Tandem aldol condensation-Diels–Alder-aromatization sequence of reactions: a new pathway for the synthesis of 2-tetralone derivatives

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This paper is dedicated to Professor Dale E. Ward for 30 years of professorship at U of S.

Abstract: A series of new polysubstituted derivatives of 2-tetralones possessing two ester groups were synthesized via a tandem aldol condensation-Diels–Alder-aromatization sequence of reactions. All the three steps took place in one pot and in the presence of aminofunctionalized silica coated Fe_3O_4 nanoparticles as the catalyst. *In situ* formed dienes reacted with diethyl acetylenedicarboxylate at room temperature and the process was followed by spontaneous aromatization of the cycloadducts to produce high yields of the final tetralone products. Further studies suggest that the process goes through an initial aldol condensation-cycloaddition sequence followed by oxidation and rearrangement steps. After completion of the reactions, the catalyst could be recycled and reused efficiently in next reactions.

Key words: tandem reaction, tetralones, aldol condensation, Diels–Alder reaction, aromatization.

Resume:

Introduction

Tetralones constitute a group of organic intermediates which are used in the synthesis of several biologically important compounds[1-3] or in the preparation of other chemicals such as lipodioxigenase,[4] substituted naphthols,[5] or laser pigments.[6] In addition, tetralone derivatives are used in the synthesis of sertraline, a potent drug for the treatment of depression and anxiety related problems.[7] Different methods are reported for the synthesis of tetralones such as intramolecular cyclization of phenylbutyric acid,[8-10] reductive cleavage of naphthyl ethers,[11] or the Haworth reaction.[12]

The [4+2] Diels–Alder (DA) cycloaddition is arguably one of the most versatile reactions in synthetic organic chemistry and after almost one century from its discovery,[13] the DA reaction still finds every day applications as the key step in the synthesis of important compounds,[14,15] intermediates,[16,17] natural products,[18] and pharmaceuticals.[19] Nowadays, a fast growing and interesting strategy involves the use of the DA reaction in tandem protocols[20,21] for rapid and efficient access to diverse libraries of complex products[22] and target molecules.[23,24]

In the framework of our studies on aldol condensation reactions, we have reported the synthesis of a series of styrylcyclohex-2-enone dienes (e.g. **4a'**) in the presence of $LiClO_4$ and $TMSNEt_2$ and under solvent-free conditions.[25] Subsequently, these dienes were explored for their DA reactivities with *N*-phenylmaleimide,[26] methyl acrylate,[21,27] and maleic anhydride.[21,28] The results led us to the synthesis of several derivatives of dehydrodecaline skletone with different substitution patterns. In continuation of using heterogeneous catalysts,[29,30] here we introduce a new pathway for efficient synthesis of tetralone derivatives via a tandem aldol condensation-DA-oxidative aromatization sequence, as exemplified in Figure 1 for the synthesis of **4a**. The whole process takes place in one pot by the use of magnetically separable silica-coated functionalized nanoparticles of Fe_3O_4 (FN-Fe_3O_4). The catalyst, which was prepared by using a known procedure,[31] consists of a superparamagnetic

core of iron oxide coated with silica and functionalized with 3-aminopropyl-triethoxysilane and was used to produce a new series of polysubstituted tetralone derivatives. Consequently, single products are obtained in high yields and the nanocatalyst is recoverable[32,33] so that it can be recycled into the next reactions without considerable loss of its efficiency.

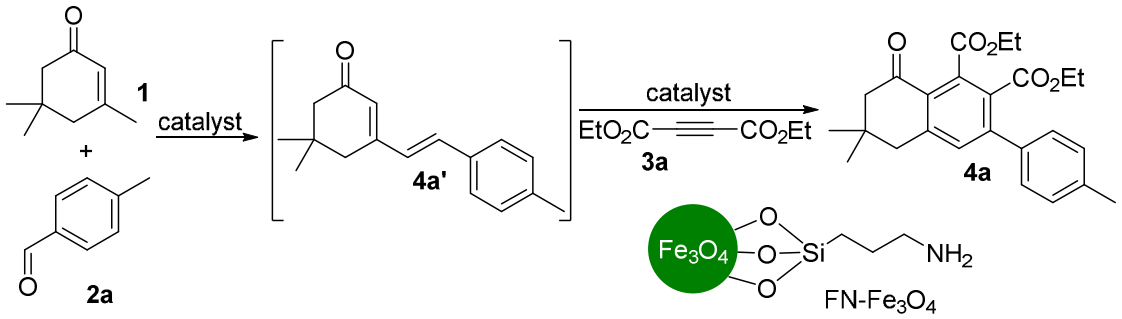


Figure 1. One-pot aldol condensation-DA reaction-aromatization pathway for the synthesis of **4a**.

Results and discussion

We first studied a model reaction by reacting enone **1** with 4-MeC_6H_4CHO (**2a**) and dienophile **3a** under various sets of conditions (Table 1). Treatment of an equimolar mixture of **1** and **2a** with substoichiometric amounts of the catalyst followed by the addition of a toluene solution of diethyl acetylenedicarboxylate (DEAD, **3a**) led to 73% and 52% formation of **4a** under refluxing (entry 1) or 50 ^{o}C (entry 2) conditions, respectively. Repeating the reaction without the catalyst gave no product and reactants were recovered entirely (entry 3). To see if fully functionalized iron oxide particles are required to promote the reactions, some amines were used, where lower quantities of **4a** were obtained (entries 4-6). Search to find the optimum solvent for the process supported that toluene can favour the highest conversion of the reactants to **4a** (entries 7-11).

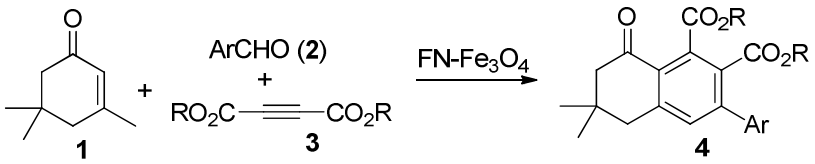
Table 1. Optimization of One-Pot Synthesis of **4a**.

Entry	Catalyst	Solvent	Yield (%)[a,b]
1	FN-Fe_3O_4	PhMe	73
2	FN-Fe_3O_4	PhMe	52[c]
3	none	PhMe	0
4	Et_3N	PhMe	10
5	Et_2NH	PhMe	15
6	Et_2NSiMe_3	PhMe	20
7	FN-Fe_3O_4	EtOH	50
8	FN-Fe_3O_4	H_2O	50
9	FN-Fe_3O_4	MeCN	20
10	FN-Fe_3O_4	MeOH	30
11	FN-Fe_3O_4	THF	0

[a]Isolated yields.
[b](i) **1** + **2a** + catalyst, rt, 6 h; (ii) DEAD (in refluxing solvent), 18 h.
[c]50 ^oC.

To show the generality of the process, the optimized conditions were used to evaluate the reactions of **1** with **3** and other aldehydes (Table 2). Therefore, benzaldehyde (entry 2) and its derivatives bearing electron donating (entries 1 & 3-5) and electron withdrawing (entries 6-8) substituents underwent a one-pot sequence of reactions with **1** and **3** to produce the respective products **4** in good yields. All reactions were complete within 20-24 h and gave a derivative of **4** as the major product of the process.

Table 2. One-pot synthesis of derivatives of **4**.



Entry	Ar	**3** (R)	Product	Yield (%)[a]
1	4-MeC_6H_4	**3a** (Et)	**4a**	73
2	C_6H_5	**3a** (Et)	**4b**	74
3	3-MeC_6H_4	**3a** (Et)	**4c**	80
4	4-MeC_6H_4	**3b** (Me)	**4d**	77
5	4-MeOC_6H_4	**3a** (Et)	**4e**	81
6	3-MeOC_6H_4	**3a** (Et)	**4f**	75
7	4-ClC_6H_4	**3a** (Et)	**4g**	75
8	2-thienyl	**3a** (Et)	**4h**	82

[a]Isolated yields.

The structure of the products was elucidated by ^{1}H-NMR and ^{13}C-NMR spectroscopic methods. In the proton spectrum, the relative numbers of both aliphatic and aromatic protons were diagnostic in determining the structure. In high field, signals consist of two ethoxy, two equivalent geminal methyl, and two different methylene groups indicating the corporation of reactants **3** and **1** in the structure of the product. On the other hand, besides the aromatic protons of the aldehyde residue, the presence of an additional singlet aromatic proton at slightly above 7.0 ppm was a strong indication for the aromatization of the final adduct. To confirm the structure of the adducts, a single crystal of **4a** was also prepared and subjected to X-ray analysis. The results are depicted in Figure 2 and confirm the proposed structure.

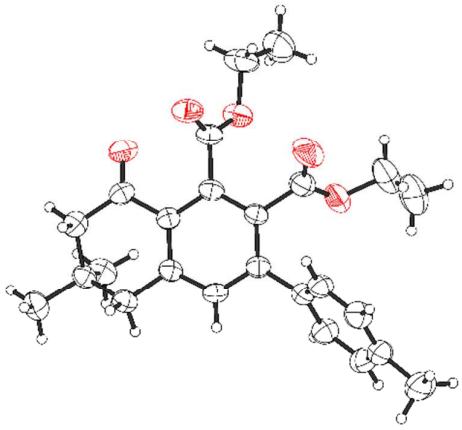


Figure 2. Crystal structure of **4a**. Displacement ellipsoids at 50% probability level.

Next, the recyclability of the catalyst was studied by using the recovered particles in the model reaction (Figure 3, top). Thus, after completion of the process, the catalyst was separated by using an external magnetic field (Figure 3, bottom) and reused in next reactions, where it could be effective for at least additional 5 consecutive runs without showing significant decrease in its performance.

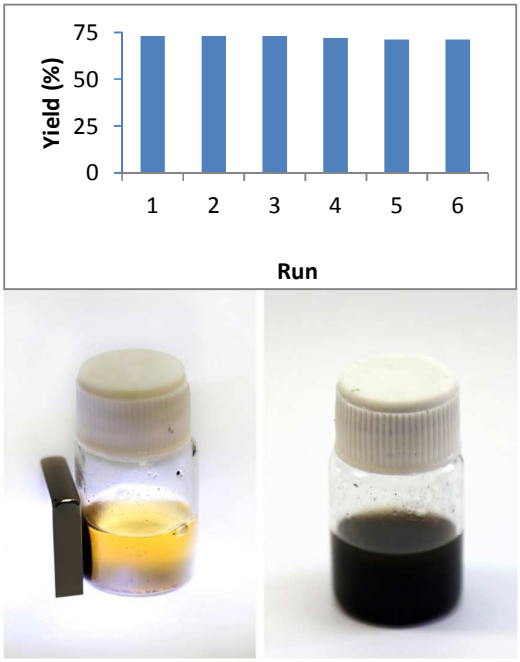


Figure 3. Successful reuse of the catalyst.

It can be concluded from the results that the process initiates with an aldol condensation to produce the respective diene **4'** (Figure 4). The formation of the diene is then followed by a DA cycloaddition with **3** so that **4''** is formed. The final stabilizing rearrangement and aromatization steps give the ultimate product **4**.

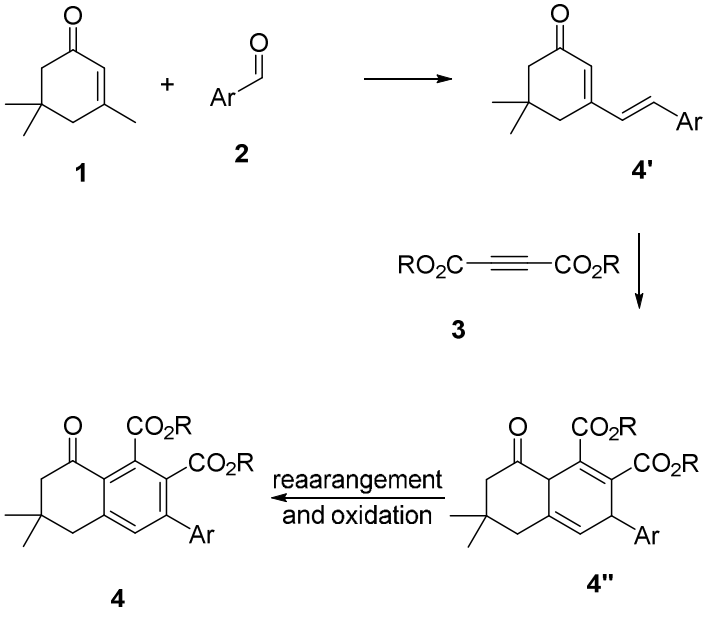


Figure 4. Suggested reaction pathway.

In order to shed light on the mechanism of the process, derivatives of **4'** were prepared separately and when treated with **3** in refluxing toluene under atmospheric air pressure, the expected products **4** were formed within 15-18 h. Moreover, when the addition of **1** to **3b** and 4-MeC_6H_4CHO was conducted under inert atmosphere, the direct cycloaddition adduct **5** was separated and characterized by ^{1}H-NMR spectroscopy. Then, this intermediate was independently converted to **4d** in refluxing toluene to further confirm the suggested pathway of the reaction (Figure 5).

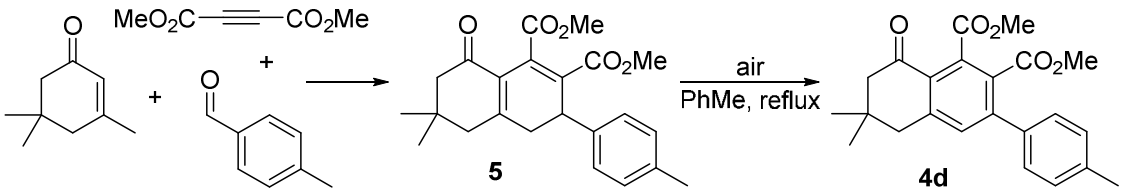


Figure 5. One-pot formation of **5** and its stepwise conversion to **4d**.

Conclusion

In summary, we succeeded in developing a new procedure for the synthesis of polysubstituted tetralone derivatives by using a one-pot procedure. As a result, the three reactants combine to produce the desired products in high yields and the catalyst could be recovered and reused in next reactions efficiently. We are planning to extend the results to the same reactions of unsubstituted derivatives of **1** (3-methylcyclohex-2-enone) to evaluate the feasibility of synthesizing polysubstituted naphthols (Figure 6). The study with other singly activated dienophiles and heterodienophiles are also underway.

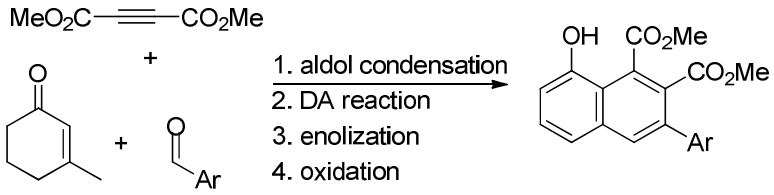


Figure 6. A one-pot sequence of four steps to polysubstituted naphthols.

Experimental

General

Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Shimadzu Prestige-21 spectrometer. NMR spectra were obtained on a FT-NMR Bruker Avance (300 MHz) or FT-NMR Bruker Ultra Shield^{TM} (500 MHz) as $CDCl_3$ solutions using Me_4Si as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 eV. TLC experiments were carried out on pre-coated silica gel plates using petroleum ether/EtOAc (4:1) as the eluent. Dienes **1** were synthesized using a known method.[21] All reagents and starting materials were purchased from commercial sources. Aldehydes were redistilled or recrystallized before being used. All products are new and were identified based on their physical and spectral properties.

General procedure for the synthesis of products 4

A mixture of isophorone **1** (690 mg, 5.0 mmol), an aldehyde **2** (5.0 mmol), and FN-Fe_3O_4 (100 mg) was stirred for 6 h at room temperature until TLC showed disappearance of the reactants and formation of the intermediate dienes **2**. At this point, a solution of DEAD **3a** (800 μL, 5.0 mmol) in toluene (5.0 mL) was added to the mixture and was refluxed for 18 h under atmospheric air pressure. After completion of the reaction, the catalyst was separated by using an external magnetic bar. The remaining solution was concentrated under reduced pressure and the product was isolated from the residue by column chromatography (EtOAc/hexane, 1:3). Products were characterized by NMR, IR, and mass spectroscopy.

Characterization data of new products

Diethyl 6,6-dimethyl-8-oxo-3-(*p*-tolyl)-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4a)

M.p. 137-139 ˚C. IR (KBr): 1742, 1690, 1735, 1588 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29-7.20 (*m*, 5H); 4.43 (*q*, *J* = 7.0 Hz, 2H); 4.06 (*q*, *J* = 7.0 Hz, 2H); 2.90 (*s*, 2H); 2.56 (*s*, 2H); 2.39 (*s*, 3H); 1.39 (*t*, *J* = 7.0 Hz, 3H); 1.11 (*s*, 6H); 0.99 (*t*, *J* = 7.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.4; 167.6; 166.6; 145.5; 144.4; 137.9; 135.6; 132.9; 131.9; 129.3; 129.1; 127.8; 127.3; 61.2; 61.1; 51.8; 42.5; 33.4; 27.5; 20.7; 13.7; 13.4. MS (70 eV) m/z 408 (M^+), 335, 178, 165, 29. Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.66; H, 6.71.

Diethyl 6,6-dimethyl-8-oxo-3-phenyl-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4b)

M.p. 105-107 ˚C. IR (KBr): 1736, 1679, 1585 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41-7.26 (*m*, 6H); 4.44 (*q*, *J* = 6.5 Hz, 2H); 4.02 (*q*, *J* = 6.5 Hz, 2H); 2,91 (*s*, 2H); 2.56 (*s*, 2H); 1.39 (*t*, *J* = 6.5 Hz, 3H); 1.11 (*s*, 6H); 0.94 (*t*, *J* = 6.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.3; 168.5; 167.1; 145.6; 144.9; 139.5; 134.1; 131.9; 130.2; 128.4; 128.2; 128.1; 128.0; 61.9; 61.5;

52.6; 43.9; 33.7; 28.1; 13.9, 13.4. MS (70 eV) m/z 394 (M^+), 351, 351, 322, 265; 167. Anal. Calcd for $C_{24}H_{26}O_5$: C, 73.08; H, 6.64. Found: C, 73.19; H, 6.37.

Diethyl 6,6-dimethyl-8-oxo-3-(*m*-tolyl)-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4c)

M.p. 95-97 °C. IR (KBr): 1743, 1689, 1590 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29-7.26 (*m*, 2H); 7.18-7.12 (*m*, 3H); 4.43 (*q*, *J* = 7.0 Hz, 2H); 4.04 (*q*, *J* = 7.0 Hz, 2H); 2.90 (*s*, 2H); 2.55 (*s*, 2H); 2.37 (*s*, 3H); 1.39 (*t*, *J* = 7.0 3H); 1.10 (*s*, 6H); 0.96 (*t*, *J* = 7.0, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.3; 168.6; 167.2; 145.7; 144.9; 139.3; 138.0; 134.0; 131.8; 128.9; 128.7; 128.3; 127.9; 126.0; 125.1; 61.9; 61.5; 52.5; 43.7; 33.7; 28.0; 21.3; 13.8; 13.5. MS (70 eV) m/z 408 (M^+), 379, 364, 304, 211. Anal. Calcd for $C_{25}H_{28}O_5$: C, 73.51; H, 6.91. Found: C, 73.56; H, 6.69.

Dimethyl 6,6-dimethyl-8-oxo-3-(*p*-tolyl)-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4d)

M.p. 187-189 °C. IR (KBr): 1745, 1689, 1585 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.30 (*s*, 1H); 7.26-7.23 (*m*, 4H); 3.94 (*s*, 3H); 3.59 (*s*, 3H); 2.99 (*s*, 2H); 2.55 (*s*, 2H); 2.39 (*s*, 3H); 1.10 (*s*, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): 196.8; 169.7; 168.2; 146.1; 145.5; 138.8; 136.8; 134.4; 132.5; 130.3; 129.7; 128.4; 128.3; 53.3; 53.0; 52.8; 44.2; 34.1; 28.5; 21.6. MS (70 eV) m/z 380 (M^+), 349, 321, 238, 165. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.76; H, 6.51.

Diethyl 3-(4-methoxyphenyl)-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4e)

M.p. 153-155 °C. IR (KBr): 1739, 1694, 1608, 1588 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29 (*d*, *J* = 8.5 Hz, 2H); 7.26 (*s*, 1H); 6.93 (*d*, *J* = 8.5 Hz, 2H); 4.43 (*q*, *J* = 7.0 Hz, 2H); 4.07 (*q*, *J* = 7.0 Hz, 2H); 3.84 (*s*, 3H); 2.90 (*s*, 2H); 2.55 (*s*, 2H); 1.39 (*t*, *J* = 7.0 Hz, 3H); 1.10 (*s*, 6H); 1.02 (*t*, *J* = 7.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.3; 167.6; 166.7; 159.5; 145.5;

144.1; 132.9; 131.8; 130.8; 129.3; 129.2; 127.1; 114.1; 61.2; 61.0; 55.2; 51.8; 42.5; 33.3; 27.5; 13.7; 13.4. MS (70 eV) m/z 424 (M^+), 300, 262, 295, 224. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.66; H, 6.77.

Diethyl 3-(3-methoxyphenyl)-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4f)

M.p. 103-105 ^{o}C. IR (KBr): 1717, 1679, 1587, 1495 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25-7.20 (*m*, 2H); 6.87-6.84 (*m*, 2H); 6.82-6.80 (*m*, 1H); 4.36 (*q*, *J* = 7.0 Hz, 2H); 3.97 (*q*, *J* = 7.0 Hz, 2H); 3.74 (*s*, 3H); 2.84 (*s*, 2H); 2.49 (*s*, 2H); 1.32 (*t*, *J* = 7.0 Hz, 3H); 1.04 (*s*, 6H); 0.90 (*t*, *J* = 7.0 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.3; 168.5; 167.2; 159.6; 145.5; 145.0; 140.8; 134.1; 131.8; 130.3; 129.5; 128.2; 120.5; 114.2; 113.4; 62.0; 61.6; 55.3; 52.6; 43.8; 33.8; 28.1; 13.9; 13.5. MS (70 eV) m/z 424 (M^+), 380, 352, 295. Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.59; H, 6.51.

Diethyl 3-(4-chlorophenyl)-6,6-dimethyl-8-oxo-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4g)

M.p. 139-141 ˚C. IR (KBr): 1740, 1690, 1588, 1489 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39 (*d*, *J* = 6.5 Hz, 2H); 7.27 (*d*, *J* = 6.5 Hz, 2H); 7.22 (*s*, 1H); 4.43 (*q*, *J* = 6.5 Hz, 2H); 4.05 (*q*, *J* = 6.5 Hz, 2H); 2.91 (*s*, 2H); 2.56 (*s*, 2H); 1.39 (*t*, *J* = 6.5 Hz, 3H); 1.11 (*s*, 6H); 1.01 (*t*, *J* = 6.5 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.2; 168.4; 166.9; 145.1; 144.3; 137.9; 134.5; 131.8; 129.4; 128.6; 128.4; 128.2; 128.0; 62.0; 61.7; 52.6; 43.8; 33.7; 28.1; 13.9; 13.6. MS (70 eV) m/z 428 (M^+), 384, 358, 299, 264, 228. Anal. Calcd for $C_{24}H_{25}ClO_5$: C, 67.21; H, 5.88. Found: C, 67.38; H, 5.55.

Diethyl 6,6-dimethyl-8-oxo-3-(thiophen-2-yl)-5,6,7,8-tetrahydronaphthalene-1,2-dicarboxylate (4h)

M.p. 105-107 ˚C. IR (KBr): 2963, 1726, 1683, 1586, 1367 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34 (*dd*, *J* = 1.0, 4.0 Hz, 1H); 7.05 (*dd*, *J* = 2.0, 2.5 Hz, 1H); 7.01-6.99 (*m*, 2H); 4.35 (*q*, *J* =

6.0 Hz, 2H); 4.01 (*q*, *J* = 6.0 Hz, 2H); 2.83 (*s*, 2H); 2.47 (*s*, 2H); 1.31 (*t*, *J* = 6.0, 3H); 1.03 (*t*, *J* = 6.0, 3H); 1.02 (*m*, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): 196.2; 168.3; 167.2; 144.8; 140.0; 137.6; 133.9; 132.0; 130.3; 128.3; 127.8; 127.4; 127.3; 62.0; 61.9; 52.6; 43.7; 33.7; 28.1; 13.9; 13.7. MS (70 eV) m/z 400 (M^+), 356, 328, 271, 172, 39. Anal. Calcd for $C_{22}H_{24}O_5S$: C, 65.98; H, 6.04. Found: C, 66.11; H, 6.22.

Dimethyl 6,6-dimethyl-8-oxo-3-(*p*-tolyl)-3,4,5,6,7,8-hexahydronaphthalene-1,2-dicarboxylate (5)

^{1}H-NMR (300 MHz, $CDCl_3$): 7.06 (*s*, 4H); 4.03 (*dd*, *J* = 2.5, 8.5 Hz, 1H); 3.95-3.92 (*m*, 1H); 3.91 (*s*, 3H); 3.64 (*s*, 3H); 3.93-3.59 (*m*, 1H); 3.02 (*dd*, *J* = 9.0, 18.0 Hz, 1H); 2.50 (*dd*, *J* = 3.0, 18.0 Hz, 1H); 2.38-2.28 (*m*, 1H); 2.28 (*s*, 3H); 2.15 (*d*, *J* = 19.0 Hz, 1H); 2.28 (*s*, 3H); 2.28 (*s*, 3H).

X-ray crystal structure analysis of 4a

Crystallographic data for **4a** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-1455609. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html].

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Graphical Abstract

Tandem aldol condensation-Diels–Alder-aromatization sequence of reactions: a new pathway for the synthesis of 2-tetralone derivatives

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