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# Syntheses of methylenolactocin and nephrosterinic acid via diastereoselective acylation and chemoselective reduction–lactonization

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ABSTRACT

The syntheses of methylenolactocin, nephrosterinic acid and their derivatives can be achieved by using the efficient diastereoselective acylation of dimethyl itaconate–anthracene adduct followed by tandem chemoselective reduction–lactonization.



## 1. Introduction

The paraconic acids are a group of highly substituted γ-butyrolactones isolated from different species of moss, lichens, fungi and cultures of *Penicillium* sp.[1,2] Among them, methylenolactocin,[3,4] nephrosterinic acid,[5,6] and protolichesterinic acid,[7,8] are noted for their biological activities, being antibacterial agents,[9a–l] antifungal,[9b] antitumor,[9h] anti-inflammatory[9m] and displaying inhibitory activity on 12(*S*)-HETE production in human platelets[9n] while some of these compounds also display growth-regulating effects.[9o] Due to their important potential pharmacological applications,[10] several formal and total syntheses of members of this class of metabolite have attracted widespread attention.

Previous work has reported the total syntheses of methylenolactocin, nephrosterinic acid and protolichesterinic acid in both racemic and enantiomerically pure forms employing the versatile starting material, dimethyl itaconate–anthracene adduct (**1**)[11] via tandem aldol–lactonization reactions, isomerization of the C-4′ configuration followed by flash vacuum pyrolysis and hydrolysis of the ester group (Scheme 1).[4n,r]

This present work aims at controlling the stereochemistries at C-4′ and C-5′ using diastereoselective acylation and tandem chemoselective reduction–lactonization as key steps. The process is outlined in Scheme 2.

## 2. Results and discussion

In a typical diastereoselective acylation using alkanoyl chloride; *n*-heptanoyl chloride (**10b**) was added to the lithium ester enolate **9** at −78 °C for 15 min and the mixture stirred at 0 °C for 1 h. The crude product was subjected to column chromatography (silica gel, using EtOAc/hexane=0.5:9.5 as eluent) to yield **7b** in 63% yield and the minor product, **8b**, in 4% yield after crystallization from ethyl acetate/hexane. The relative stereochemistries at the α-position of the β-ketodiester adducts **7b** and **8b** were determined by NOE experiments (Fig. 1). In the case of compound **7b**, the proton $H_c$ ($\delta$ appeared at 3.03 ppm) showed greater interaction with $H_b$ than $H_y$; thus the orientation of $H_c$ is on the upper face as shown. Conversely, the orientation of proton $H_c$ ($\delta$ appeared at 3.43 ppm) of compound **8b** is on the opposite face. However, the NOE results could not unequivocally confirm the orientations of the COOMe and *n*-$C_7H_{15}CO$ groups.

These NOE results were compared with geometry optimizations of compounds **7b** and **8b** carried out using Gaussian 03 Programs[12,13] at the B3LYP/6-31G level of Density Functional Theory (DFT). The optimized structures are shown in Figure 2. From these calculations, compound **8b** is thermodynamically more stable than compound **7b** with a lower energy of 3.96 kcal/mol. The **7b** model showed that the distance from $H_c$ to $H_a$, $H_b$, and $H_y$ are 2.41, 3.10, and 3.89 Å respectively. In comparison, $H_c$ is displaced from $H_a$, $H_b$, and $H_y$ at distance of 3.70, 4.10, and 2.51 Å respectively in the minimized structure of **8b**. Results from the computational calculation are in agreement with the NOE results.

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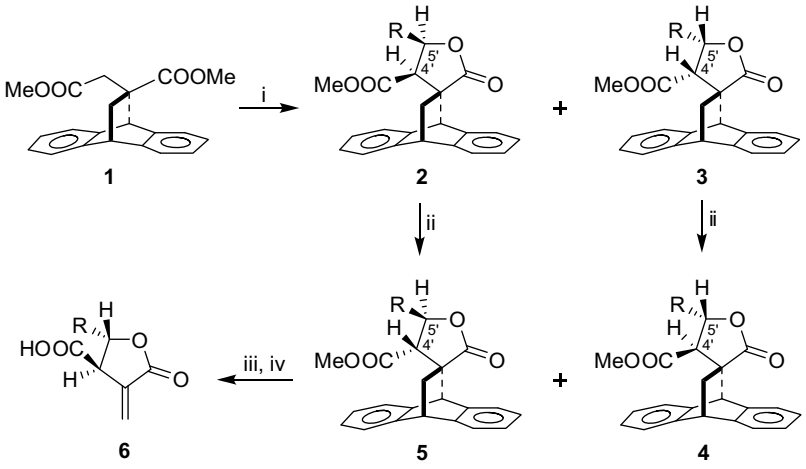
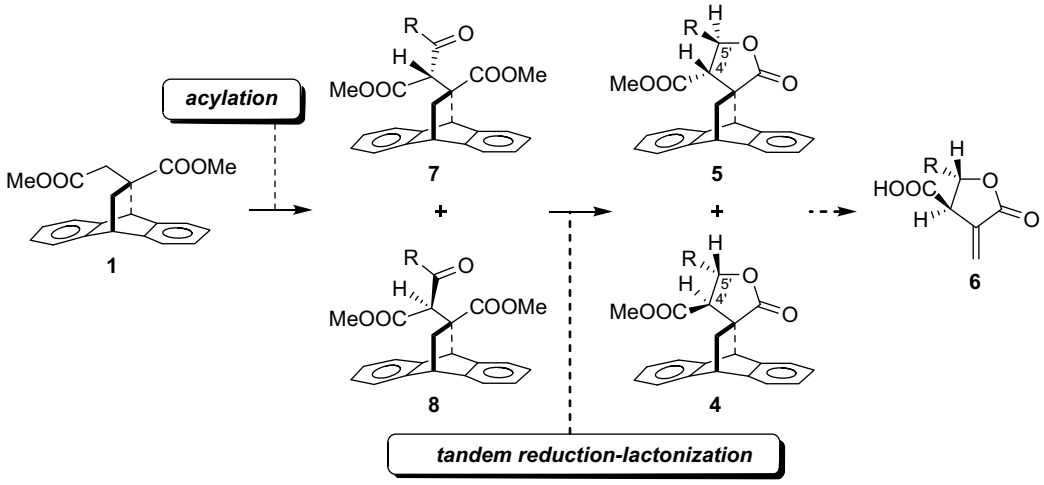



**6**; **R** = *n*-$C_5H_{11}$ (Methylenolactocin); *n*-$C_{11}H_{23}$ (Nephrosterinic acid) and *n*-$C_{13}H_{27}$ (Protolichesterinic acid)

**Scheme 1.** Total syntheses of methylenolactocin, nephrosterinic acid and protolichesterinic acid. Reagents and conditions: (i) a. 1.2 equiv LDA, THF, −78 °C to 0 °C, 2 h, b. 1.2 equiv RCHO, 0 °C to rt, 3 h, c. aq $NH_4Cl$, 30% HCl; (ii) 0.5 equiv NaOMe, THF/MeOH (2:1), rt, 6 days; (iii) FVP; (iv) 2-butanone, 6 N HCl, reflux, 2 h.




**Scheme 2.** Synthetic pathway of *trans*-**6** via acylation and tandem reduction–lactonization reactions.

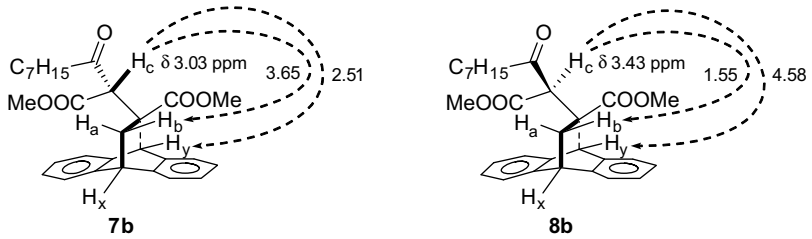



**Figure 1.** NOE results of β-ketodiester adducts **7b** and **8b**.

The stereochemical outcome of the acylation reaction can be explained by the chair-like transition states: **A** and **B** (Scheme 3). The transition structure **A** would lead to the major product **7b**. In contrast, the transition structure **B** would lead to the formation of the minor product **8b**. The latter is less favorable due to the large steric repulsion between the Cl atom and the anthracene ring.[4n]

Under similar reaction conditions, the lithium ester enolate **9** was allowed to react with various alkanoyl chlorides (**10a**–**e**), e.g., R=*n*-$C_5H_{11}$; *n*-$C_9H_{19}$; *n*-$C_{11}H_{23}$ and $C_6H_5$, to yield **7a**–**e** as the major products and **8a**–**e** as the minor products, respectively as detailed in Table 1.

It is possible that the β-ketodiester adducts **8** might be the result of isomerization of **7** under acylation conditions. To prove this hypothesis, three extra reaction conditions were carried out and results are as follows: treatment of the lithium ester enolate **9** with benzoyl chloride (**10e**) at −78 °C for 15 min and quickly quenching with saturated $NaHCO_3$ gave only recovered **1** in 98% yield. Secondly, the reaction mixture of the lithium ester enolate **9** and **10e** at −78 °C was left stirring at 0 °C for 15 min to also yield the recovered **1**. Lastly, addition of **10e** to the lithium ester enolate **9** at 0 °C for 15 min provided the β-ketodiester adducts **7e** and **8e**

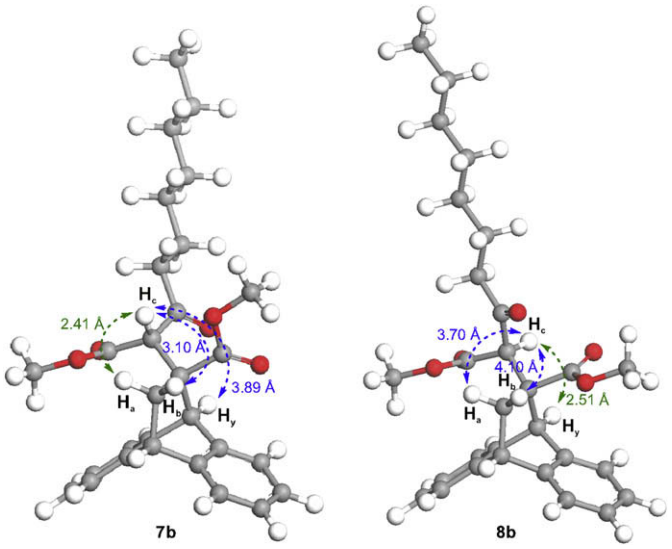
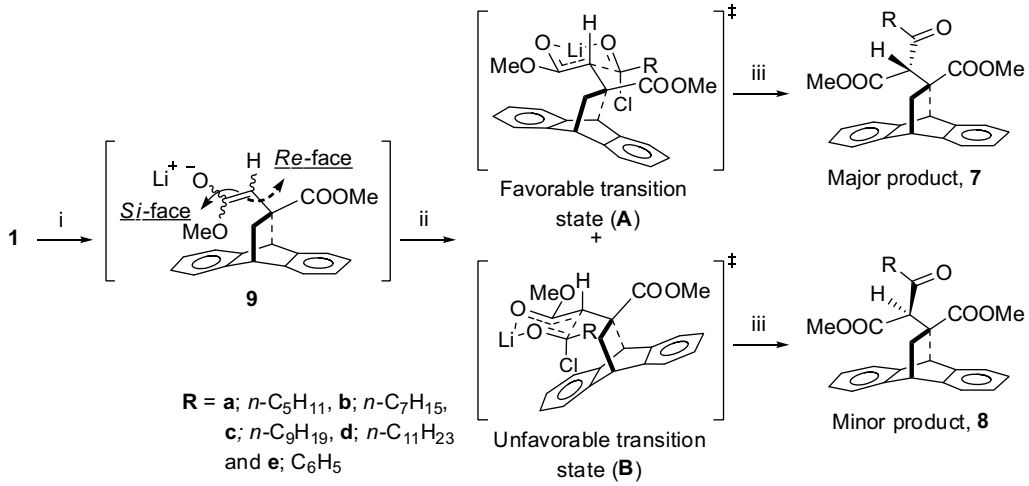



**Figure 2.** Structures of **7b** and **8b** from Gaussian 03 Programs at the B3LYP/6-31G level of DFT.

Having efficiently prepared the β-ketodiester adducts **7**, attention was turned to their chemoselective reduction to obtain spiro-lactones **5**.[14] Initially, we began by optimizing reaction conditions of the diastereoslective reduction of the model compound, the β-ketodiester adduct **7e**, using various amounts of $NaBH_4$ (1, 3, 5 and 10 equiv) in THF/MeOH (1:3) (Table 2). Results showed that the use of 5 equiv of $NaBH_4$ (Entry 3) gave high yields of spiro-lactones **3e** and **5e**, respectively (17 and 61% yields).

The structure of compounds *cis*-**3e** and *trans*-**5e** were determined from their $^1H$ NMR, $^{13}C$ NMR, IR and mass spectroscopic data.[4n] In the $^1H$ NMR spectrum of *cis*-**3e**, the protons $H_c$ and $H_d$ appeared at 2.54 and 5.51 ppm with a coupling constant *J* of 5.6 Hz while the same protons in *trans*-**5e** appeared at 3.05 and 6.05 ppm with a coupling constant *J* of 10.2 Hz. By observations from NOE experiments of compound *cis*-**3e** and *trans*-**5e**, the relative stereochemistries of these compounds were finally confirmed (Fig. 3). Irradiation of the proton $H_d$ of *cis*-**3e** gave only a NOE effect on the proton $H_c$; thus the orientation of proton $H_d$ is on the upper face and *syn*- with proton $H_c$. Furthermore, irradiation of proton $H_d$ of *trans*-**5e** caused only NOE effect on the proton $H_y$, while irradiation of the proton $H_c$ gave only NOE effects on the proton $H_b$; thus the orientation of proton $H_d$ is at the lower face and *anti*- to proton $H_c$.




**Scheme 3.** A plausible reaction mechanism of diastereoselective acylation of the adduct **1** with acid chloride. Reagents and conditions: (i) 1.2 equiv LDA, THF, −78 °C to 0 °C, 2 h; (ii) 1.2 equiv RCOCl (**10**), −78 °C to 0 °C, 1 h; (iii) saturated $NaHCO_3$.

in 75 and 18% yields respectively. The above results clearly indicated that no isomerization took place under acylation conditions. It should be added that upon treatment of the β-ketodiester adduct **7e** with LDA (1.2 equiv) under acylation conditions employed the isomerized products **8e** was obtained in 12% yield (87% unchanged material).

**Table 1**
Diastereoselective acylation reactions of adduct **1** with various alkanoyl chlorides (**10a–e**)

| Entry | RCOCl (**10**) | Yield[a,b] (%) | | Diastereomeric ratio[b] of **7**/**8** |
|---|---|---|---|---|
| | | **7** | **8** | |
| 1 | **10a**: *n*-$C_5H_{11}$COCl | 58 | 4 | 94:6 |
| 2 | **10b**: *n*-$C_7H_{15}$COCl | 63 | 4 | 94:6 |
| 3 | **10c**: *n*-$C_9H_{19}$COCl | 53 | 6 | 90:10 |
| 4 | **10d**: *n*-$C_{11}H_{23}$COCl | 49 | 11 | 82:18 |
| 5 | **10e**: $C_6H_5$COCl | 73 | 19 | 79:21 |

[a] Compounds **7a–e** and **8a–e** were fully characterized by $^1H$ NMR, $^{13}C$ NMR, IR and HRMS (ESI).

[b] Yields and diastereomeric ratios of acylation products (**7a–e** and **8a–e**) were determined by $^1H$ NMR analysis.

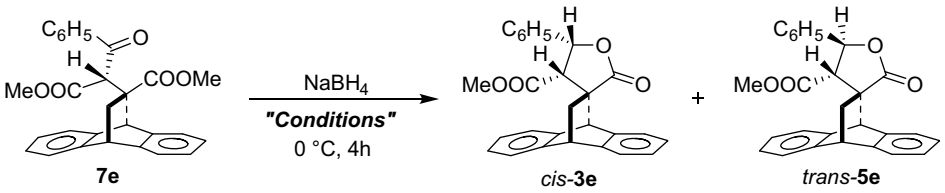
These results strongly confirm the orientation of the α-proton of β-ketodiester adduct **7e** is upper face and can be considered to be representative of **7a–d**. In addition, the β-ketodiester adducts **8e** was also obtained (colourless oil, 19%). $NaBH_4$ reduction of **8e** furnished the spiro-lactone *cis*-**2e** (white solid, mp 204.9–206.0 °C ($CH_2Cl_2$/hexane), 44% yield) as the only product isolated. The stereochemistry of *cis*-**2e** was fully confirmed by NOE experiments (Fig. 4).

In order to increase the diastereoselectivity of the reduction product (hence the final product), we decided to perform the $NaBH_4$ reduction in wet-THF system as previously reported by several groups.[15,16] Results are presented in Table 3 which demonstrates that the highest diastereoselectivity of **7e** were achieved by using $NaBH_4$ (5 equiv) in THF/$H_2O$ (8:1) at 0 °C for 4 h (Entry 5).

These conditions were therefore employed for the reduction reactions of compounds **7a–d** and the results are shown in Table 4.

We have indepently demonstrated that the trans-products obtained were not the results of base induced isomerization of the carbon-bearing the ester functionality (C-4′). Thus treatment of *cis*-**3e**, obtained earlier, with $NaBH_4$ or NaOMe in MeOH or MeOH/THF provided only the recovered starting material.

**Table 2**
Reduction of β-ketodiester adduct **7e** with various amounts of $NaBH_4$ in THF/MeOH




| Entry | Equiv of $NaBH_4$ | Conditions | Yield[a] (%) | | Diastereomeric ratio of *trans*-**5e**/*cis*-**3e** | % Conversion |
|---|---|---|---|---|---|---|
| | | | *cis*-**3e** | *trans*-**5e** | | |
| 1 | 1 | THF/MeOH (1:3) | 22 | 58 | 73:27 | 54 |
| 2 | 3 | THF/MeOH (1:3) | 22 | 60 | 73:27 | 100 |
| 3 | 5 | THF/MeOH (1:3) | 17 | 61 | 78:22 | 100 |
| 4 | 10 | THF/MeOH (1:3) | 18 | 35 | 66:34 | 100 |

[a] Yields of isolated compounds.

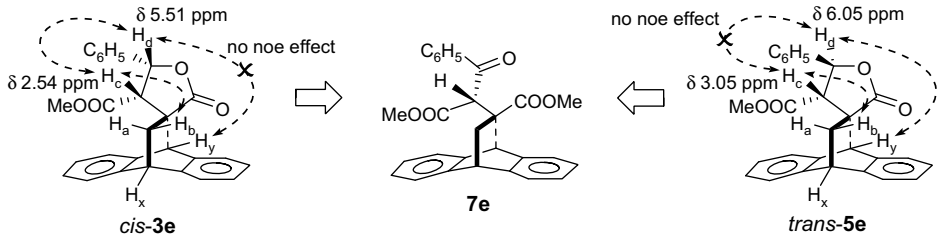



**Figure 3.** NOE results of spiro-lactones (*cis*-**3e** and *trans*-**5e**).

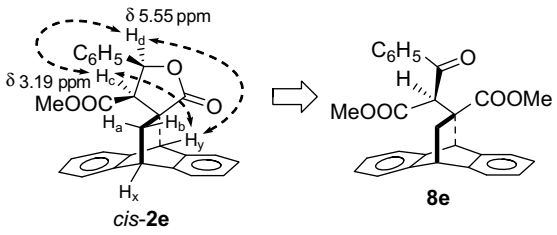


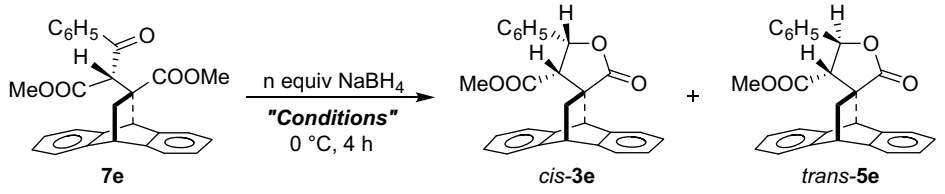

**Figure 4.** NOE results of spiro-lactone (*cis*-**2e**).

A plausible reaction mechanism is depicted in Scheme 4 which involves the Felkin–Anh model (**C**). The reduction of β-ketodiester **7** with $NaBH_4$ in a wet-THF system proceeds via the Felkin–Anh face to give the alkoxide **11** which, upon workup, furnished the final *trans*-**5**. trans-Products (**5a–e**) can be transformed to natural products, e.g., methylenolactocin (R=*n*-$C_5H_{11}$) and nephrosterinic acid (R=*n*-$C_{11}H_{23}$), and unnatural products (R=*n*-$C_7H_{15}$, *n*-$C_9H_{19}$ and $C_6H_5$) by flash vacuum pyrolysis and hydrolysis, respectively.[4n]

## 3. Conclusion

Synthetic methodology for methylenolactocin, nephrosterinic acid and their derivatives using diastereoselective acylation and tandem chemoselective reduction–lactonization as key steps has been developed. The approach is short, practical, efficient with high stereoselectivity and can be applied to both alkyl and aryl groups. The methodology is very useful for enantiomeric synthesis of compounds in this class.

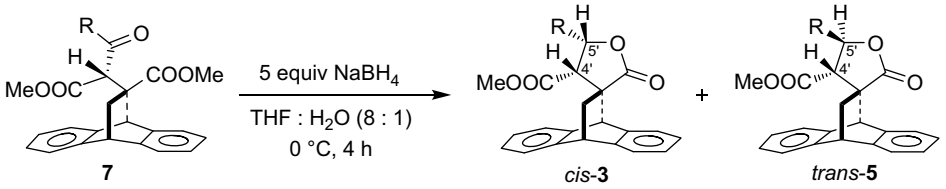
**Table 3**
Reduction of β-ketodiester adducts **7e** with various amounts of $NaBH_4$ in wet-THF systems




| Entry | Equiv of $NaBH_4$ | Conditions | Yield[a] (%) | | Diastereomeric ratio of *trans*-**5e**/*cis*-**3e** | % Conversion |
|---|---|---|---|---|---|---|
| | | | *cis*-**3e** | *trans*-**5e** | | |
| 1 | 5.0 | THF/$H_2O$ (2:1) | 15 | 80 | 84:16 | 100 |
| 2 | 5.0 | THF/$H_2O$ (4:1) | 7 | 72 | 91:9 | 100 |
| 3 | 1.5 | THF/$H_2O$ (8:1) | 1 | 53 | 98:2 | 77 |
| 4 | 3.0 | THF/$H_2O$ (8:1) | 4 | 65 | 94:6 | 98 |
| 5 | 5.0 | THF/$H_2O$ (8:1) | 2 | 70 | 97:3 | 100 |
| 6 | 7.0 | THF/$H_2O$ (8:1) | 3 | 77 | 96:4 | 99 |
| 7 | 5.0 | THF/$H_2O$ (16:1) | 5 | 92 | 95:5 | 67 |

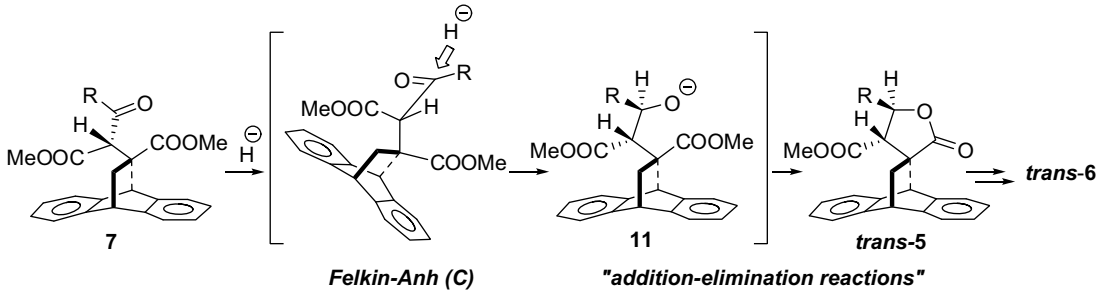
[a] Yields of isolated compounds.

**Table 4**
Reduction of β-ketodiester adducts (**7a**–**e**) with 5 equiv of $NaBH_4$ in THF/$H_2O$ (8:1)




| Entry | R | Yield[a] (%) | | Diastereomeric ratio of *trans*-**5e**/*cis*-**3e** | % Conversion |
|---|---|---|---|---|---|
| | | *cis*-**3e** | *trans*-**5e** | | |
| 1 | **7a**: *n*-$C_5H_{11}$ | 6 | 70 | 92:8 | 84 |
| 2 | **7b**: *n*-$C_7H_{15}$ | 19 | 78 | 80:20 | 81 |
| 3 | **7c**: *n*-$C_9H_{19}$ | 4 | 90 | 96:4 | 76 |
| 4 | **7d**: *n*-$C_{11}H_{23}$ | 8 | 89 | 92:8 | 81 |
| 5 | **7e**: $C_6H_5$ | 2 | 70 | 97:3 | 100 |

[a] Yields of isolated compounds.




**R** = **a**; *n*-$C_5H_{11}$, **b**; *n*-$C_7H_{15}$, **c**; *n*-$C_9H_{19}$, **d**; ***n***-$C_{11}H_{23}$ and **e**; $C_6H_5$

**Scheme 4.** Tandem chemoselective reduction–lactonization reactions with $NaBH_4$ via the attachment of hydride ($H^-$) and β-ketodiester adducts (**7a**–**e**).

## 4. Experimental section

### 4.1. General methods

All reactions were carried out under nitrogen or argon. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Gallenkamp Electrothermal apparatus and were uncorrected. The $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker DRX 400 MHz spectrometers and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). All NMR spectra were measured in $CDCl_3$ and chemical shifts were reported as $\delta$-values in parts per million (ppm) relative to residue $CHCl_3$ as internal reference ($^1H$: $\delta$ 7.26, $^{13}C$: $\delta$ 77.00) and coupling constants ($J$ values) were reported in hertz (Hz). Peak multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), dt (doublet of triplets), ddd (doublet of doublet of doublets) and m (multiplet). Infrared spectra were taken with a FT-IR model TENSER 27 (Bruker) spectrometer and absorption frequencies were reported in reciprocal centimeters ($cm^{-1}$). Mass spectra (electrospray ionization mode, ESI-MS) were measured on a micromass Q-TOF-2™ (Waters) spectrometer. Flash column chromatography was performed employing Merck silica gel 60 and Merck silica gel 60H. Preparative thin layer chromatography (PLC) plates were carried out using Merck silica gel 60 $PF_{254}$. Analytical thin layer chromatography was performed with Merck silica gel 60 $F_{254}$ aluminum plates. Solvents were dried over $CaH_2$ and distilled before used. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl under nitrogen. Diisopropylamine was distilled over $CaH_2$ and stored under nitrogen. *n*-Butyllithium was purchased from Fluka and Across as solution in hexane and titrated periodically according to the 2,5-dimethoxybenzyl alcohol method. Acid chlorides were freshly distilled under reduce pressure.

### 4.2. Chemistry

*4.2.1. General procedure for the synthesis of 11-carbomethoxy-11-(1′-alkanoyl or 1′-benzoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7a**–**e** and **8a**–**e**)*

To a 100 mL round-bottomed flask equipped with a magnetic stirrer bar, fitted with a three-way stopcock and nitrogen inlet. *n*-Butyllithium (1.30 mL, 1.80 mmol, 1.4 M in hexane) was added to a stirring solution of diisopropylamine (0.30 mL, 2.16 mmol) in THF (5 mL) at −78 °C, then stirred at 0 °C for 1 h. To the LDA solution, dimethyl itaconate–anthracene adduct (**1**) (504.6 mg, 1.50 mmol) in THF (10 mL) was added at −78 °C and stirred at 0 °C for 2 h. At −78 °C, alkanoyl or benzoyl chloride (**10**) (1.80 mmol) was added to the reaction mixture and left stirring at 0 °C for 1 h. The resulting mixture was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with $CH_2Cl_2$ (3×15 mL). The combined organic layer were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc/hexane=1:9 as eluent) followed by preparative thin layer chromatography (EtOAc/hexane=1:9 as developing solvent) gave the β-ketodiester adducts **7** and **8**.

*4.2.1.1. 11-Carbomethoxy-11-(1′-hexanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7a** and **8a**).* Compound **7a** (58%): white solid; mp 198–199 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.25; $\nu_{max}$ (KBr) 2956, 2868, 1745, 1468, 1241 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.83 (3H, t, $J$=7.2 Hz, *Me*), 0.98, 2.86, 4.26 (3H, ABX system, $J$=13.2, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 1.04–1.50 (6H, m, C$H_2$),

2.05 (1H, dt, $J$=17.8, 7.2 Hz, C*H*CO), 2.42 (1H, dt, $J$=17.8, 7.6 Hz, C*H*CO), 3.03 (1H, s, COC*H*COOMe), 3.35 (3H, s, COO*Me*), 3.84 (3H, s, COO*Me*), 5.01 (1H, s, ArC*H*), 7.02–7.66 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 13.8, 22.3, 22.8, 30.9, 37.8, 43.9, 44.1, 50.2, 52.1, 52.4, 53.7, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 457.1990. $C_{27}H_{30}O_5Na$ requires 457.1991.

Compound **8a** (4%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.27; $\nu_{max}$ (liquid film) 2952, 2864, 1756, 1719, 1460, 1242 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, $J$=6.9 Hz, *Me*), 1.69, 2.83, 4.28 (3H, ABX system, $J$=13.2, 3.2, 2.3 Hz, C$H_2$, ArC*H*), 1.12–1.70 (6H, m, C$H_2$), 2.23 (1H, ddd, $J$=17.6, 8.3, 6.2 Hz, C*H*CO), 2.48 (1H, ddd, $J$=17.6, 8.4, 6.6 Hz, C*H*CO), 3.34 (3H, s, COO*Me*), 3.39 (1H, s, COC*H*COOMe), 3.48 (3H, s, COO*Me*), 4.70 (1H, s, ArC*H*), 6.99–7.53 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 13.9, 22.5, 23.1, 31.1, 35.1, 41.4, 44.0, 51.0, 52.1, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 457.1991. $C_{27}H_{30}O_5Na$ requires 457.1991.

*4.2.1.2. 11-Carbomethoxy-11-(1′-octanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7b** and **8b**).* Compound **7b** (63%): white solid; mp 200–202 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.23; $\nu_{max}$ (KBr) 2940, 2850, 1720, 1741, 1712, 1450, 1250 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, $J$=7.1 Hz, *Me*), 0.98, 2.86, 4.26 (3H, ABX system, $J$=13.2, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 1.06–1.48 (10H, m, C$H_2$), 2.05 (1H, dt, $J$=17.7, 7.2 Hz, C*H*CO), 2.42 (1H, dt, $J$=17.7, 7.6 Hz, C*H*CO), 3.03 (1H, s, COC*H*COOMe), 3.36 (3H, s, COO*Me*), 3.85 (3H, s, COO*Me*), 5.01 (1H, s, ArC*H*), 7.01–7.64 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.0, 22.6, 23.2, 28.7, 28.9, 31.6, 37.8, 43.9, 44.2, 50.2, 52.1, 52.4, 53.8, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 485.2305. $C_{29}H_{34}O_5Na$ requires 485.2304.

Compound **8b** (4%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.34; $\nu_{max}$ (liquid film) 2929, 2849, 1748, 1719, 1460, 1247 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, $J$=7.1 Hz, *Me*), 1.05–1.65 (10H, m, C$H_2$), 1.69, 2.83, 4.28 (3H, ABX system, $J$=13.2, 3.1, 2.2 Hz, C$H_2$, ArC*H*), 2.23 (1H, ddd, $J$=17.6, 8.4, 6.2 Hz, C*H*CO), 2.47 (1H, ddd, $J$=17.6, 8.6, 6.3 Hz, C*H*CO), 3.34 (3H, s, COO*Me*), 3.42 (1H, s, COC*H*COOMe), 3.48 (3H, s, COO*Me*), 4.70 (1H, s, ArC*H*), 7.00–7.53 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 29.0, 29.3, 29.4, 29.5, 29.7, 31.9, 35.2, 41.5, 44.0, 51.0, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.1, 143.5, 144.5, 169.7, 174.1, 203.5; (ESI) $m/z$: $(M+Na)^+$, found 485.2304. $C_{29}H_{34}O_5Na$ requires 485.2304.

*4.2.1.3. 11-Carbomethoxy-11-(1′-decanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7c** and **8c**).* Compound **7c** (53%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.30; $\nu_{max}$ (liquid film) 2930, 2870, 1748, 1720, 1450, 1240 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, $J$=7.1 Hz, *Me*), 0.99, 2.86, 4.26 (3H, ABX system, $J$=13.2, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 1.06–1.48 (14H, m, C$H_2$), 2.04 (1H, dt, $J$=17.6, 7.2 Hz, C*H*CO), 2.42 (1H, dt, $J$=17.6, 7.6 Hz, C*H*CO), 3.03 (1H, s, COC*H*COOMe), 3.36 (3H, s, COO*Me*), 3.84 (3H, s, COO*Me*), 5.01 (1H, s, ArC*H*), 7.00–7.66 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.6, 23.2, 28.7, 29.2, 29.3, 31.8, 37.8, 43.9, 44.2, 50.1, 52.1, 52.4, 53.7, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 173.9, 204.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 513.2617. $C_{31}H_{38}O_5Na$ requires 513.2617.

Compound **8c** (6%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.36; $\nu_{max}$ (liquid film) 2926, 2855, 1740, 1720, 1460, 1244 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.87 (3H, t, $J$=7.1 Hz, *Me*), 1.05–1.75 (14H, m, C$H_2$), 1.79, 2.83, 4.28 (3H, ABX system, $J$=13.2, 3.2, 2.3 Hz, C$H_2$, ArC*H*), 2.23 (1H, ddd, $J$=17.6, 8.4, 6.1 Hz, C*H*CO), 2.47 (1H, ddd, $J$=17.6, 8.6, 6.3 Hz, C*H*CO), 3.34 (3H, s, COO*Me*), 3.42 (1H, s, COC*H*COOMe), 3.48 (3H, s, COO*Me*), 4.70 (1H, s, ArC*H*), 7.00–7.52 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 29.0, 29.3, 29.4, 29.7, 31.9, 35.1, 41.5, 44.0, 51.0, 52.1, 52.2, 54.6, 65.3, 123.0, 123.6, 124.2, 125.4, 125.7, 126.5, 126.6, 127.0, 139.0, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 513.2617. $C_{31}H_{38}O_5Na$ requires 513.2617.

*4.2.1.4. 11-Carbomethoxy-11-(1′-dodecanoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7d** and **8d**).* Compound **7d** (49%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.33; $\nu_{max}$ (liquid film) 2931, 2858, 1748, 1720, 1458, 1236 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (t, $J$=7.1 Hz, *Me*), 0.98, 2.86, 4.26 (3H, ABX system, $J$=13.2, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 1.07–1.48 (18H, m, C$H_2$), 2.04 (1H, dt, $J$=17.7, 7.2 Hz, C*H*CO), 2.42 (1H, dt, $J$=17.7, 7.6 Hz, C*H*CO), 3.03 (1H, s, COC*H*COOMe), 3.36 (3H, s, COO*Me*), 3.88 (3H, s, COO*Me*), 5.01 (1H, s, ArC*H*), 7.00–7.66 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.2, 28.8, 29.3, 29.4, 29.6, 31.9, 37.8, 43.9, 44.2, 50.2, 52.1, 52.4, 53.8, 64.2, 122.9, 123.5, 124.4, 125.8, 126.6, 126.7, 139.5, 143.2, 143.9, 168.5, 174.0, 204.5; HRMS (ESI) $m/z$: $(M+H)^+$, found 519.3115. $C_{33}H_{43}O_5$ requires 519.3110.

Compound **8d** (11%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.39; $\nu_{max}$ (liquid film) 2925, 2853, 1756, 1720, 1460, 1246 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.87 (3H, t, $J$=7.0 Hz, *Me*), 1.10–1.42 (18H, m, C$H_2$), 1.68, 2.82, 4.28 (3H, ABX system, $J$=13.2, 3.2, 2.3 Hz, C$H_2$, ArC*H*), 2.22 (1H, ddd, $J$=17.6, 8.5, 6.0 Hz, C*H*CO), 2.46 (1H, ddd, $J$=17.6, 8.6, 6.3 Hz, C*H*CO), 3.33 (3H, s, COO*Me*), 3.42 (1H, s, COC*H*COOMe), 3.47 (3H, s, COO*Me*), 4.69 (1H, s, ArC*H*), 6.97–7.52 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.7, 23.4, 28.9, 29.3, 29.5, 29.6, 31.9, 35.1, 41.5, 44.0, 51.0, 52.1, 52.2, 54.6, 65.2, 123.0, 123.6, 124.2, 125.4, 125.6, 126.5, 126.6, 127.0, 138.9, 140.0, 143.5, 144.5, 169.7, 174.1, 203.5; HRMS (ESI) $m/z$: $(M+Na)^+$, found 541.2930. $C_{33}H_{42}O_5Na$ requires 541.2930.

*4.2.1.5. 11-Carbomethoxy-11-(1′-benzoyl-1′-carbomethoxymethyl)-9,10-dihydro-9,10-ethanoanthracenes (**7e** and **8e**).* Compound **7e** (73%): white solid; mp 188–190 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.10; $\nu_{max}$ (KBr) 2947, 1740, 1606, 1438, 1234 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.05, 2.96, 4.25 (3H, ABX system, $J$=13.3, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 3.42 (3H, s, COO*Me*), 3.74 (3H, s, COO*Me*), 3.91 (1H, s, COC*H*COOMe), 5.12 (1H, s, ArC*H*), 7.03–7.76 (13H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 37.9, 43.9, 50.3, 52.2, 52.5, 54.3, 59.8, 123.0, 123.6, 124.4, 125.8, 126.6, 126.9, 128.0, 128.7, 133.5, 136.6, 139.5, 143.3, 143.9, 168.5, 174.1, 194.0; HRMS (ESI) $m/z$: $(M+Na)^+$, found 463.1521. $C_{28}H_{24}O_5Na$ requires 463.1521.

Compound **8e** (19%): colourless oil; $R_f$ (10% EtOAc/hexane) 0.13; $\nu_{max}$ (liquid film) 2950, 1737, 1691, 1597, 1448, 1232 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.51, 2.94, 4.36 (3H, ABX system, $J$=13.7, 2.9, 2.8 Hz, C$H_2$, ArC*H*), 3.17 (3H, s, COO*Me*), 3.31 (3H, s, COO*Me*), 4.60 (1H, s, COC*H*COOMe), 4.87 (1H, s, ArC*H*), 6.94–7.87 (13H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 33.3, 44.2, 52.2, 53.9, 61.4, 123.4, 123.5, 124.5, 124.9, 125.5, 126.3, 126.6, 126.7, 128.3, 128.6, 133.4, 136.2, 138.7, 140.7, 143.9, 144.9, 167.8, 174.5, 194.1; HRMS (ESI) $m/z$: $(M+Na)^+$, found 463.1522. $C_{28}H_{24}O_5Na$ requires 463.1521.

*4.2.2. General procedure for the synthesis of tetrahydro-4′-carbomethoxy-5′-(alkyl or phenyl)-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3a–e** and trans-**5a–e**) by using $NaBH_4$ in wet-THF system*

To a cooled (0 °C) solution of β-ketodiester adduct (**7**) (0.23 mmol) in THF (4 mL) and $H_2O$ (0.5 mL) was added $NaBH_4$ (1.20 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 4 h and then quenched by dropwise addition of acetone (1 mL). After that the resulting solution was extracted with $CH_2Cl_2$ (3×15 mL) and the combined organic portions were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc/hexane=1:9 as eluent) followed by preparative thin layer chromatography (EtOAc/hexane=1:9 as developing solvent) obtained *cis*-**3** as the minor product and *trans*-**5** as the major product.

*4.2.2.1. Tetrahydro-4′-carbomethoxy-5′-pentyl-2′-furanone-3′-spiro-11-9, 10-dihydro-9,10-ethanoanthracenes (cis-**3a** and trans-**5a**).* Compound *cis*-**3a** (6%): white solid; mp 211.1–212.2 °C ($CH_2Cl_2$/hexane) [lit.[4n] mp 210–212 °C ($CH_2Cl_2$/hexane)]; $R_f$ (10% EtOAc/hexane) 0.17; $\nu_{max}$ (KBr) 2946, 2865, 1785, 1734, 1464, 1204, 1163 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.85 (3H, t, *J*=6.8 Hz, *Me*), 1.17–1.64 (8H, m, C$H_2$), 1.99, 2.09, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, C$H_2$, ArC*H*), 2.24 (1H, d, *J*=5.2 Hz, C*H*COOMe), 3.83 (3H, s, COO*Me*), 4.31 (1H, dt, *J*=8.3, 5.2 Hz, C*H*O), 4.64 (1H, s, ArC*H*), 7.00–7.51 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 13.8, 22.3, 25.4, 30.9, 31.4, 40.7, 43.7, 46.8, 50.6, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126. 7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m*/*z*: $(M+H)^+$, found 405.2064. $C_{26}H_{29}O_4$ requires 405.2066.

Compound *trans*-**5a** (70%): white solid; mp 117.5–118.9 °C ($CH_2Cl_2$/hexane) [lit.[4n] mp 118–119 °C (hexane)]; $R_f$ (10% EtOAc/hexane) 0.30; $\nu_{max}$ (KBr) 2946, 2870, 1780, 1449, 1212, 1164 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=6.8 Hz, *Me*), 1.24–1.73 (8H, m, C$H_2$), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.1, 2.4 Hz, C$H_2$, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, C*H*COOMe), 3.00 (3H, s, COO*Me*), 4.50 (1H, s, ArC*H*), 5.02 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, C*H*O), 7.04–7.31 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 13.9, 22.4, 25.3, 31.4, 34.2, 37.1, 43.8, 46.7, 51.1, 51.7, 56.1, 77.5, 123.1, 123.4, 124.6, 125.1, 125.8, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m*/*z*: $(M+Na)^+$, found 427.1891. $C_{26}H_{28}O_4Na$ requires 427.1885.

*4.2.2.2. Tetrahydro-4′-carbomethoxy-5′-heptyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3b** and trans-**5b**).* Compound *cis*-**3b** (19%): white solid; mp 131.0–132.2 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.15; $\nu_{max}$ (KBr) 2930, 2857, 1782, 1730, 1460, 1210, 1172 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.85 (3H, t, *J*=6.7 Hz, *Me*), 1.16–1.64 (12H, m, C$H_2$), 1.98, 2.08, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, C$H_2$, ArC*H*), 2.23 (1H, d, *J*=5.1 Hz, C*H*COOMe), 3.82 (3H, s, COO*Me*), 4.31 (1H, dt, *J*=8.3, 5.1 Hz, C*H*O), 4.64 (1H, s, ArC*H*), 7.00–7.52 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.0, 22.5, 25.7, 28.9, 29.2, 31.0, 31.6, 40.7, 43.7, 46.8, 50.6, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m*/*z*: $(M+Na)^+$, found 455.2198. $C_{28}H_{32}O_4Na$ requires 455.2198.

Compound *trans*-**5b** (78%): white solid; mp 112.4–113.4 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.18; $\nu_{max}$ (KBr) 2941, 2850, 1775, 1734, 1459, 1208, 1169 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.89 (3H, t, *J*=7.1 Hz, *Me*), 1.21–1.73 (12H, m, C$H_2$), 2.10, 2.49, 4.37 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, C$H_2$, ArC*H*), 2.76 (1H, d, *J*=10.4 Hz, C*H*COOMe), 3.01 (3H, s, COO*Me*), 4.51 (1H, s, ArC*H*), 5.03 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, C*H*O), 7.05–7.33 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.0, 22.6, 25.7, 29.0, 29.2, 31.7, 34.2, 37.2, 43.8, 46.7, 51.1, 51.6, 56.1, 77.5, 123.1, 123.4, 124.7, 125.1, 125.9, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m*/*z*: $(M+H)^+$, found 433.2379. $C_{28}H_{33}O_4$ requires 433.2379.

*4.2.2.3. Tetrahydro-4′-carbomethoxy-5′-nonyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3c** and trans-**5c**).* Compound *cis*-**3c** (4%): white solid; mp 120–121.1 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.19; $\nu_{max}$ (KBr) 2929, 2857, 1782, 1734, 1460, 1204, 1173 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=6.7 Hz, *Me*), 1.15–1.68 (16H, m, C$H_2$), 1.99, 2.09, 4.40 (3H, ABX system, *J*=12.4, 3.1, 2.1 Hz, C$H_2$, ArC*H*), 2.24 (1H, d, *J*=5.1 Hz, C*H*COOMe), 3.83 (3H, s, COO*Me*), 4.31 (H, dt, *J*=8.2, 5.1 Hz, C*H*O), 4.65 (1H, s, ArC*H*), 7.01–7.53 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 28.9, 29.2, 29.3, 29.4, 31.0, 31.6, 40.7, 43.7, 46.8, 50.7, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.9, 126.1, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m*/*z*: $(M+Na)^+$, found 483.2508. $C_{30}H_{36}O_4Na$ requires 483.2511.

Compound *trans*-**5c** (90%): white solid; mp 115.5–115.6 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.23; $\nu_{max}$ (KBr) 2941, 2850, 1780, 1734, 1454, 1204, 1159 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.1 Hz, *Me*), 1.22–1.71 (16H, m, C$H_2$), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, C$H_2$, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, C*H*COOMe), 3.00 (3H, s, COO*Me*), 4.49 (1H, s, ArC*H*), 5.01 (1H, ddd, *J*=10.4, 8.3, 3.0 Hz, C*H*O), 7.04–7.31 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 29.2, 29.3, 29.4, 31.8, 34.2, 37.2, 43.8, 46.7, 51.1, 51.7, 56.1, 77.5, 123.1, 123.4, 124.6, 125.1, 125.9, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3; HRMS (ESI) *m*/*z*: $(M+Na)^+$, found 483.2511. $C_{30}H_{36}O_4Na$ requires 483.2511.

*4.2.2.4. Tetrahydro-4′-carbomethoxy-5′-undecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3d** and trans-**5d**).* Compound *cis*-**3d** (8%): white solid; mp 160–161 °C ($CH_2Cl_2$/hexane) [lit.[4n] mp 159–160 °C ($CH_2Cl_2$/hexane)]; $R_f$ (10% EtOAc/hexane) 0.22; $\nu_{max}$ (KBr) 2926, 2854, 1770, 1729, 1454, 1223, 1164 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.87 (3H, t, *J*=7.0 Hz, *Me*), 1.17–1.64 (20H, m, C$H_2$), 1.99, 2.09, 4.39 (3H, ABX system, *J*=12.4, 3.2, 2.2 Hz, C$H_2$, ArC*H*), 2.23 (1H, d, *J*=5.1 Hz, C*H*COOMe), 3.82 (3H, s, COO*Me*), 4.30 (1H, dt, *J*=8.3, 5.1 Hz, C*H*O), 4.64 (1H, s, ArC*H*), 7.00–7.51 (8H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.6, 25.7, 29.2, 29.3, 29.4, 29.6, 31.0, 31.9, 40.7, 43.7, 46.8, 50.7, 51.7, 58.2, 76.6, 122.3, 123.9, 124.3, 125.9, 126.2, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9; HRMS (ESI) *m*/*z*: $(M+H)^+$, found 489.3008. $C_{32}H_{41}O_4$ requires 489.3005.

Compound *trans*-**5d** (89%): white solid; mp 78.9–79.1 °C ($CH_2Cl_2$/hexane) [lit.[4n] mp 78–79 °C (hexane)]; $R_f$ (10% EtOAc/hexane) 0.31; $\nu_{max}$ (KBr) 2926, 2870, 1785, 1734, 1469, 1212, 1164 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.88 (3H, t, *J*=7.1 Hz, *Me*), 1.21–1.71 (20H, m, C$H_2$), 2.09, 2.48, 4.36 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, C$H_2$, ArC*H*), 2.75 (1H, d, *J*=10.4 Hz, C*H*COOMe), 2.99 (3H s, COO*Me*), 4.50 (1H, s, ArC*H*), 5.01 (1H, ddd, *J*=10.4, 8.4, 3.0 Hz, C*H*O), 7.05–7.30 (8H, m, ArH, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 14.1, 22.7, 25.7, 29.3, 29.4, 29.5, 29.6, 31.9, 34.3, 37.2, 43.9, 46.7, 51.2, 51.8, 56.2, 77.6, 123.1, 123.4, 124.7, 125.1, 125.9, 126.5, 126.6, 127.6, 137.9, 140.0, 143.3, 145.5, 168.7, 176.4; HRMS (ESI): $(M+H)^+$, found 489.3006. $C_{32}H_{41}O_4$ requires 489.3005.

*4.2.2.5. Tetrahydro-4′-carbomethoxy-5′-phenyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes (cis-**3e** and trans-**5e**).* Compound *cis*-**3e** (2%): white solid; mp 220–221 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.09; $\nu_{max}$ (KBr) 2951, 1795, 1734, 1454, 1208, 1143 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.20, 2.26, 4.49 (3H, ABX system, *J*=12.4, 3.1, 2.3 Hz, C$H_2$, ArC*H*), 2.54 (1H, d, *J*=5.6 Hz, C*H*COOMe), 3.28 (3H, s, COO*Me*), 4.77 (1H, s, ArC*H*), 5.51 (1H, d, *J*=5.6 Hz, C*H*O), 6.97–7.56 (13H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 40.8, 43.8, 46.9, 50.9, 51.4, 61.0, 76.9, 124.0, 124.4, 125.4, 126.0, 126.3, 126.8, 127.5, 128.2, 128.5, 139.3, 140.7, 142.0, 169.3, 176.7; HRMS (ESI): $(M+H)^+$, found 411.1594. $C_{27}H_{23}O_4$ requires 411.1596.

Compound *trans*-**5e** (70%): white solid; mp 228.9–229.9 °C ($CH_2Cl_2$/hexane); $R_f$ (10% EtOAc/hexane) 0.12; $\nu_{max}$ (KBr) 2951, 2870, 1774, 1734, 1459, 1205, 1161 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.11, 2.55, 4.38 (3H, ABX system, *J*=12.5, 3.0, 2.4 Hz, C$H_2$, ArC*H*), 2.96 (3H, s, COO*Me*), 3.05 (1H, d, *J*=10.2 Hz, C*H*COOMe), 4.66 (1H, s, ArC*H*), 6.05 (1H, d, *J*=10.2 Hz, C*H*O), 7.05–7.44 (13H, m, Ar*H*); $\delta_C$ (100.6 MHz, $CDCl_3$) 37.4, 43.8, 46.7, 51.5, 51.8, 59.0, 78.4, 123.2, 123.4, 124.8, 125.2, 126.0, 126.3, 126.6, 126.7, 127.6, 128.6, 128.9, 137.2, 137.8, 139.9, 143.3, 168.1, 176.0; HRMS (ESI): $(M+H)^+$, found 411.1595. $C_{27}H_{23}O_4$ requires 411.1596.

### 4.3. Computational procedure

The calculations were carried out in a Pentium IV-based PC computer. Density functional calculations were performed with the Gaussian 03 program[12] (Revision C.02, Gaussian, Inc., Wallingford CT) at the B3LYP/6-31G level. The three-dimensional molecular graphics of the energetically optimized **7b** and **8b** were produced from the GaussView program, version 3.09.[13]

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