Et_2NH/H_2O catalyzed tandem aldol condensation - Diels-Alder cycloaddition sequence for the one-pot synthesis of (2*R*,3*S*)-*rel*-3-aryl-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylates

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.344

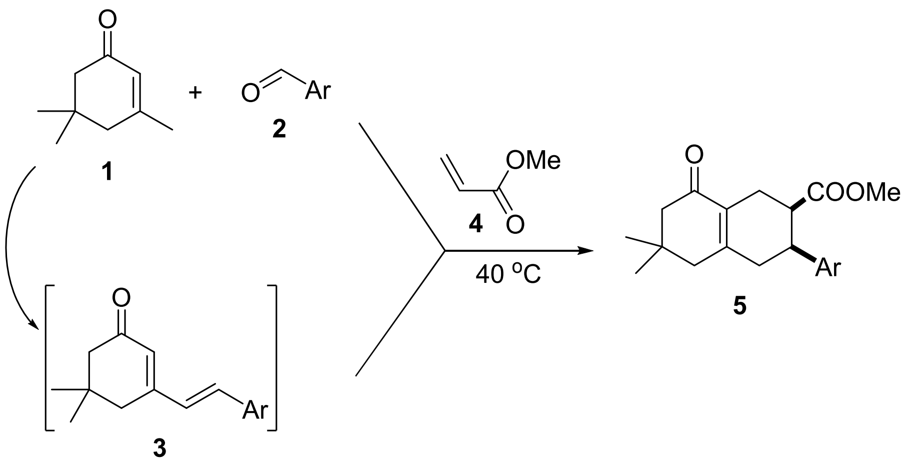
Abstract
A tandem aldol condensation – Diels-Alder cycloaddition process is developed to combine isophorone (3,5,5-trimethyl-2-cyclohexen-1-one), aromatic aldehydes, and methyl acrylate in an efficient stereoselective one-pot synthesis of methyl (2*R*,3*S*)-*rel*-3-aryl-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylates using trace quantities of ammonium ions under aqueous conditions. Alternatively, the respective conjugated dienes which are formed *in situ* from the condensation of isophorone with the aldehydes can also react with methyl acrylate in a stepwise fashion leading to the same products.

Keywords: Tandem reaction, organocatalysis, aldol condensation, Diels–Alder reaction, stereoselectivity

Introduction

The 4+2 Diels-Alder (DA) reaction[1] is one of the most widely used organic transformations in synthetic organic chemistry[2-4] since it has the potential to construct a six-membered ring via simultaneous formation of two carbon-carbon bonds. In addition, the reaction can lead to the creation of up to four stereogenic centers with predictable stereoselectivity in a one step operation.[5] Numerous studies are reported in recent years enhancing the reactivity and the selectivity features of DA cycloadditions by using chiral catalysts,[6,7] enantioselective reagents,[8,9] temporarily tethered reactants,[10,11] and self-assembled systems.[12,13] These approaches and use of intramolecular and transannular variants of the reaction have led to the preparation of natural product molecules[14,15] and complex polycyclic systems.[16]

Within the framework of our studies on the aldol condensation reaction[17,18] and its application in tandem processes,[19] we reported the synthesis of a series of 3-styryl-2-cyclohex-1-ones **3**,[20] obtained from the condensation of **1** with **2** (Scheme 1). These dienes were then examined for their DA activity,[21] and were further studied in a one-pot aldol condensation - DA process to construct the octahydronaphthalene structures directly. However, the results were limited to the reactions with doubly activated dienophiles, and singly activated dienophiles such as methyl acrylate (**4**) could react only under stepwise conditions.[22] In continuation, we would like to report here the application of this strategy to the reactions of **4**, which cycloadds to *in situ* formed dienes **3**, solely producing *cis*-octahydronaphthalene type cycloadducts **5** (Scheme 1), a structural unit which is found in several natural products and perfumes.[23] Reactions take place in aqueous medium using catalytic quantities of a simple amine.



Scheme 1. One-pot and stepwise pathways for the synthesis of **5**.

Results and Discussion

We optimized the conditions by examining the reaction of **1** with 2,6-dichlorobenzaldehyde (**2a**) and methyl acrylate (**4**), as shown in Table 1. The progress of the reaction was monitored by GC experiments. In the presence of water and catalytic quantities of diethylamine, the intermediate diene was formed *in situ*. Addition of methyl acrylate (**4**) and dilute HCl to the mixture led to 75% formation of *cis* **5a** after 11 h (entry 1). Use of different quantities of the amine showed that 25 mol% would be the optimum amounts (entries 2-4). When the reaction was conducted in the absence of water (entry 5), hydrochloric acid (entry 6), or the amine (entry 7), either no product was obtained or the reaction progress was not considerable. Without water or HCl, only the formation of the intermediate was noticed, while in the absence of the amine, no reaction occurred. Use of other amines also led to the formation of **5a**, but in lower quantities (entries 8-10). These results showed that the optimum conditions (entry 1) could be employed to explore the one-pot combination of the three reactants to access octahydronaphthalene derivatives of type **5** directly.

Table 1. Optimization of the one-pot reaction for the synthesis of **5a** Ar = 2,4-dichlorophenyl

Entry	Medium	Amine (mol%)	Time (h)	Yield (%)[a]
1	H_2O/HCl	Et_2NH (25)	10	75
2	H_2O/HCl	Et_2NH (15)	10	50
3	H_2O/HCl	Et_2NH (5)	10	30
4	H_2O/HCl	Et_2NH (50)	10	77
5	HCl	Et_2NH (25)	24	0
6	H_2O	Et_2NH (25)	24	<5
7	H_2O/HCl	-	24	0
8	H_2O/HCl	Et_3N (25)	10	55
9	H_2O/HCl	Pyrrolidine (25)	10	48
10	H_2O	NH_4Cl (25)	10	15

[a] yields determined by GC.

To show the generality of the procedure, the optimum conditions (Table 1, entry 1) were used to conduct the reactions with other aldehydes (Table 2). Therefore, the same process with aldehydes bearing electron withdrawing (entries 1-6) and electron releasing (entries 7-10) groups proceeded within comparable time periods. Similarly, unsubstituted homocyclic (entry 11) and heterocyclic aromatic aldehydes (entry 12) gave results equally well.

In all cases formation of a single DA product was observed. The structure of these products was assigned based on their ^{1}H NMR spectra. The H-2 and H-3 signals appeared at about 3 and 3.5 ppm, respectively. These two vicinal protons exhibited a "medium" $^3J_{H-H}$ of about 5-6 Hz. This coupling constant is proportional with the *endo* stereoisomer as opposed to the *exo* structure, which is expected to show a larger $^3J_{H-H}$. In order to confirm the suggested *cis* structure for the adducts, a single crystal of **5l** was prepared and analyzed by X-ray crystallography. As it is clear from Figure 1, migration of the double bond to the more stable doubly endocyclic position and the relative configuration of the two adjacent stereogenic centers correspond to the suggested structures in Table 2.

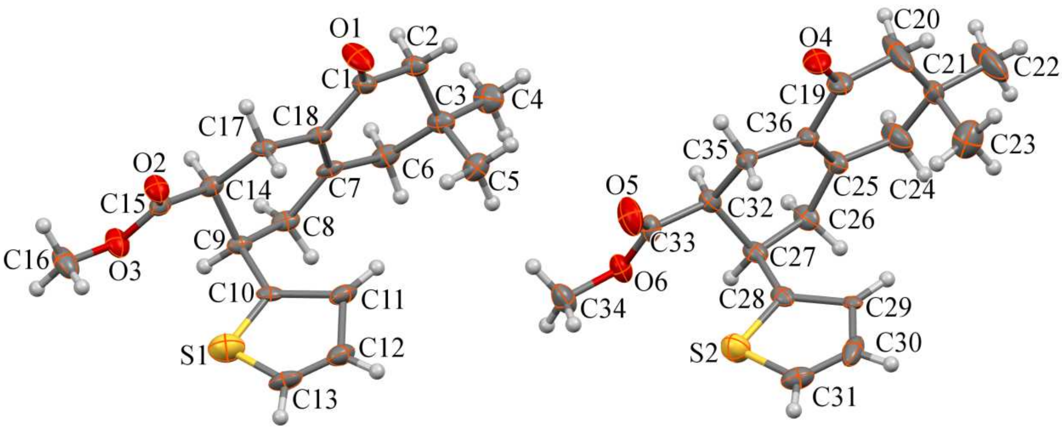


Figure 1. Asymmetric unit of **5l**. Displacement ellipsoids at 30% probability level.

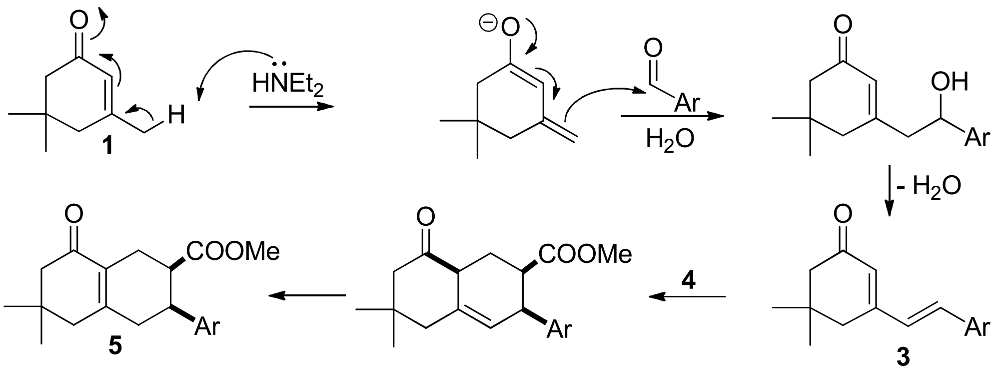
Table 2. H_2O/Et_2NH catalyzed one-pot synthesis of compounds **5**.

Entry	Product	Ar in **2** and **5**	Reaction time (h)	Yield of **5** (%)[a]
1	**5a**	2,6-dichlorophenyl	11	75
2	**5b**	4-bromophenyl	11	75
3	**5c**	3-bromophenyl	12	77
4	**5d**	3-nitrophenyl	8	73
5	**5e**	3-methoxyphenyl	8	75
6	**5f**	3,5-dimethoxyphenyl	10	87
7	**5g**	4-methoxyphenyl	9	82
8	**5h**	3-methylphenyl	10	78
9	**5i**[22]	4-methylphenyl	8	82
10	**5j**	2,4-dimethylphenyl	10	80
11	**5k**	phenyl	10	81
12	**5l**	2-thienyl	8	85

[a] Isolated yields.

Based on these results, a mechanism (Scheme 2) can be suggested for the process. The starting enone **1** is first deprotonated by the amine organocatalyst to give the respective enolate. The enolate is then added to the aldehyde **2** to produce the aldol intermediate, which after dehydration gives the diene **3**. TLC and GC experiments prove the formation of this diene prior to addition of methyl acrylate (**4**). Finally addition of the dienophile **4** to the reaction mixture led to the formation of the DA adduct, which spontaneously isomerizes to the final product **5** by rearranging the double bond to the more stable doubly endocyclic position. To support the suggested mechanism, intermediate **3** was prepared separately (for Ar = C_6H_5, 4-$CH_3C_6H_4$, and

4-$CH_3OC_6H_4$), by addition of **1** to the aldehydes, and subjected to react with **4** in a parallel experiment to obtain **5**.



Scheme 2. A suggested mechanism for the synthesis of methyl (2*R*,3*S*)-*rel*-3-aryl-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylates **5**.

Conclusions

In summary, we have developed an efficient and general one-pot protocol for the synthesis of various methyl (2*R*,3*S*)-*rel*-3-aryl-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylates **5**. Under aqueous conditions and in the presence of catalytic quantities of Et_2NH, a three-component process takes place and the *in situ* formed diene **3** reacts with methyl acrylate (**4**) to form the final products **5**. The development of the process by using more diverse dienes and dienophiles is under further study.

Experimental Section

General. Reactions were monitored by TLC using silica-gel coated plates and ethyl acetate/hexanes mixtures as the mobile phase. Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions are reported as wave numbers (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan MAT 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. All reagents were purchased from commercial sources and were freshly used after being purified by standard procedures. New products **5a-h,j-l** were characterized based on their spectral and physical data.

Typical Procedure for the Synthesis of Methyl (2*R*,3*S*)-*rel*-3-Aryl-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylates 5. A mixture of enone **1** (276 mg, 2.0 mmol), an aldehyde (2.0 mmol), water (2.0 mL), and Et_2NH (52 μL, 0.5 mmol, 0.25 mol%) was stirred at 40 °C for 1-2 h, until TLC showed the starting materials are converted to the intermediate diene **3**. To this mixture were added **4** (543 μL, 6.0 mmol) and HCl (0.01 M, 2 mL) and stirring was continued for another 6-10 h. At this point, TLC showed complete disappearance of the starting materials and the intermediate. The mixture was diluted by EtOAc (5 mL) and washed sequentially with saturated $NaHCO_3$ and brine solutions. The organic layer was dried over Na_2SO_4 and the volatile portion was evaporated under reduced pressure. The residue was fractionated by column chromatography using EtOAc/hexanes mixture (1:3) as the eluent to obtain the final product **5**. All products were obtained as white crystals (after recrystallization from ethyl acetate).

Methyl (2*R*,3*S*)-*rel*-3-(2,6-Dichlorophenyl)-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5a**). Mp 156-157 ºC. ^{1}H NMR (400 MHz) δ 1.09 [s, 6H, $(CH_3)_2$-6], 2.20-2.66 (m, 3H), 2.32 (s, 2H), 2.48-2.53 (m, 1H), 2.80 (d, *J* 18.0 Hz, 1H), and 3.09 (dd, *J* 3.5, 6.5 Hz, 1H) (H_2-1,4,5,7) 3.57 (s, 3H, $COOCH_3$), 3.75-3.83 (m, 1H, H-2), 4.00 (ddd, *J* 3.5, 4.0, 12.5 Hz, 1H, H-3), 7.12 (t, *J* 8.0 Hz, 1H, H-4'), 7.31 (d, *J* 8.0 Hz, 2H, H-3',5') ppm; ^{13}C NMR (100 MHz) δ 26.1, 26.7, and 29.7 [C-1, $(CH_3)_2$-6], 31.9 (C-4), 33.4 (C-6), 39.9 (C-3), 41.2 and 45.4 (C-2,5), 51.4 and 51.9 (C-7 and $COO\underline{C}H_3$), 128.2 and 128.4 (C-1',4'), 129.6 and 130.0 (C-3',5',8a), 136.3 (C-2',6'), 154.0 (C-4a), 173.8 ($\underline{C}OOCH_3$), 198.8 (C-8) ppm. IR 1735, 1655, 1433 cm^{-1}. MS *m/z* (%) 382 (7), 380 (M^+, 11), 319 (100), 263 (75), 165 (22), 91 (17). Anal. Calcd for $C_{20}H_{22}Cl_2O_3$: C, 63.00; H, 5.82. Found: C, 63.21; H, 6.15 %.

Methyl (2*R*,3*S*)-*rel*-3-(4-Bromophenyl)-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5b**). Mp. 117-118 ºC. ^{1}H NMR (250 MHz) δ 1.06 (s, 3H) and 1.08 (s, 3H) [$(CH_3)_2$-6], 2.26 (s, 2H) and 2.33 (s, 2H) (H_2-5,7), 2.44-2.47 (m, 1H) and 2.63-2.76 (m, 3H) (H_2-1,4), 2.96 (ddd, *J* 2.0, 5.5, 9.5 Hz, 1H, H-2), 3.40 (dd, *J* 5.5, 9.5 Hz, 1H, H-3), 3.55 (s, 3H, $COOCH_3$), 7.00 (d, *J* 8.5 Hz, 2H, H-2',6'), 7.37 (d, *J* 8.5 Hz, 2H, H-3',5') ppm; ^{13}C NMR (62.5 MHz) δ 22.3 (C-1), 28.1 and 28.5 [$(CH_3)_2$-6], 33.3 and 36.0 (C-4,6), 39.4 (C-5), 43.4 and 45.1 (C-2,3), 51.3 and 51.5 (C-7, $COO\underline{C}H_3$), 120.8 (C-4'), 129.1, 129.3, and 131.5 (C-2',3',5',6',8a), 140.7 (C-1'), 153.4 (C-4a), 173.5 ($\underline{C}OOCH_3$), 198.4 (C-8) ppm. IR 1737, 1657, 1440 cm^{-1}. MS *m/z* (%) 392 (23), 390 (M^+, 23), 331 (100), 275 (50), 251 (20), 175 (12). Anal. Calcd for $C_{20}H_{23}BrO_3$: C, 61.39; H, 5.92. Found: C, 61.66; H, 6.01 %.

Methyl (2*R*,3*S*)-*rel*-3-(3-Bromophenyl)-1,2,3,4,5,6,7,8-octahydro-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5c**). Mp. 139-140 ºC. ^{1}H NMR (300 MHz) δ 1.01 (s, 3H) and 1.03 (s, 3H) [$(CH_3)_2$-6], 2.21 (s, 2H) and 2.26 (s, 2H) (H_2-5,7), 2.33-2.39 (m, 1H) and 2.53-2.63 (m, 3H) (H_2-1,4), 2.90 (ddd, *J* 2.0, 6.5, 12.0 Hz, 1H, H-2), 3.37 (dd, *J* 5.5, 10.0 Hz, 1H, H-3), 3.50 (s, 3H, $COOCH_3$), 6.98 (d, *J* 7.5 Hz, 1H, H-6'), 7.09 (dd, *J* 7.0, 7.5 Hz, 1H, H-5'), 7.20 (s, 1H, H-2'), 7.27 (d, *J* 7.0 Hz, 1H, H-4') ppm; ^{13}C NMR (75 MHz) δ 22.1 (C-1), 27.6 and 28.5 [$(CH_3)_2$-6], 33.0 and 35.6 (C-4,6), 39.5, 43.2, and 44.8 (C-2,3,5), 51.1 and 51.2 (C-7, $COO\underline{C}H_3$), 122.2 (C-3'), 125.7 (C-6'), 128.7, 129.7, 130.0, and 130.4 (C-2',4',5',8a), 143.8 (C-1'), 152.9 (C-4a), 173.1

($\underline{C}OOCH_3$), 198.0 (C-8) ppm. IR 1732, 1656, 1446 cm^{-1}. MS *m/z* (%) 392 (60), 390 (M^+, 62), 332 (100), 276 (52), 175 (22), 115 (9), 91 (15). Anal. Calcd for $C_{20}H_{23}BrO_3$: C, 61.39; H, 5.92. Found: C, 61.53; H, 5.96 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-6,6-dimethyl-3-(3-nitrophenyl)-8-oxo-2-naphthalenecarboxylate (**5d**). Mp. 113-114 ºC. ^{1}H NMR (250 MHz) δ 1.09 (s, 3H) and 1.12 (s, 3H) [$(CH_3)_2$-6], 2.30 (s, 2H, H_2-5), 2.36 (s, 2H, H_2-7), 2.42-2.48 (m, 1H), 2.66-2.70 (m, 1H), and 2.71-2.81 (m, 2H) (H_2-1,4), 3.00-3.07 (m, 1H, H-2), 3.53-3.56 (m, 1H, H-3), 3.58 (s, 3H, $COOCH_3$), 7.45-7.47 (m, 2H, H-5',6'), 8.02 (s, 1H, H-2'), 8.05-8.13 (m, 1H, H-4') ppm; ^{13}C NMR (62.5 MHz) δ 22.3 (C-1), 27.9 and 28.7 [$(CH_3)_2$-6], 33.3 (C-4), 35.7 (C-6), 39.6, 43.4, and 45.1 (C-2,3,5), 51.3 and 51.7 (C-7, $COO\underline{C}H_3$), 122.2 and 122.6 (C-2',4'), 129.2, 129.4, and 133.8 (C-5',6',8a), 143.7 (C-1'), 148.5 (C-3'), 152.7 (C-4a), 173.1 ($\underline{C}OOCH_3$), 198.4 (C-8) ppm. IR 1733, 1657, 1528, 1352 cm^{-1}. MS *m/z* (%) 357 (M^+, 8), 339 (100), 279 (30), 241 (7). Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49. Found: C, 67.33; H, 6.40 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-3-(3-methoxyphenyl)-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5e**). Mp. 103-104 ºC. ^{1}H NMR (250 MHz) δ 1.06 (s, 3H) and 1.09 (s, 3H) [$(CH_3)_2$-6], 2.26 (s, 2H, H_2-5), 2.30 (s, 2H, H_2-7), 2.39-2.43 (m, 1H), 2.58-2.65 (m, 2H), and 2.70-2.73 (m, 1H) (H_2-1,4), 2.93-3.00 (m, 1H, H-2), 3.37-3.44 (m, 1H, H-3), 3.56 (s, 3H, $COOCH_3$), 3.79 (s, 3H, OCH_3-3'), 6.56-6.69 (m, 2H) and 6.77 (dd, *J* 3.0, 8.5 Hz, 1H) (H-2',4',6'), 7.17 (t, *J* 8.5 Hz, 1H, H-5') ppm; ^{13}C NMR (62.5 MHz) δ 22.4 (C-1), 28.1 and 28.6 [$(CH_3)_2$-6], 33.2 and 36.2 (C-4,6), 40.0 (C-5), 43.6 and 45.2 (C-2,3), 51.4 (C-7), 55.1 ($COO\underline{C}H_3$), 67.0 (OCH_3-3'), 112.0 (C-4'), 113.6 (C-2'), 119.8 (C-6'), 129.2 and 129.3 (C-5',8a), 143.3 (C-1'), 153.7 (C-4a), 159.6 (C-3'), 173.7 ($\underline{C}OOCH_3$), 198.5 (C-8) ppm. IR 1732, 1664, 1596 cm^{-1}. MS *m/z* (%) 342 (M^+, 12), 310 (12), 281 (100), 226 (38), 121 (12). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.85; H, 7.93 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-3-(3,5-dimethoxyphenyl)-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5f**). Mp. 110-111 ºC. ^{1}H NMR (250 MHz) δ 1.07 (s, 3H) and 1.09 (s, 3H) [$(CH_3)_2$-6], 2.26 (s, 2H, H_2-5), 2.32 (s, 2H, H_2-7), 2.41-2.50 (m, 1H), 2.59-2.65 (m, 2H), and 2.77 (dd, *J* 5.5, 19.0 Hz, 1H) (H_2-1,4), 2.94-2.99 (m, 1H, H-2), 3.38 (ddd, *J* 2.0, 6.0, 8.0 Hz, 1H, H-3), 3.58 (s, 3H, $COOCH_3$), 3.78 (s, 6H, OCH_3-3',5'), 6.26 (d, *J* 2.5 Hz, 2H, H-2',6'), 6.33 (t, *J* 2.5 Hz, 1H, H-4') ppm. ^{13}C NMR (62.5 MHz) δ 22.4 (C-1), 28.0 and 28.6 [$(CH_3)_2$-6], 33.3 and 36.2 (C-4,6), 40.3 (C-5), 43.6 and 45.2 (C-2,3), 51.4 and 51.5 (C-7, $COO\underline{C}H_3$), 55.2 (OCH_3-3',5'), 98.6 (C-4'), 105.8 (C-2',6'), 129.1 (C-8a), 144.1 (C-1'), 153.7 (C-4a), 160.7 (C-3',5'), 174.0 ($\underline{C}OOCH_3$), 198.6 (C-8) ppm. MS *m/z* (%) 372 (M^+, 25), 311 (100), 255 (36), 151 (12). Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.69; H, 7.41 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-3-(4-methoxyphenyl)-6,6-dimethyl-8-oxo-2-naphthalenecarboxylate (**5g**). Mp. 120-121 ºC. ^{1}H NMR (300 MHz) δ 1.02 (s, 3H) and 1.05 (s, 3H) [$(CH_3)_2$-6], 2.24 (s, 2H, H_2-5), 2.28 (s, 2H, H_2-7), 2.39-2.50 (m, 2H) and 2.58-2.65 (m, 2H) (H_2-1,4), 2.85-2.90 (m, 1H, H-2), 3.36-3.39 (m, 1H, H-3), 3.51 (s, 3H, $COOCH_3$), 3.73 (s, 3H, OCH_3-4'), 6.75 (d, *J* 8.5 Hz, 2H, H-3',5'), 6.97 (d, *J* 8.5 Hz, 2H, H-2',6') ppm; ^{13}C NMR (75 MHz) δ 21.8 (C-1), 27.9 and 28.3 [$(CH_3)_2$-6], 33.0 and 36.3 (C-4,6), 39.0 (C-5), 43.5 and 44.9

(C-2,3), 51.0 (C-7), 54.9 and 55.0 (COO<u>C</u>H_3, OCH_3-4'), 113.5 (C-3',5'), 128.3 and 128.7 (C-2',6',8a), 133.5 (C-1'), 153.6 (C-4a), 173.6 (C-4'), 174.6 (<u>C</u>$OOCH_3$), 198.2 (C-8) ppm. IR 1732, 1656, 1444 cm^{-1}. MS *m/z* (%) 342 (M^+, 75), 282 (100), 226 (50), 175 (45), 121 (56), 91 (12). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.76; H, 7.81 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-6,6-dimethyl-3-(3-methylphenyl)-8-oxo-2-naphthalenecarboxylate (**5h**). Mp. 99-100 ºC. ^{1}H NMR (400 MHz) δ 1.07 (s, 3H) and 1.09 (s, 3H) [$(CH_3)_2$-6], 2.26 (s, 2H, H_2-5), 2.30 (s, 3H, CH_3-3'), 2.33 (s, 2H, H_2-7), 2.40-2.43 (m, 1H), 2.50-2.59 (m, 2H), and 2.74 (dd, *J* 6.0, 18.5 Hz, 1H) (H_2-1,4), 2.96-3.07 (m, 1H, H-2), 3.37 (ddd, *J* 2.5, 6.0, 10.0 Hz, 1H, H-3), 3.54 (s, 3H, $COOCH_3$), 6.88 (d, *J* 8.5 Hz, 1H, H-4'), 6.90 (s, 1H, H-2'), 7.03 (d, *J* 8.5 Hz, 1H, H-6'), 7.15 (t, *J* 7.5 Hz, 1H, H-5') ppm; ^{13}C NMR (100 MHz) δ 21.5 (CH_3-3'), 22.5 (C-1), 27.8 and 28.8 [$(CH_3)_2$-6], 33.3 and 36.1 (C-4,6), 40.0 (C-5), 43.7 and 45.2 (C-2,3), 51.3 and 51.4 (C-7, COO<u>C</u>H_3), 124.4 (C-6'), 127.7, 128.3, 128.4, and 129.1 (C-2',4',5',8a), 137.9 and 141.7 (C-1',3'), 153.8 (C-4a), 173.8 (<u>C</u>$OOCH_3$), 198.5 (C-8) ppm. IR 1723, 1661, 1454 cm^{-1}. MS *m/z* (%) 326 (M^+, 12), 265 (100), 210 (60), 105 (20). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.25; H, 8.11 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-6,6-dimethyl-3-(2,4-dimethylphenyl)-8-oxo-2-naphthalenecarboxylate (**5j**). Mp. 103-104 ºC. ^{1}H NMR (300 MHz) δ 1.07 (s, 3H) and 1.08 (s, 3H) [$(CH_3)_2$-6], 2.25 (s, 2H, H_2-5), 2.29 (s, 3H) and 2.30 (s, 3H) (CH_3-2',4'), 2.33 (s, 2H, H_2-7), 2.51 (dd, *J* 4.5, 18.5 Hz, 1H), 2.77 (dd, *J* 4.0, 18.5 Hz, 1H), 2.97-3.02 (m, 2H), and 3.36-3.45 (m, 2H) (H_2-1,4,H-2,3), 3.48 (s, 3H, $COOCH_3$), 6.95-7.04 (m, 3H, H-3',5',6') ppm; ^{13}C NMR (75 MHz) δ 19.3 (CH_3-2'), 20.8 (CH_3-4'), 25.1 (C-1), 27.2 and 29.2 [$(CH_3)_2$-6], 33.3, 34.7, and 35.6 (C-3,4,6), 41.9 (C-5), 45.3 (C-2), 51.1 and 51.4 (C-7, COO<u>C</u>H_3), 125.9 and 126.7 (C-5',6'), 128.2 (C-3'), 131.5 and 135.5 (C-1',8a), 136.1 and 136.9 (C-2',4'), 154.7 (C-4a), 173.9 (<u>C</u>$OOCH_3$), 198.7 (C-8) ppm. IR 1732, 1649, 1501 cm^{-1}. MS *m/z* (%) 340 (M^+, 68), 339 (100), 264 (68), 175 (38), 119 (62). Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.51; H, 8.26 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-6,6-dimethyl-8-oxo-3-phenyl-2-naphthalenecarboxylate (**5k**). Mp. 90-91 ºC. ^{1}H NMR (300 MHz) δ 1.06 (s, 3H) and 1.09 (s, 3H) [$(CH_3)_2$-6], 2.26 (s, 2H, H_2-5), 2.33 (s, 2H, H_2-7), 2.38-2.46 (m, 1H), 2.58-2.62 (m, 1H), 2.66 (dd, *J* 6.0, 11.0 Hz, 1H), and 2.73 (dd, *J* 6.0, 11.0 Hz, 1H) (H_2-1,4), 2.93-2.99 (m, 1H, H-2), 3.44 (dd, *J* 6.0, 10.0 Hz, 1H, H-3), 3.54 (s, 3H, $COOCH_3$), 7.09 (d, *J* 6.5 Hz, 2H) and 7.20-7.28 (m, 3H) (H-2'-6') ppm; ^{13}C NMR (75 MHz) δ 22.2 (C-1), 28.0 and 28.4 [$(CH_3)_2$-6], 33.1 and 36.1 (C-4,6), 39.9 (C-5), 43.6 and 45.1 (C-2,3), 51.2 and 51.3 (C-7, COO<u>C</u>H_3), 126.9, 127.4, 128.3, and 129.1 (C-2'-6',8a), 141.6 (C-1'), 153.6 (C-4a), 173.6 (<u>C</u>$OOCH_3$), 198.4 (C-8) ppm. IR 1732, 1697, 1444 cm^{-1}. MS *m/z* (%) 312 (M^+, 65), 252 (100), 196 (55), 115 (8), 91 (24). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 77.01; H, 7.88 %.

Methyl (2*R*,3*S*)-*rel*-1,2,3,4,5,6,7,8-Octahydro-6,6-dimethyl-8-oxo-3-(2-thienyl)-2-naphthalenecarboxylate (**5l**). Mp. 115-116 ºC. ^{1}H NMR (500 MHz) δ 1.09 (s, 3H) and 1.13 (s, 3H) [$(CH_3)_2$-6], 2.28 (s, 2H, H_2-5), 2.33 (d, *J* 16.0 Hz, 2H), 2.37 (d, *J* 16.0 Hz, 2H), 2.50-2.55 (m, 1H), 2.69-2.73 (m, 2H), and 2.68 (dd, *J* 2.5, 16.0 Hz, 1H) (H_2-1,4), 3.00 (ddd, *J* 3.5, 5.5, 10.0 Hz, 1H, H-2), 3.67 (s, 3H, $COOCH_3$), 3.88 (dd, *J* 5.5, 10.0 Hz, 1H, H-3), 6.80 (d, *J* 3.5 Hz, 1H, H-3'), 6.93 (dd, *J* 3.5, 5.0 Hz, 1H, H-4'), 7.16 (dd, *J* 1.0, 5.0 Hz, 1H, H-5') ppm; ^{13}C NMR (125 MHz) δ 21.7 (C-1), 28.3 and 28.4 [$(CH_3)_2$-6], 33.1 and 35.6 (C-4,6), 38.0 (C-3), 43.7 (C-5), 45.2 (C-2), 51.5 and 51.6 (C-7, COO$\underline{C}H_3$), 123.8 and 124.7 (C-3',5'), 126.5 (C-4'), 129.3 (C-8a), 144.1 (C-2'), 152.3 (C-4a), 173.3 ($\underline{C}OOCH_3$), 198.4 (C-8) ppm. IR 1732, 1656, 1442 cm^{-1}. MS *m/z* 318 (%) (M^+, 87), 258 (100), 202 (52), 175 (28), 115 (7). Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96. Found: C, 67.98; H, 7.05 %.

X-ray data for compound 5l. $C_{18}H_{22}O_3S$, M = 318.43 g/mol, triclinic system, space group $P2_1/n$, a = 12.9132(6), b = 14.1858(9), c = 18.5594(9) Å, β = 92.068(4), V = 3397.6(3) Å^3, Z = 8, Dc = 1.245 g.cm^{-3}, μ(Mo-Kα) = 0.200 mm^{-1}, crystal dimension of 0.50 × 0.48 × 0.45 mm. The structure was solved by using SHELXS. The structure refinement and data reduction were carried out with SHELXL. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.1531, wR_2 = 0.3201 and S = 1.594 with 392 parameters using 4132 independent reflection (θ range = 1.96 - 29.33°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **5l** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC, Union Road, Cambridge CB2 1EZ, UK, quoting deposition number 1412435 (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Authors would like to thank Iran National Science Foundation (INSF-92024196) for financial support of this work.

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