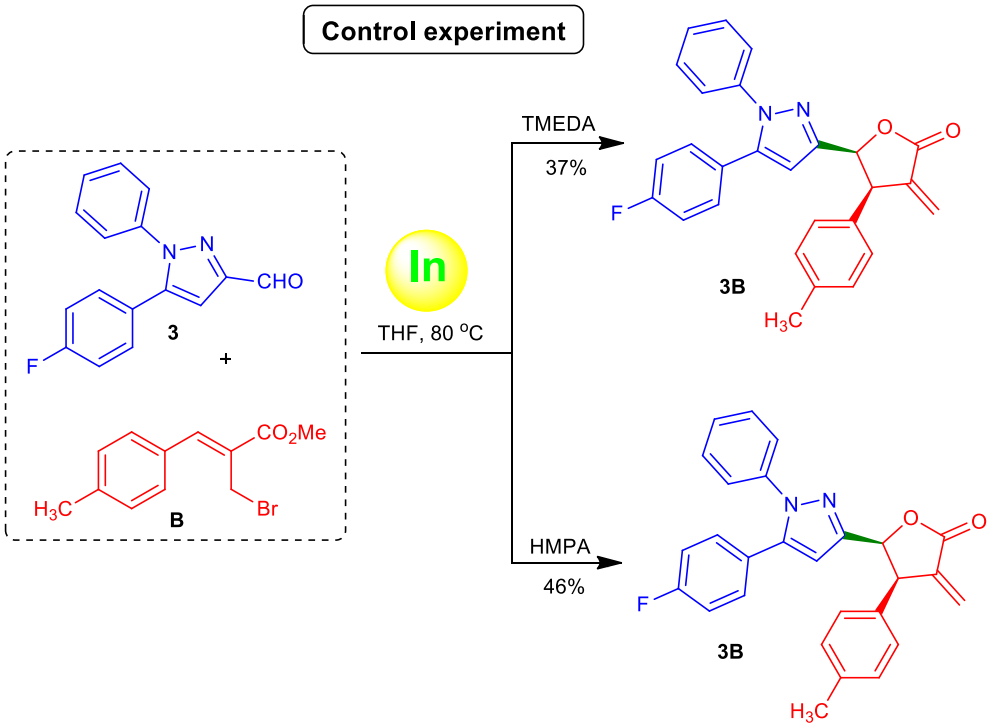
Scheme 2. In-mediated synthesis of 4-iodopyrazole C3 linked butyrolactones

After the successful exploration of pyrazole-3-carbaldehydes, next we directed our efforts towards the investigation of pyrazole C4 carbaldehydes [46] **10-11** as displayed in Scheme 3. It was surprising to note that reaction of pyrazole-4-carbaldehydes **10-11** with allyl bromide **B** could not deliver the pyrazole C4 substituted butyrolactone derivatives but rather reaction ceased after the formation of homoallyl alcohols **10-11B**. The pyrazole C4 linked homoallyl alcohols **10-11B** were obtained in low yield (21-43%) under similar reaction conditions along with the inseparable mixture of products.



Scheme 3. Synthesis of pyrazole C4 linked homoallyl alcohol derivatives

To probe the mechanistic pathway of the reaction, we conducted a set of control experiments in the presence of tetramethylethylenediamine (TMEDA) (3.0 equiv.) and hexamethylphosphoramide (HMPA) (3.0 equiv.) under standard reaction condition with the starting precursor **3** and **B** as presented in Scheme 4. It was observed that a significant decrease in the yield of product **3B** was observed because these metal solvating additives (TMEDA and HMPA) interacted with the In metal during formation of the desired product **3B**. Due to the interaction of indium with TMEDA and HMPA; a decrease in the yield of the anticipated product clearly indicated that In plays a key role in the formation of the anticipated product **3B**.

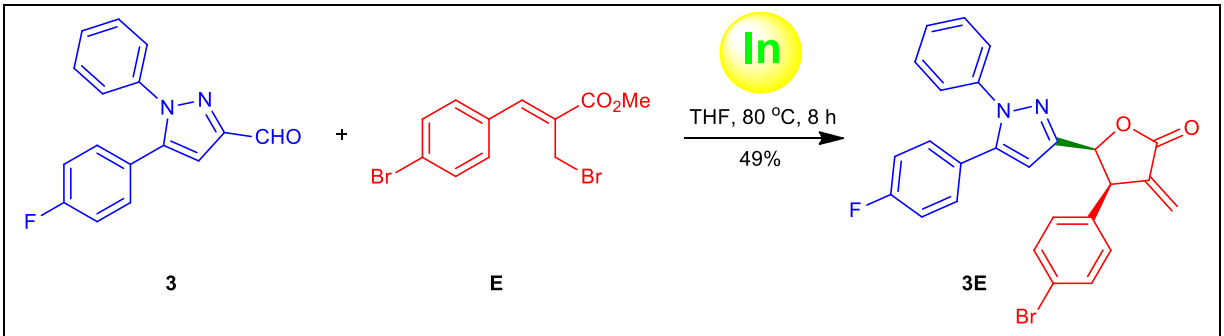


Scheme 4. Control experiments with TMEDA and HMPA

Thereafter, two pH experiments were also conducted in the presence and absence of base under standard reaction conditions as depicted in Tables 2-3. The pyrazole-3-carbaldehyde **3** and bromo-substituted allyl bromide **E** were chosen as model substrate for pH study. First, the experiment was examined in the absence of base and it was observed that after 2 h of mixing of reactants, the pH of medium was 5.35, and at completion of reaction, it was 4.21 (8 h) (Table 2).

Next, we conducted a pH experiment in the presence of 1.0 equiv. of triethylamine as a base under similar reaction conditions. As shown in Table 3, after the completion of reaction, the pH of the reaction medium was observed to be 5.12 (8 h). On the basis of pH experiment, it was concluded that the acidic pH of the reaction medium and the heating conditions were found to be responsible for *in situ* lactonisation of homoallyl alcohols.

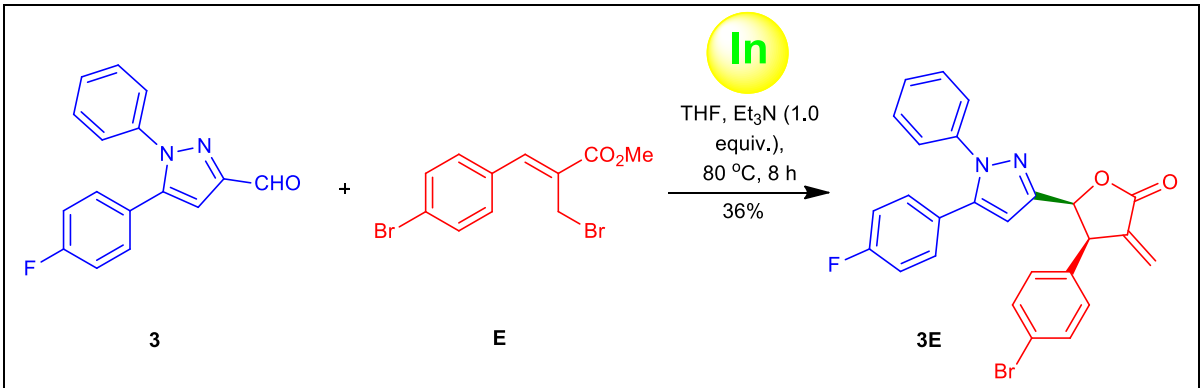
Table 2. pH experiment in the absence of base[a]



Entry	Time	Observed pH
1	0 min	5.71
2	2 h	5.35
3	4 h	5.05
4	8 h	4.21

[a]pH was measured at room temperature.

Table 3. pH experiment in the presence of base[a]

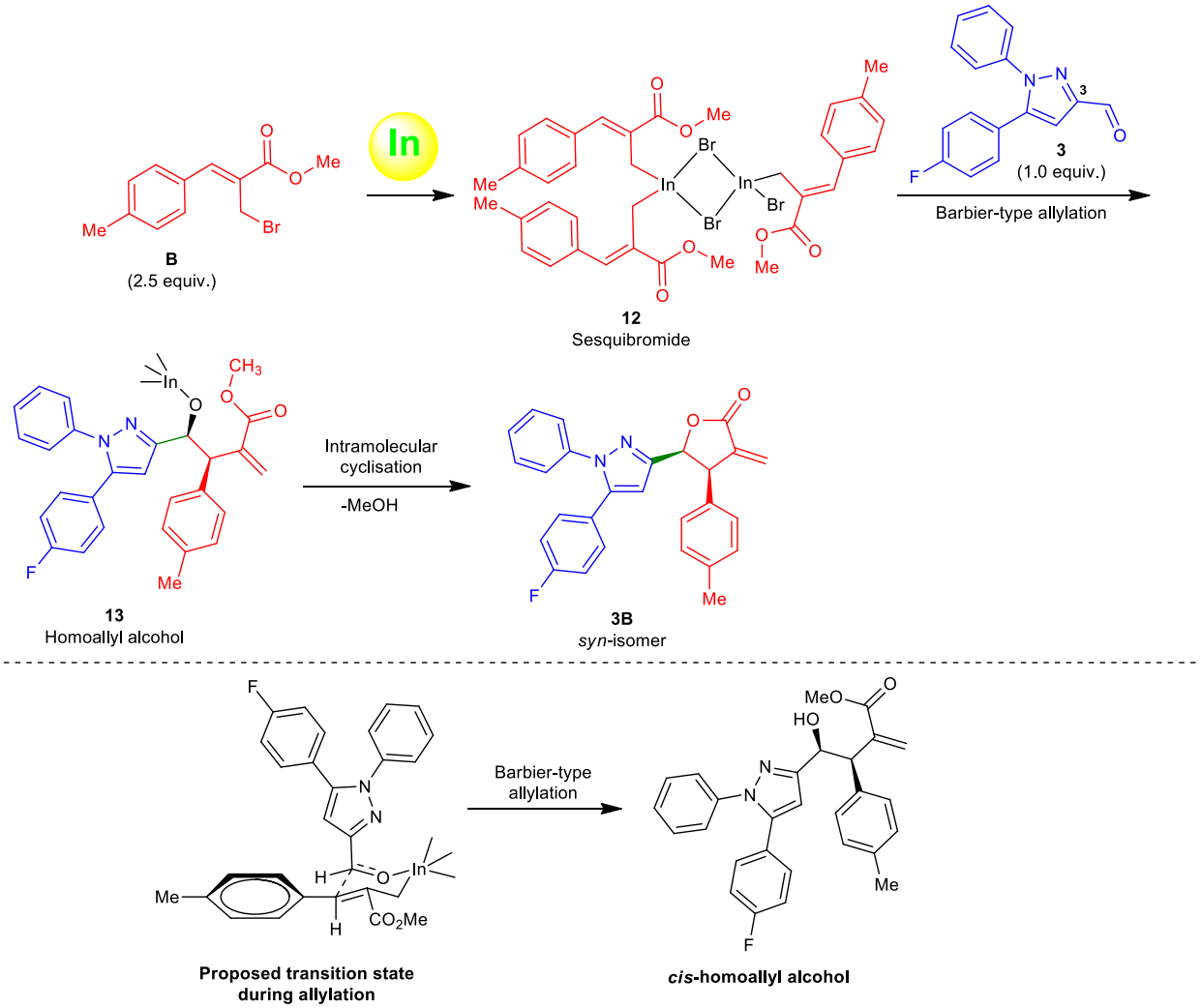


Entry	Time	Observed pH
1	0 min	8.14
2	2 h	6.14
3	4 h	5.31
4	8 h	5.12

[a]pH was measured at room temperature.

Based on the outcome of control experiment and pH study, a tentative mechanism is outlined in Scheme 5 with model reactants **3** and **B** [42-44]. Expectedly, In reacts with cinnamyl bromide **B** to produce the intermediate sesquibromide **12**. The generation of organoindium intermediate **12** is reinforced by the fact that a 1:1 ratio of cinnamyl

bromide **B** and indium could not lead to completion of the reaction. Furthermore, 2.5 equiv. of **B** (allyl bromide) was mandatory for the completion of this transformation. The present allylation reaction was noticed to be highly regiospecific in nature as the cinnamyl bromide **B** reacted through the *γ*-position with pyrazole carbaldehyde **3** to generate the homoallyl alcohol **13** with *syn* stereochemistry. The consecutive *in situ* intramolecular lactonisation approach furnished the **3B** with the *syn* stereochemistry.



Scheme 5. Tentative mechanistic route and transition state for the synthesis of pyrazole linked *α*-methylene-*γ*-butyrolactone

Conclusions

In sum-up, a new simple and convenient domino strategy towards the synthesis of novel pyrazole C-3 tethered *α*-methylene-*γ*-butyrolactone based molecular frameworks by the application of indium-mediated one-pot Barbier-Type allylation reaction followed by *in situ* intramolecular lactonisation approach. The present project was accomplished by the reaction of highly diversified pyrazole-3-carbaldehydes and substituted cinnamyl bromide in the presence of THF as a reaction medium. This protocol offers several advantages such as one-pot procedure, high functional group tolerance, easy purification process, easy to handle, high diastereo-selectivity and high yields of products. The biological studies of these molecular architectures could be exciting and reported in due course of time.

Experimental

General information

All chemicals and reagents were purchased from Sigma Aldrich, Acros, Avera Synthesis, Spectrochem Pvt. Ltd. and used without further purification. Commercially available anhydrous solvents (THF, DMF, DMSO, Toluene, MeOH, EtOH and CH_2Cl_2 spectrochem) were used in the reactions. Thin-layer chromatography (TLC) was performed using pre-coated aluminium plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using 60–120 mesh silica gels. Melting points were determined on Precision Digital melting point apparatus with open capillary tubes. IR spectra were recorded on an Agilent FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on an Avance III Bruker or JEOL JNM-ECS spectrometer at operating frequencies of 200/400/500 MHz (^{1}H) and or 100/125 MHz (^{13}C) as indicated in the individual spectrum using TMS as an internal standard. The room temperature varied between 25 ^{o}C to 35 ^{o}C. The multiplicities in the ^{1}HNMR spectra are presented as s for singlet, d for doublet, dd for doublet of doublet, t for triplet and m for multiplet.

General procedure for the synthesis of compounds 1C, 2B, 3A-B, 3D-E, 4C-D and 5A as exemplified for (4*S*,5*S*)-5-(5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)-3-methylene-4-(*p*-tolyl)dihydrofuran-2(3*H*)-one (3B): To a stirred solution of pyrazole-3-

carbaldehyde **3** (0.20 g, 0.75 mmol) and allyl bromide **B** (0.502 g, 1.87 mmol) in anhydrous THF, indium metal (In, 0.085 g, 0.75 mmol) was added. The reaction flask was heated under stirring at 80 ^{o}C for 12 h. After completion of the reaction, as monitored by the TLC, the reaction mixture was cooled to room temperature followed by the addition of water and the product was extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine and dried over anhydrous sodium sulphate which was further concentrated under reduced pressure to afford a crude product **3B.** The crude product **3B** was purified by silica gel (60-120 mesh) column chromatography using hexane and ethyl acetate (90:10, v/v) as an eluent to obtain the analytically pure product **3B** in 73% yield (0.23 g from 0.20 g; R_f = 0.61, (hexane/EtOAc, 90:10, v/v)) as a white solid.

General procedure for the synthesis of compounds 6B-D, 7B, 8A-B, 8D and 9B as exemplified for (4*S*,5*S*)-5-(5-(4-fluorophenyl)-4-iodo-1-phenyl-1*H*-pyrazol-3-yl)-3-methylene-4-phenyldihydrofuran-2(3*H*)-one (8A): To a stirred solution of 4-iodopyrazole-3-carbaldehyde **8** (0.20 g, 0.51 mmol) and cinnamyl bromide **A** (0.324 g, 1.28 mmol) in dry THF; indium metal (In, 0.058 g, 0.51 mmol) was added. The reaction flask was heated with stirring at 80 ^{o}C for 6.5 h. After completion of the reaction, as confirmed by the TLC, the reaction mixture was cooled to room temperature, water was added and the product was extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine and dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated under reduced pressure to afford a crude product **8A**. The product **8A** was purified by silica gel column chromatography (60-120 mesh) using hexane and ethyl acetate (93:07, v/v) as an eluent to obtain analytically pure product **8A** in 75% yield (0.18 g from 0.20 g; R_f = 0.72, (hexane/EtOAc, 93:07, v/v)) as a white solid.

General procedure for the synthesis of compounds 10-11B as exemplified for ethyl 4-((1*R*,2*R*)-1-hydroxy-3-(methoxycarbonyl)-2-(*p*-tolyl)but-3-en-1-yl)-1-(*p*-tolyl)-1*H*-pyrazole-3-carboxylate (10B): To a stirred solution of pyrazole-4-carbaldehyde **10** (0.20 g, 0.77 mmol), (*Z*)-methyl 2-(bromomethyl)-3-(4-methylphenyl)acrylate (**B**, 0.517 g, 1.93 mmol) in dry THF was added indium metal (In,

0.132 g, 1.16 mmol). The reaction flask was heated under stirring at 80 ^{o}C for 3 h. After completion of the reaction, as observed by the TLC, reaction mixture was cooled to room temperature, water was added and the product was extracted with ethyl acetate (3 x 25 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate which was further concentrated under reduced pressure to afford a crude product **10B**. The product **10B** was purified by silica gel column chromatography (60-120 mesh) by using hexane and ethyl acetate (90:10, v/v) as an eluent to obtain analytically pure product **10B** in 43% yield (0.08 g from 0.20 g; R_f = 0.84, (hexane/EtOAc, 90:10, v/v)) as a white solid.

Supporting Information

Supporting Information File 1:

File Name: Supp. Info

File Format: MS Word 2010

Title: Indium-mediated Domino Lactonisation Approach towards Diastereoselective Synthesis of Pyrazole C-3 Linked Butyrolactones

Acknowledgments

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