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Synthesis of tetrahydrochromenes and dihydronaphthofurans *via* a cascade process of [3 + 3] and [3 + 2] annulation reactions: mechanistic insight for 6-*endo-trig* and 5-*exo-trig* cyclisation†

 Yeruva Pavankumar Reddy,^a V. Srinivasadesikan,^a Rengarajan Balamurugan,^b M. C. Lin^c and Shaik Anwar^{id}*^a

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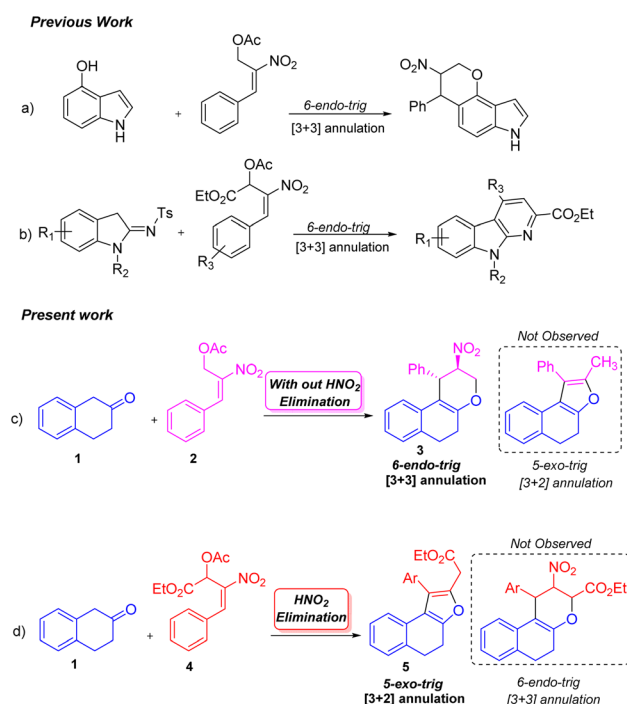
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Substituted tetrahydrochromenes and dihydronaphthofurans are easily accessible by the treatment of β -tetralone with *trans*- β -nitro styrene derived Morita–Baylis–Hillman (MBH) acetates through a formal [3 + 3]/[3 + 2] annulation. The reaction proceeds through a cascade Michael/oxa-Michael pathway with moderate to good yields. A DFT study was carried out to account for the formation of the corresponding six and five-membered heterocycles *via* 6-*endo-trig* and 5-*exo-trig* cyclization.

The ability to synthesize diverse molecules utilizing nitro allylic MBH acetates in various cascade reactions has received considerable interest.¹ A few molecules synthesized using nitro allylic acetates have shown promising cytotoxic, trypanocidal and AchE inhibition² activity in pharmaceutical and medicinal chemistry. Nitro allylic MBH acetates have been used as main precursors in organocatalysis³ and heterocyclic chemistry,⁴ and as bicyclic skeletons⁵ for the construction of elegant building blocks like tetrahydro-pyranquinolinones,⁶ sulfonyl furans,⁷ pyranonaphthoquinones,⁸ arenopyrans/arenylsulfanes,⁹ triazoles,^{10a} tetrasubstituted furans,^{10b} fused furans,^{10c,d} tetrasubstituted pyrroles,^{11a} benzofuranones,^{11b} and tetrahydropyran scaffolds/pyranocoumarins.¹² The nitro allylic MBH-acetates can also undergo asymmetric benzylic^{13a} and allylic alkylation^{13b} reactions as well as kinetic resolution [KR]^{13c,d} under normal conditions. These acetates undergo a range of cascade [2 + 3],¹⁴ [3 + 2]¹⁵ and [3 + 3]¹⁶ ring annulation reactions using different substrates. They have been widely utilized in [3 + 2]^{17a} and [3 + 3]^{17b} annulation reactions due to their unique nature of 1,2-/1,3-biselectrophilic reactivity to form either five or six membered rings depending on the nature of nucleophiles employed in the reaction^{17c,d}. These adducts are also stable under NHC catalytic conditions to yield cyclopentanes.¹⁸

Peng-Fei Xu *et al.* (Scheme 1, eqn (a)) synthesised tetrahydropyranoindoles through organocatalytic asymmetric C–H functionalization of indoles *via* [3 + 3] annulation through 6-*endo trig* cyclization.¹⁹ The Namboothiri group recently developed a metal free regioselective synthesis of α -carbolines *via* [3 + 3] annulation involving secondary MBH acetate (Scheme 1, eqn (b)).²⁰ Previously, our group carried out a [3 + 3] cyclization



Scheme 1 [3 + 3] and [3 + 2] annulation reactions using 1°- and 2°-nitro allylic MBH acetate.

^aDepartment of Chemistry, School of Applied Sciences and Humanities, Vignana's Foundation for Science Technology and Research-VFSTR (Deemed to be University), Vadlamudi-522213, Guntur, Andhra Pradesh, India. E-mail: shaikanwarcu@gmail.com; drsa_sh@vignana.ac.in; Web: <https://www.vignana.ac.in/bshanwar.php>; Tel: +91-8632344700

^bSchool of Chemistry, University of Hyderabad, Gachibowli, Hyderabad, India, 500046

^cDepartment of Applied Chemistry, National Yang Ming Chiao Tung University, Hsinchu 30010, Taiwan

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reaction of β -naphthol with primary MBH acetate to study the scope of S_N2' vs. S_N2 reaction.²¹ With our ongoing interest in using nitro styrene derived MBH adducts²² explored the reactivity of primary and secondary MBH acetate with β -tetralone **1** as our model reaction. Initially, the reaction carried out using β -tetralone **1** with primary MBH-acetate **2**, predominantly gave a tetrahydrochromene **3** *via* [3 + 3] annulation involving 6-*endo* trig cyclization through Michael/oxa-Michael cascade process. The possible dihydronaphthofuran product was not observed under the present conditions as primary MBH acetate **2** acts as 1,3-biselectrophile instead of 1,2-biselectrophile (Scheme 1, eqn (c)).

On the other hand, the reaction of β -tetralone **1** with secondary MBH acetate **4** gave dihydronaphthofuran instead of the possible tetrahydrochromene product due to the 1,2-biselectrophile nature of secondary MBH acetate (Scheme 1, eqn (d)). The formation of dihydronaphthofuran **5** occurs in an S_N2' fashion *via* [3 + 2] annulation involving 5-*exo-trig* cyclization through Michael followed by intramolecular oxa-Michael reaction with the elimination of HNO_2 . Subsequently, we have carried out a DFT calculation to prove the formation of tetrahydrochromene **3** using primary MBH acetate **2** and dihydronaphthofuran **5** in the case of secondary MBH acetate **4**.

Initially, we carried out the optimization conditions for constructing tetrahydrochromenes **3a** using β -tetralone **1** with MBH nitro allylic primary acetate **2a** with different bases and solvents. Reaction with organic base, *i.e.* DABCO using a polar

aprotic solvent such as acetonitrile at room temperature gave the desired product in 27% (Table 1, entry 1). Using chlorinated solvents like $CHCl_3$ and CH_2Cl_2 resulted in meagre yield (*i.e.*, 22 and 19%, respectively) with the recovery of starting material (Table 1, entries 2 and 3). The yield of the product was increased to 40% in the presence of DMAP and THF solvent (Table 1, entry 4). We obtained similar yields *i.e.* 45 and 44% in the presence of triethylamine, triphenylphosphine respectively (Table 1, entries 5 and 6). The reaction carried out using an inorganic base such as K_2CO_3 in THF solvent led to an increase in yield *i.e.*, 60% (Table 1, entry 7). A maximum yield of 77% was observed when the reaction was carried out in the presence of Cs_2CO_3 as base and THF as a solvent at room temperature for 4 h (Table 1, entry 8). The reaction with reduced base equivalents led to reduced yields concluded that 2.0 equiv. of Cs_2CO_3 is desirable to yield tetrahydrochromene **3a** under the present reaction conditions (Table 1, entries 9–11). Further, increase of Cs_2CO_3 with 3.0 equiv. led to unclean reaction mixture with decreased yield of the product **3a** (Table 1, entry 12). Notably, excellent diastereoselectivity of 99 : 1 dr was retained in all the cases of solvent/base optimisation studies. The stereocenter of the compound **3a** was further confirmed by 1H , ^{13}C NMR, HRMS, and single crystal XRD²³ (CCDC-2149875) (Table 2).

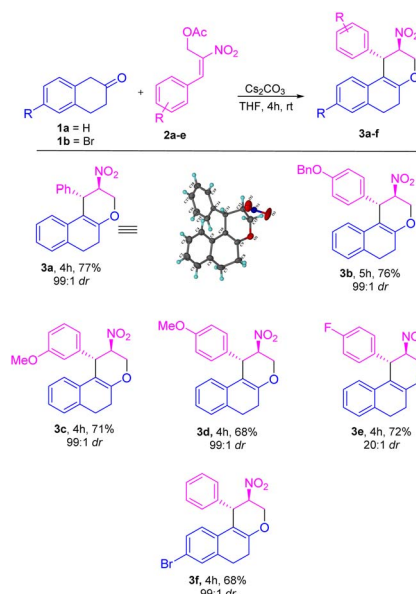
Based on the best optimized conditions, we studied the scope of different nitro allylic MBH primary acetates (**2a–e**) with β -tetralone **1**. The reaction accommodates various electron rich substituents on the primary MBH acetates (**2a–e**). The electron rich substituent containing **2b** gave 76% yield for the benzyloxy product **3b**. The substrate having *meta*-OMe and *para*-OMe gave the desired product **3c** and **3d** with 71% and 68% of yield, respectively. Furthermore, using fluoro substituent at *para* position of the MBH adduct gave the product **3e** with 72% yield. Reaction carried

Table 1 Optimization of reaction conditions for the synthesis of tetrahydrochromene **3a**^a

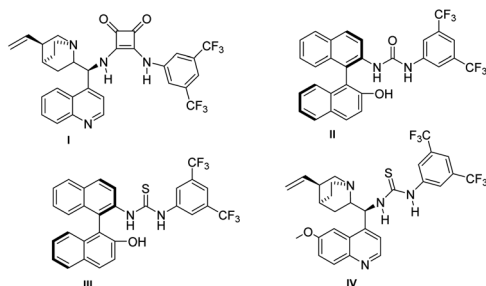
Entry	Base	Solvent	Time (h)	Yield (%)	dr ^b
1	DABCO	CH_3CN	5	27	99 : 1
2	DABCO	CH_2Cl_2	5	22	99 : 1
3	DABCO	$CHCl_3$	5	19	99 : 1
4	DMAP	THF	5	40	99 : 1
5	TEA	THF	5	45	99 : 1
6	PPh_3	THF	5	44	99 : 1
7	K_2CO_3	THF	4	60	99 : 1
8	Cs_2CO_3	THF	4	77	99 : 1
9 ^c	Cs_2CO_3	THF	8	50	99 : 1
10 ^d	Cs_2CO_3	THF	5	61	99 : 1
11 ^e	Cs_2CO_3	THF	4	65	99 : 1
12 ^f	Cs_2CO_3	THF	4	60	n.d

^a Unless otherwise noted, reactions were carried out by and (0.11 mmol) of **1** with (0.11 mmol) of **2a** using 0.22 mmol of a base in 1 ml of THF solvent. ^b Determined by 1H -NMR analysis of crude reaction mixture. ^c Reaction was carried out using 0.5 equiv. of Cs_2CO_3 . ^d Reaction was carried out using 1.0 equiv. of Cs_2CO_3 . ^e Reaction was carried out using 1.5 equiv. of Cs_2CO_3 . ^f Reaction was carried out using 3.0 equiv. of Cs_2CO_3 .

Table 2 Substrate scope for tetrahydrochromenes **3a–f**



out using 6-bromo tetralone **1b** gave the corresponding product **3f** in 68% of yield. Notably, remarkable diastereoselectivity of 99 : 1 dr was observed in all the cases of base screening and substrate scope of MBH primary acetate.



Encouraged, by the high diastereoselectivity for various tetrahydrochromenes derivatives **3a–e**, we pursued our studies towards asymmetric synthesis of **3a** using different chiral catalysts (I–IV). We observed the poor ee for the product formation in the presence of cinchona based squaramide catalyst I & BINAM based urea catalyst II (Table 3, entries 1 and 2). BINAM derived thiourea catalyst III resulted in a 10% enantiomeric excess (Table 3, entry 3). We obtained a moderate enantiomeric excess (49% ee) with good diastereoselectivity (99 : 1) in the presence of thiourea based hydrogen bonding catalyst IV (Table 3, entry 4). The use of various Lewis base catalysts also could not enhance the enantioselectivity.

We next focused our studies on understand the reactivity of secondary MBH acetate **4a** using β -tetralone **1**. Interestingly, the reaction followed an S_N2' Michael/intramolecular oxa-Michael pathway to form dihydronaphthofuran **5a** via [3 + 2] annulation instead of an alternate path resulting in the formation of chromene product via 3 + 3 annulation (*i.e.*, Scheme 1; eqn (d)). To recognize the optimal reaction condition, we carried out the reaction in the presence of CS_2CO_3 in THF solvent to get the desired dihydronaphthofuran **5a** in 35% yield (Table 4, entry 1). Next, we investigated the influence of chlorinated solvents on the product formation **5a**. Solvents such as CH_2Cl_2 , $CHCl_3$, and CCl_4 failed to enhance the yield for the product formation (Table 4, entries 2–4). Furthermore, an organic base such as TEA in THF gave the required product **5a**

Table 4 Optimization of reaction conditions for the synthesis of dihydronaphthofuran **5a**^a

Entry	Base	Solvent	Time (h)	Yield (%)
1	CS_2CO_3	THF	6	35
2	CS_2CO_3	CH_2Cl_2	4.5	31
3	CS_2CO_3	$CHCl_3$	4.5	27
4	CS_2CO_3	CCl_4	4.5	16
5	TEA	THF	5	46
6	DABCO	CH_3CN	6	41
7	PPh_3	CH_3CN	5	27
8	K_2CO_3	CH_3CN	4	72
9 ^b	K_2CO_3	CH_3CN	7	59
10 ^c	K_2CO_3	CH_3CN	6	63
11 ^d	K_2CO_3	CH_3CN	5	68
12 ^e	K_2CO_3	CH_3CN	4	65

^a Unless otherwise noted, reactions were carried out with (0.11 mmol) of **1** with (0.11 mmol) of **4a** using 0.22 mmol% of base in 1 ml of acetonitrile solvent. ^b Reaction was carried out using 0.5 equiv. of K_2CO_3 . ^c Reaction was carried out using 1.0 equiv. of K_2CO_3 . ^d Reaction was carried out using 1.5 equiv. of K_2CO_3 . ^e Reaction was carried out using 3.0 equiv. of K_2CO_3 .

with 46% of yield (Table 4, entry 5). A drop in the yield was observed using DABCO in presence of a polar aprotic solvent such as acetonitrile (Table 4, entry 6). Unfortunately, the yield drastically dropped to 27% using triphenylphosphine as a base (Table 4, entry 7). Finally, a good yield was observed with an inorganic base, *i.e.* K_2CO_3 using acetonitrile as a solvent to furnish the desired product **5a** in 72% of yield (Table 4, entry 8).

The reaction with reduced base equivalents, led to reduced yields confirming that 2.0 equiv. of K_2CO_3 is desirable to yield dihydronaphthofuran **5a** at room temperature within 4 h (Table 4, entries 9–11). It was observed that a low yield was obtained when the reaction was carried out with 3.0 equiv. of base (Table 4, entries 12).

Utilizing the established optimized reaction conditions, *i.e.* (Table 4, entry 8), the substrate scope of this formal [3 + 2] annulation was explored towards the construction of substituted dihydronaphthofurans **5b–g** (Table 5). The *meta*-OMe and *para*-OMe on the phenyl ring gave the good yield of 67 and 62%, respectively, for products **5b** and **5c**. The di substituted 2,4-dimethoxy, and 2,5-dimethoxy containing substrates gave a moderate yield of 60 and 58% for the desired products **5d** and **5e**. The substrate with benzyloxy substituent at the *para* position of the phenyl ring also gave the desired product **5f** in 70% of yield. A reaction carried out using substrate **1b** resulted in product **5g** in 58% yield (Table 5).

To further demonstrate our protocol's practical and scalable utility, we have carried out the gram scale preparation of tetrahydrochromene **3a** and dihydronaphthofuran **5a** in 66 and

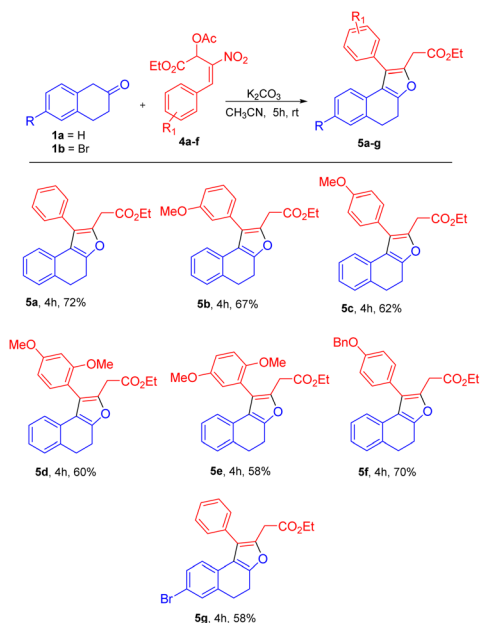
Table 3 Construction of chiral tetrahydrochromene **3a**^a

Entry	Catalyst	Time (h)	Yield (%)	ee (%)
1	I	4	59	<2
2	II	4	60	<2
3	III	4	60	10
4	IV	4	63	49

^a All the reactions were carried out with (0.11 mmol) of **1**, (0.11 mmol) of **2a**, (0.22 mmol) of base and 10 mol% in 1 ml of THF solvent.



Table 5 Substrate scope for the synthesis of dihydronaphthofurans 5a–g



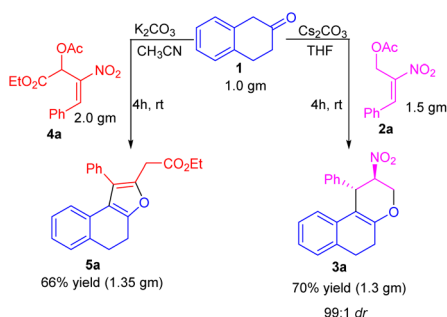
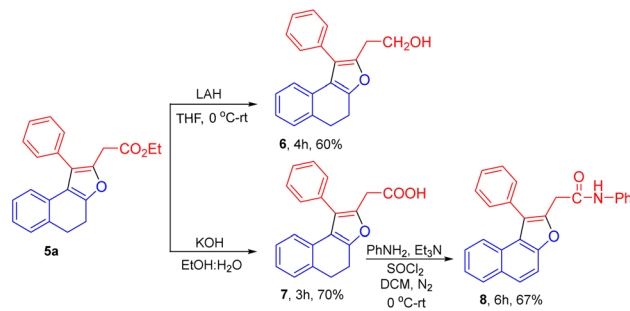
70% of yield. We observed the retention of diastereoselectivity *i.e.*, 99:1 of tetrahydrochromene **3a**, even at the gram scale condition (Scheme 2).

We have successfully applied the synthetic utility for dihydronaphthofuran **5a**. Reduction of the ester group in **5a** was feasible using LAH in THF to afford the desired alcohol product **6** with 60% of yield. Using KOH, the ester group in dihydronaphthofuran **5a** was hydrolysed to the corresponding acid derivative **7** in 70% yield. The amidation reaction of **7** with aniline accomplished oxidation of the tetralone ring providing the *N*-phenyl-2-(1-phenylnaphtho[2,1-*b*]furan-2-yl)acetamide product **8** in 67% of yield (Scheme 3).

DFT studies

Computational methods

The mechanistic pathway has been studied using the state-of-the-art density functional theory (DFT). All the computations

Scheme 2 Gram scale synthesis of tetrahydrochromene **3a** and dihydronaphthofuran **5a**.Scheme 3 Synthetic utility for the dihydronaphthofuran **5a**.

were carried out at the B3LYP²⁴ level of theory using the Gaussian 09²⁵ suite of program. The reactants, intermediates, and products were optimized at the B3LYP level of theory and confirmed no imaginary frequency. Furthermore, a minimum of one imaginary frequency were confirmed for all transition states.

Results and discussions

The reaction of β -tetralone **1(A)** with MBH nitro allylic primary acetate **2a** has produced tetrahydrochromene **3a** in this experiment. The reactant **1** was considered as an anion, where one of the protons of alpha carbon was deprotonated in the presence of base, and was allowed to interact with **2a**, resulting in the complex formation with the binding energy of -19.56 kcal mol⁻¹ as shown in the potential energy surface diagram Fig. 1 (*i.e.* P-cmplx). The respective anion attacked the alpha carbon of primary acetate **2a** *via* S_N2' fashion to form the intermediate (P-int1) with the C–C bond formation *via* P-TS1 with the activation of energy of 10.56 kcal mol⁻¹. Due to the double bond migration, the OAc was dissociated from P-int1 *via* P-TS2 with the activation energy of 2.87 kcal mol⁻¹ and produced P-int2 with the lowest energy of -10.35 kcal mol⁻¹ compared with P-int1. The unstable P-int2 immediately undergone for six-member ring cyclisation with the activation energy of 30.92 kcal mol⁻¹. The activation energy for the six-member ring cyclisation using the DFT method was in line with the previous literature report.²⁶ The product formation P-int3 with enthalpy of activation 13.37 kcal mol⁻¹. The proton transfer has occurred on P-int3 *via* P-TS4 with the activation energy of 30.85 kcal mol⁻¹ has produced the final product of naphthopyran (**3a**). The higher amount of activation energy was observed for proton transfer due to the proton migration from rich nucleophilic center to a weak electrophilic center. The Mulliken charge for the electron rich and poor centers have been shown in ESI Fig. 1.† The geometrical parameters of hydrogen bond length have been observed to be 2.161 and 1.505 Å shown in Fig. 1 (see ESI†). The exothermicity of naphthopyran (**3a**) was obtained with the -10.49 kcal mol⁻¹, exothermically. The lowest energy shows the stability of the final product **3a**. Here, we studied the five-member ring formation also to understand the stability and possibility of formation. The β -tetralone oxygen atom attacks the tertiary carbon and produced five membered cyclized product. However, the energy barrier has observed to be 41.28 kcal mol⁻¹ and the energy of five-



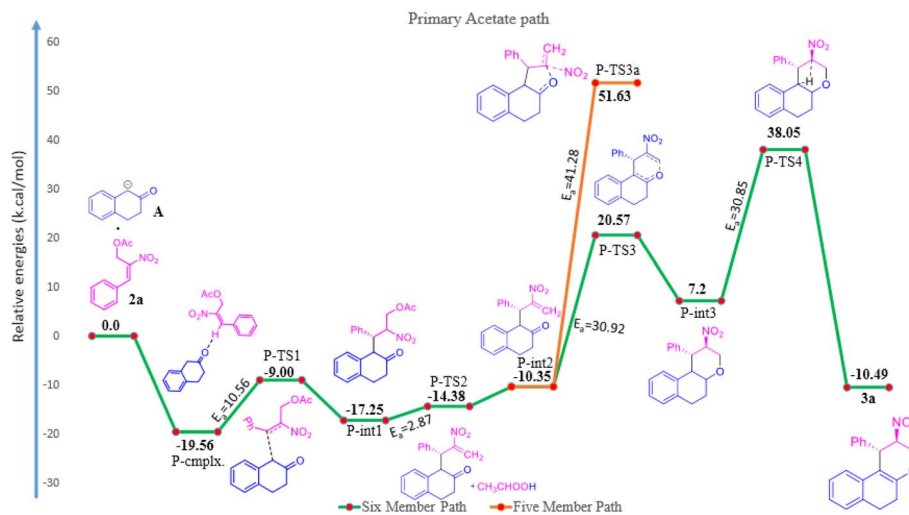


Fig. 1 Potential energy surface mechanism of primary acetate **2a** with β -tetralone **1**.

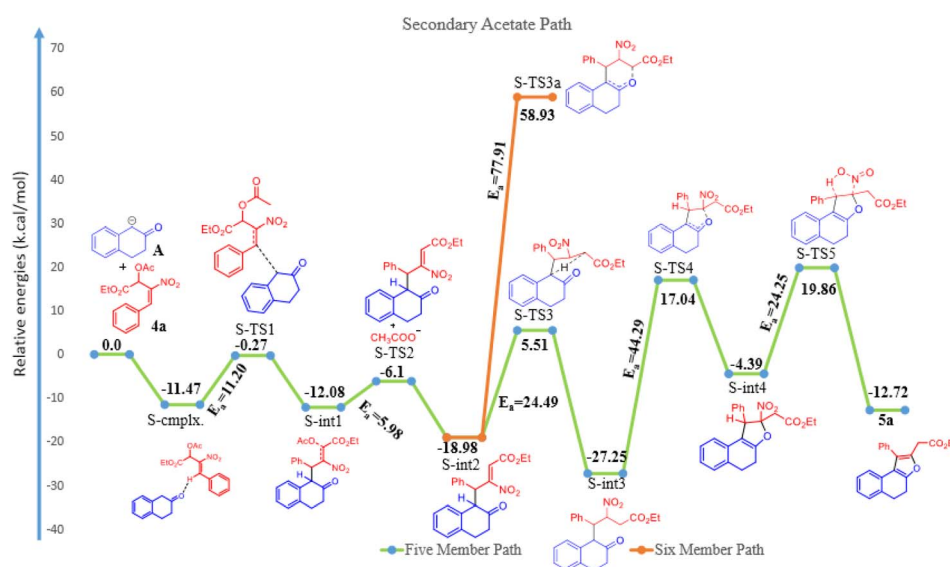


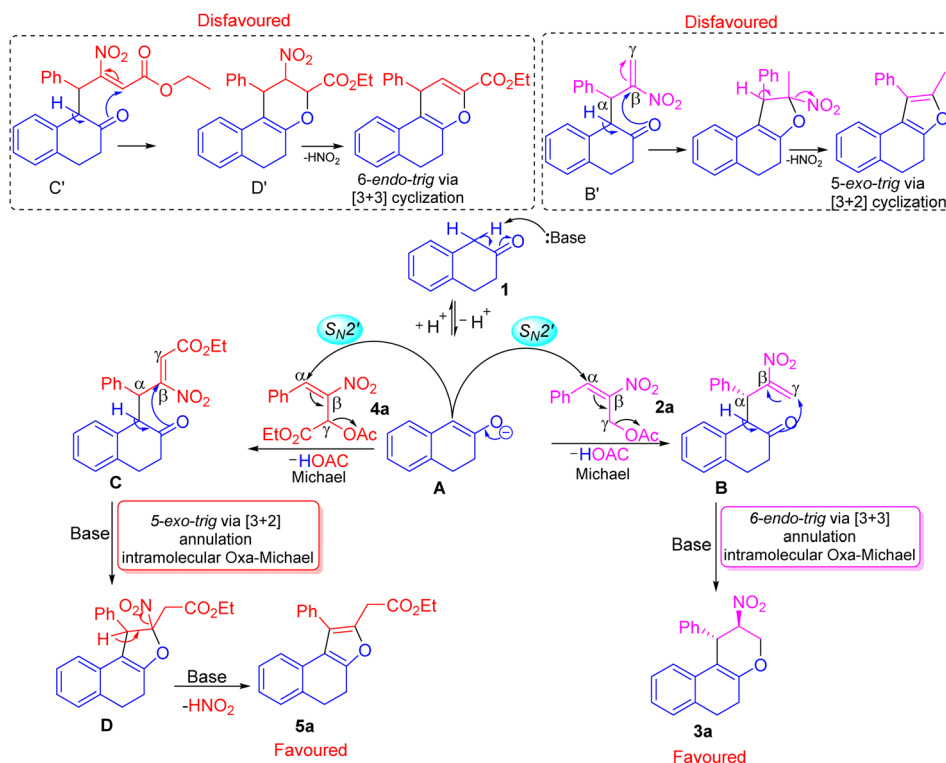
Fig. 2 Potential energy surface mechanism of secondary acetate **4a** with β -tetralone **1**.

member ring product has observed to be endothermic and shown the instability (Fig. 1 and 2).

The β -tetralone **1** reacting with nitro allylic secondary MBH acetate **4a** produced the dihydronaphthofuran derivatives, **5a–g**, which is observed experimentally as shown in Table 5. The anion of β -tetralone **1** was considered for the DFT calculation. Here, an anion of β -tetralone interacts with the MBH nitro allylic secondary acetate **4a** has produced a complex with a binding energy of -11.47 kcal mol $^{-1}$. The anion path was considered for the theoretical calculation due to the abstraction of a proton by the base, initiating the reaction observed experimentally. The anion is displacing the acetate *via* S_N2' fashion has produced the intermediate (S-int1) as C–C bond formation with the barrier energy of 11.20 kcal mol $^{-1}$. The formation of S-int1 is stable exothermically than the complex (S-cmplx). The S-TS2 was shown to be an acetate leaving group with a barrier

energy of 5.98 kcal mol $^{-1}$ and produced the product with new C–C bond formation and with dissociation the acetate group. The S-int2 initiate the proton transfer to produce the S-int3 with the stable intermediate. The barrier energy for the proton transfer has been observed as 24.49 kcal mol $^{-1}$ showed in Fig. 2. The formation of S-int3, readily undergo for five-member cyclisation. As shown in Fig. 2, the S-int3 has produced S-int4 *via* S-TS4 with a barrier energy of 44.29 kcal mol $^{-1}$. The higher barrier energy observed for cyclisation is accountable for the concern carbon has the electron-withdrawing nitro group. The highest energy barrier for cyclisation has considered as the rate determining step (RDS) for the secondary acetate path. Thus, the nitro group leave immediately after five-member ring cyclisation as HONO with the barrier energy of 24.25 kcal mol $^{-1}$ and produced the observed product **5a**. The relative energy of **5a** was observed to be -12.72 kcal mol $^{-1}$ showing the stability of the





Scheme 4 Plausible mechanism for the construction of tetrahydrochromene **3a** and dihydronaphthofuran **5a**.

product. In the secondary acetate path, we have studied the possibility of a six-member ring formation. However, the barrier energy was observed to be 77 kcal mol^{-1} (S-Ts3a) and it observed as unfavourable path.

We have explained a plausible mechanism for the formation of tetrahydrochromene **3a** and dihydronaphthofuran **5a** in correlation to density functional theory (Fig. 1 and 2). The β -tetralone **1** generates the nucleophile **A** in the presence of a base. The nucleophile **A** attacks at α -position on the benzylic carbon atom of primary MBH-acetate **2a** to generate intermediate **B**. This initial Michael attack involves the migration of double bond with the elimination of acetic acid *via* S_N2' reaction. Further deprotonation in the form of keto-enol tautomerism generates a nucleophilic oxygen atom to facilitate the oxa-Michael attack at γ -carbon atom of intermediate **B**. This intramolecular oxa-Michael addition favors 6-*endo* trig cyclization with [3 + 3] annulation to furnish the desired product **3a**.

The possible alternate pathway involving oxa-Michael attack at the β -carbon atom of **B'** is disfavoured for forming fused furan ring. Due to the 1,3-biselectrophilic nature of primary MBH acetate there exists a ring strain associated with undergoing the 5-*exo*-trig cyclization *via* [3 + 2] annulation (Scheme 4). The formation of **5a** initiates with the attack of nucleophile **A** at the α -position of the benzylic carbon atom of secondary MBH-acetate **4a**. This initial Michael addition involves migration of double bond and elimination of acetic acid through effective S_N2' reaction to generate intermediate **C**. Further deprotonation followed by tautomerism results in nucleophilic oxygen which undergoes intramolecular oxa-Michael reaction at the β -position of **4a** to give intermediate **D** with [3 + 2] annulation *via* 5-

exo-trig cyclization. Further elimination of HONO under basic conditions results in **5a** as the favoured product. Alternate oxa-Michael attack on γ -position of intermediate **C'** was disfavoured for a possible [3 + 3] annulation *via* 6-*endo*-trig cyclization. This alternate pathway towards the 4H-pyran precedes through **D'** with 1,2-elimination of HONO is disfavoured.

Conclusions

In conclusion, β -tetralone in reaction with primary MBH acetate results in six membered tetrahydrochromenes *via* [3 + 3] annulation. On the other hand, the reaction with secondary MBH acetate results in the formation of five membered dihydronaphthofuran derivatives *via* [3 + 2] annulation. The DFT result shows that the β -tetralone attacks MBH nitro allylic primary acetate through S_N2' and intramolecular oxa-Michael reaction *via* 6-*endo*-trig with a low barrier energy of $1.47 \text{ kcal mol}^{-1}$ which favors the six membered cyclization compared with five membered ring cyclization with the barrier energy of $52.63 \text{ kcal mol}^{-1}$. Similarly, secondary MBH acetate follows the S_N2' reaction and intramolecular oxa-Michael reaction *via* 5-*exo*-trig occurs with a low barrier energy of $55.29 \text{ kcal mol}^{-1}$ to obtain the 5-member ring cyclization product disfavoring 6-*endo*-trig cyclization with a barrier energy of 56 kcal mol^{-1} .

Author contribution

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Y. P. Reddy. S. A. and R. B. contributed on



additional analysis required to address the comments and issues from the reviewers. MCL and VSD contributed DFT calculations. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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