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TETRAHEDRON: *ASYMMETRY*

Synthesis of both enantiomers of methylenolactocin, nephrosterinic acid and protolichesterinic acid via tandem aldol–lactonization reactions

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Abstract—Both forms of the enantiomerically pure methylenolactocin, nephrosterinic and protolichesterinic acid have been synthesized via tandem aldol–lactonization reactions from corresponding optically active itaconate–anthracene adducts.

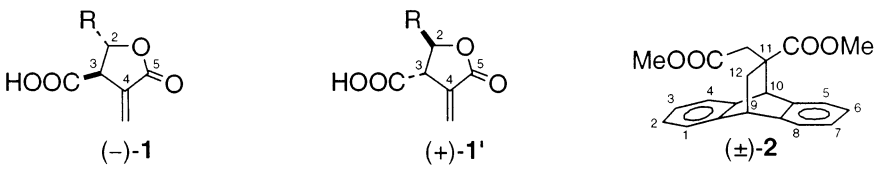
1. Introduction

Methylene-γ-butyrolactone moiety is a core skeleton in many structurally complex natural products.[1] Disubstituted α-methylene-γ-butyrolactones, for examples methylenolactocin **1a**,[2,3] nephrosterinic acid **1b**,[4] and protolichesterinic acid **1c**,[5,6] (Fig. 1) are noted for their biological activities, being antibacterial,[7a–h] antifungal,[7b] antitumor,[7h] and, in certain cases, growth regulating agents.[7i]

Although there is a report describing the isolation of (+)-protolichesterinic acid from *Cetraria islandica* and *Parmelia sinodensis*, the absolute stereochemistry of compounds in this class was later proved by synthesis to be (2*S*,3*R*) as shown in (−)-**1**. We have recently reported the synthesis of racemic **1a**–**1c** employing tandem aldol–lactonization reactions of dimethyl itaconate–anthracene adduct, (±)-**2**,[8] as the starting material and the process is outlined in Scheme 1. We now report the synthesis of both (−)-**1a**–**1c** and (+)-**1′a**–**1′c** by using optically pure (+)-**2** and (−)-**2′** as starting blocks.

2. Results and discussion

Enantiomerically pure (+)-**2** and (−)-**2′** were prepared by partial hydrolysis of (±)-**2** with KOH (1.3 equiv.) in MeOH:H_2O (2:1) followed by treatment of the resulting monoacid with (−)-(1*R*,2*S*,5*R*)-menthol in the presence of a catalytic amount of dimethylformamide in thionyl



R = **a** : *n*-C_5H_{11}-; Methylenolactocin
b : *n*-$C_{11}H_{23}$-; Nephrosterinic acid
c : *n*-$C_{13}H_{27}$-; Protolichesterinic acid

Figure 1.

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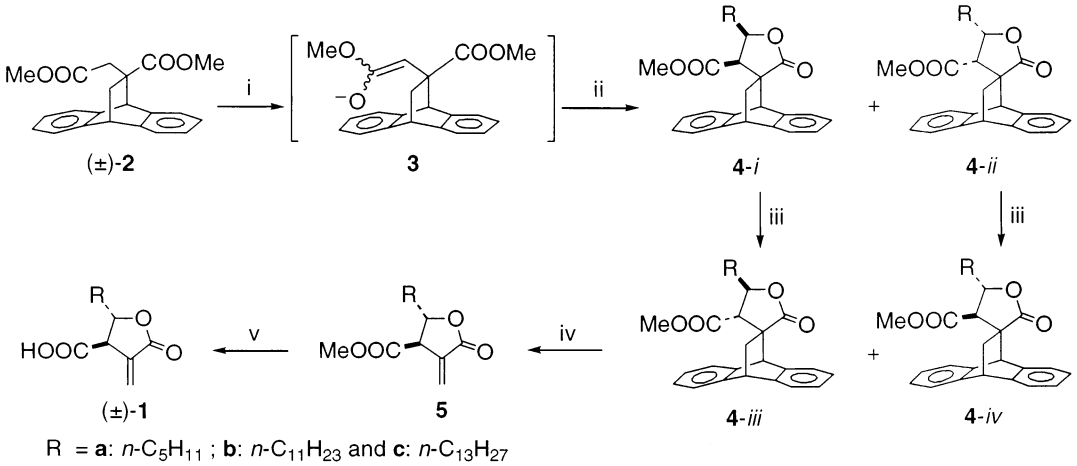


Scheme 1. *Reagents and conditions:* (i) (a) 1.2 equiv. LDA, THF, −78 to 0°C 2 h; (ii) (a) 1.2 equiv. RCHO, 0°C to rt 3 h, (b) aq. NH_4Cl, 30% HCl; (iii) 0.5 equiv. NaOMe, THF:MeOH (2:1), rt 6 days; (iv) FVP; (v) 2-butanone, 6N HCl, reflux 2 h.

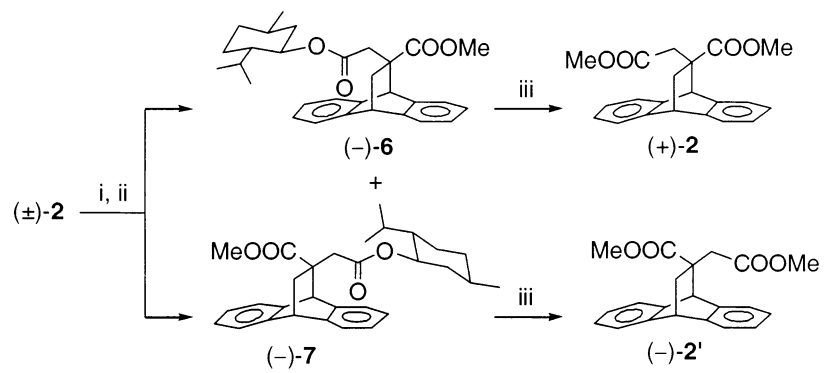
chloride solution to provide the crude diastereomeric mixture which upon purification by column chromatography (silica gel, using EtOAc:acetone:hexane = 0.5:0.3:9.2 as eluent) yielded almost pure (−)-**6** and (−)-**7**. Crystallization of (−)-**6** and (−)-**7**, respectively, from ethyl acetate–hexane and methanol gave pure (−)-**6** (34%), as a white powder (mp 185–187°C, >99% d.e.,[9] $[\alpha]_D^{30} = -109.0$ (*c*, 1.29, $CHCl_3$)) and (−)-**7** (34%), as white crystals (mp 101–103°C, >99% d.e.,[9] $[\alpha]_D^{30} = -51.4$ (*c*, 1.20, $CHCl_3$)) (Scheme 2). The absolute stereochemistry at the C(11) stereogenic center of (11*R*)-**7** (and hence (−)-**2′**) was determined by X-ray crystallographic analysis and its PLATON drawing is shown in Fig. 2.[10]

Due to the failure to obtain good quality crystals for X-ray analysis, (−)-**6** was converted to the corresponding lactone **8** via the tandem aldol–lactonization with capronaldehyde under the conditions previously reported.[8e] The spiro–lactone product, (−)-**8**, obtained as white crystals (mp 205–206°C (from dichloromethane/hexane), $[\alpha]_D^{31} = -179.5$ (*c*, 0.40, $CHCl_3$), 34% purified yield), was subjected to X-ray analysis and its absolute configuration was determined (Scheme 3, Fig. 3).[10] The X-ray result unequivocally established the (*S*)-absolute configuration at C(11) for (−)-**6**, and thus (+)-**2**.

Due to the low yield of the lactone **8** obtained from the tandem aldol–lactonization reactions of **6** as compared to that previously observed when the corresponding dimethyl ester (±)-**2** was employed, the mixed esters **6** and **7** were converted to their corresponding dimethyl ester adducts, (+)-**2** and (−)-**2′**, respectively.

Transmethylation of (−)-**6** and (−)-**7** was effected by refluxing their methanol solutions in the presence of catalytic sulfuric acid, followed by flash column chromatographic purification to yield, respectively homochiral (+)-**2** and (−)-**2′**, in 95% (>99% e.e.,[11] $[\alpha]_D^{29} = +38.7$ (*c*, 1.06, $CHCl_3$)) and 89% (>99% e.e.,[11] $[\alpha]_D^{29} = -39.0$ (*c*, 1.18, $CHCl_3$)), respectively (Scheme 2). The enantiomeric excesses of (+)-(11*S*)-**2** and (−)-(11*R*)-**2′** were determined by ^1H NMR using the chiral lanthanide shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]praseodymium(III), ($Pr(hfc)_3$).

The tandem aldol–lactonization of (+)-**2** with 1.2 equiv. of capronaldehyde was then carried out according to the published procedure[8e] to produce enantiomerically pure spiro–lactones, **4a**-*i*–**4a**-*iv*, in 19, 65, 7 and 2%, respectively. Also, (+)-**2** was allowed to react with



Scheme 2. *Reagents and conditions:* (i) 1.3 equiv. KOH, MeOH:H_2O (2:1), reflux 2 h, (97%); (ii) (a) 5.0 equiv. $SOCl_2$, DMF (cat.), N_2, reflux 2 h, (b) 1.3 equiv. (−)-(1*R*,2*S*,5*R*)-menthol, 1.3 equiv. NEt_3, benzene, reflux 2 h ((−)-**6**, 34%; (−)-**7**, 34%); (iii) excess anhydrous MeOH, H_2SO_4 (cat.), reflux 6 days ((+)-**2**, 95%; (−)-**2′**, 89%).

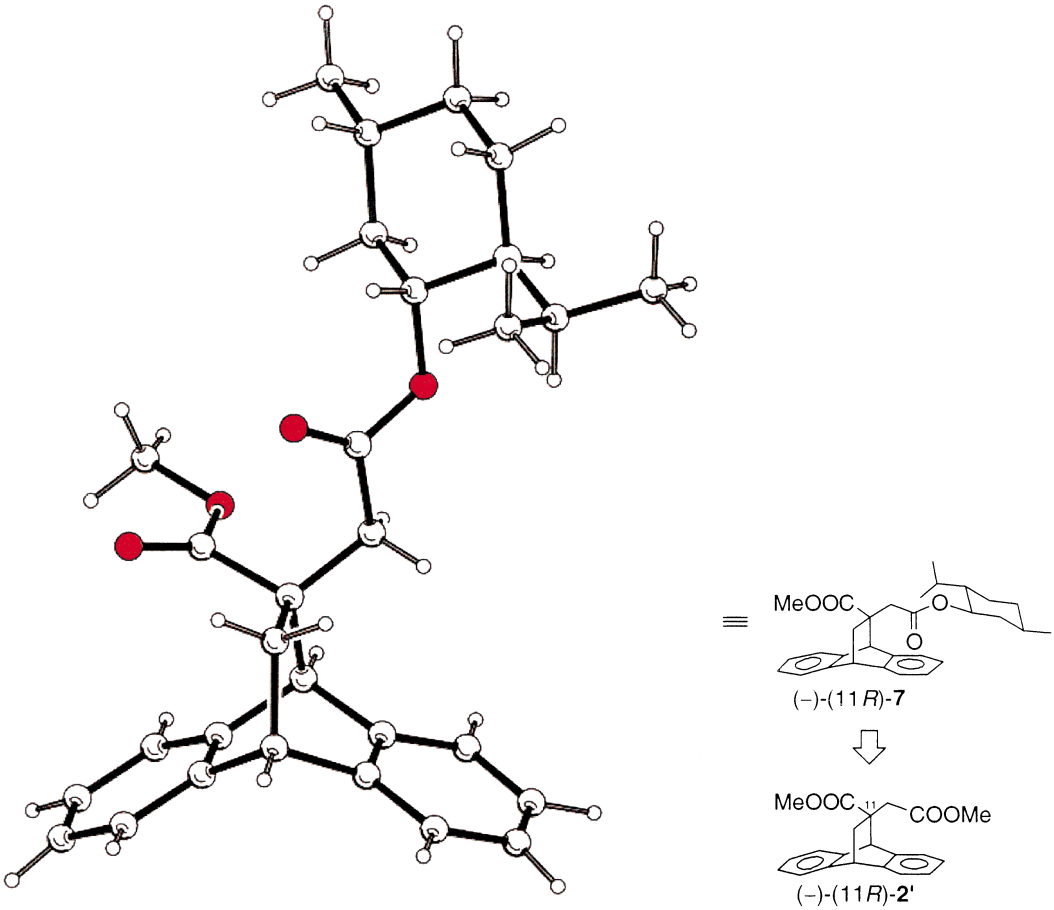
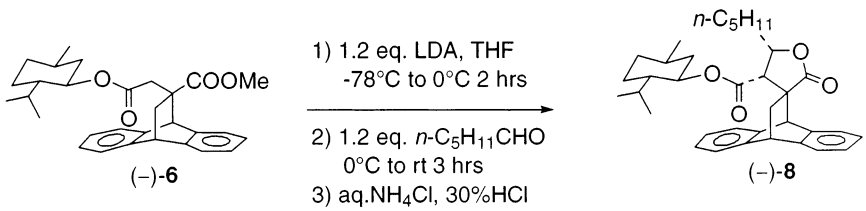


Figure 2. PLATON plot of (−)-(11*R*)-**7**.



Scheme 3.

n-dodecanal and *n*-tetradecanal to give **4b**-*i*–**4b**-*iv* (in 20, 63, 7 and 1%) and **4c**-*i*–**4c**-*iv* (in 18, 62, 7 and 2%), respectively whose results are shown in Table 1. Similar experiments were conducted with (−)-**2′** and results are summarized in Table 2.

The isomerization of the major products, *cis*-isomers, (−)-**4a**-*ii*–(−)-**4c**-*ii*, was affected by treatment with NaOMe (0.5 equiv.) in the solution of THF:MeOH (5:1) to furnish the required *trans*-(+)-**4a**-*iv*–(+)-**4c**-*iv* in good yields (Table 3). Similarly, (+)-**4′a**-*ii*, (+)-**4′b**-*ii* and (+)-**4′c**-*ii* gave (−)-**4′a**-*iv*, (−)-**4′b**-*iv* and (−)-**4′c**-*iv*, respectively and the results are displayed in Table 3.

Methyl esters of methylenolactocin, (2*S*,3*R*)-**5a**, nephrosterinic acid, (2*S*,3*R*)-**5b**, and protolichesterinic acid, (2*S*,3*R*)-**5c**, were obtained in 89, 77 and 75% yields, respectively upon flash vacuum pyrolysis of (+)-**4a**-*iv*, (+)-**4b**-*iv* and (+)-**4c**-*iv* (Table 4). Under the same conditions, (2*R*,3*S*)-**5′a**, (2*R*,3*S*)-**5′b** and (2*R*,3*S*)-**5′c** were obtained from (−)-**4′a**-*iv*, (−)-**4′b**-*iv* and (−)-**4′c**-*iv* (Table 4).

Subsequent hydrolysis of (2*S*,3*R*)-**5a** by refluxing in 2-butanone with a catalytic amount of conc. HCl afforded (−)-methylenolactocin, **1a** in 69% yield (mp 82–83°C, $[\alpha]_D^{29} = -11.6$ (*c*, 0.31 in $CHCl_3$) and $[\alpha]_D^{32} = -8.5$ (*c*, 0.31 in MeOH)). Hence, (−)-nephrosterinic acid, **1b**, (79%, mp 86–88°C, $[\alpha]_D^{32} = -10.9$ (*c*, 0.68 in $CHCl_3$) and $[\alpha]_D^{32} = -7.2$ (*c*, 0.39 in MeOH)) and (−)-protolichesterinic acid, **1c**, (70%, mp 101–103°C, $[\alpha]_D^{32} = -10.4$ (*c*, 0.46 in $CHCl_3$) and $[\alpha]_D^{31} = -8.9$ (*c*, 0.18 in MeOH)) were obtained (Table 5).

The syntheses of (+)-**1′a**, (+)-**1′b** and (+)-**1′c** were also achieved in the same manner (Table 5).

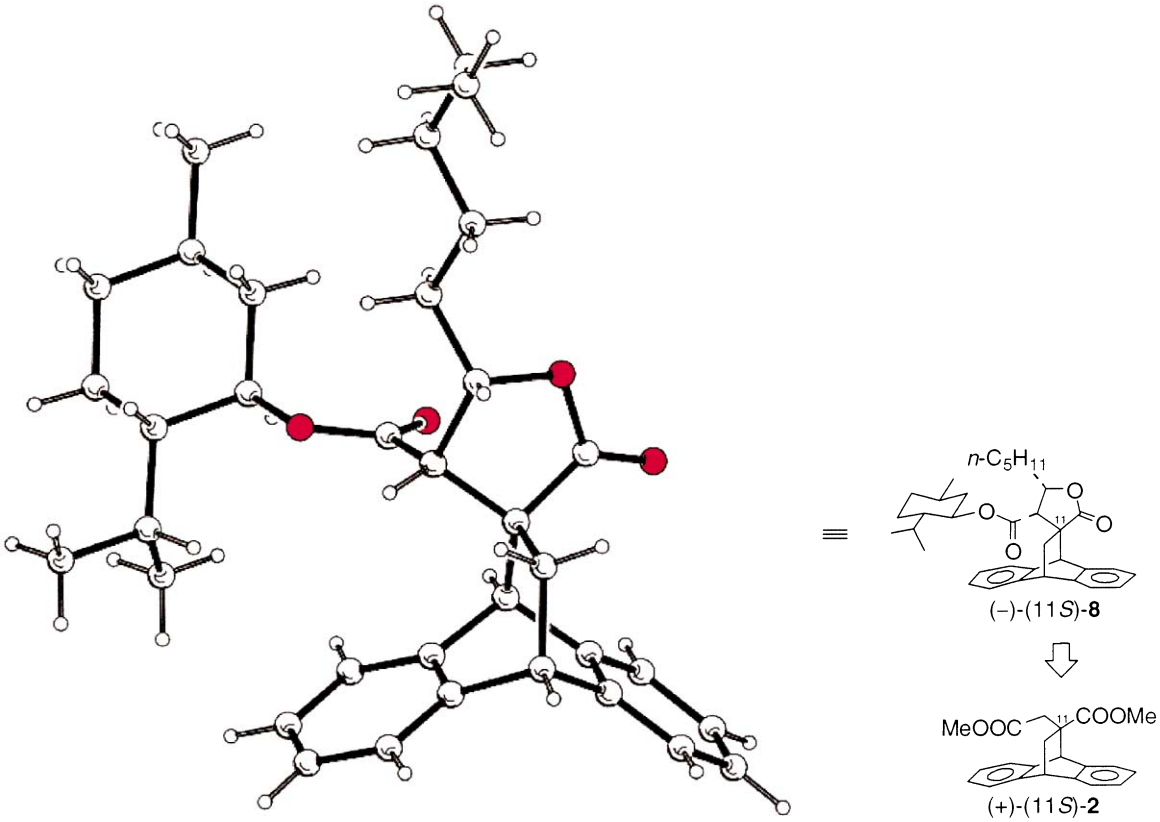
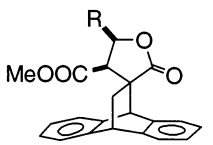
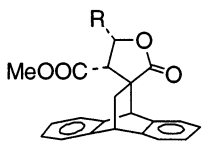
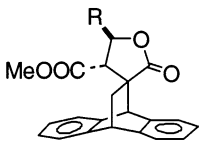


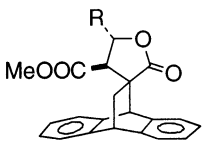
Figure 3. PLATON plot of (−)-(11*S*)-**8**.

Table 1. Yields of products, **4**-*i*–**4**-*iv*, from tandem aldol–lactonization reactions of (+)-**2**


(+)-(4′*R*,5′*R*,11*R*)-**4**-*i*


(−)-(4′*S*,5′*S*,11*R*)-**4**-*ii*


(+)-(4′*S*,5′*R*,11*R*)-**4**-*iii*


(+)-(4′*R*,5′*S*,11*R*)-**4**-*iv*

Entry	R	Enantiomeric spiro–lactone adducts, **4**-*i*–**4**-*iv*							
		i (%)	[α][a]	*ii* (%)	[α][a]	*iii* (%)	[α][a]	*iv* (%)	[α][a]
1	**a** *n*-C_5H_{11}	19	+94.2	65	–136.7	7	+61.2	2	+4.6
2	**b** *n*-$C_{11}H_{23}$	20	+78.5	63	–115.4	7	+53.8	1	+1.8
3	**c** *n*-$C_{13}H_{27}$	18	+73.1	62	–103.2	7	+48.5	2	+0.8

[a] The specific rotations were measured in $CHCl_3$.

3. Conclusion

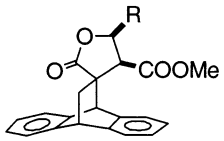
Enantiomerically pure dimethyl itaconate–anthracene adducts, (+)-(11*S*)-**2** and (−)-(11*R*)-**2**′, were obtained from resolution of the racemates which involved formation and separation of the mixed ester, **6** and **7**. Tandem aldol–lactonization reactions of (+)-(11*S*)-**2** and (−)-(11*R*)-**2**′ gave corresponding lactone–anthracene adducts, **4**, which upon pyrolysis provided **1a**–**1c** in enantiomerically pure form.

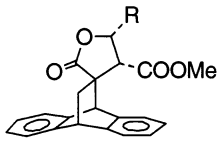
4. Experimental

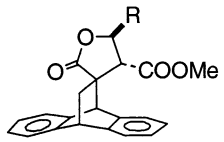
4.1. General methods

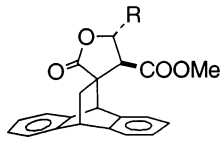
Melting points were determined using an Electrothermal Melting Point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker DPX 300 and 400 MHz spectrometers. All NMR spectra were measured in $CDCl_3$, and chemical shift are expressed in ppm relative to internal TMS. Infrared

Table 2. Yields of products, *ent*-(**4′**-*i*–**4′**-*iv*), from tandem aldol–lactonization reactions of (−)-**2′**


(−)-(4′*S*,5′*S*,11*S*)-**4′**-*i*


(+)-(4′*R*,5′*R*,11*S*)-**4′**-*ii*


(−)-(4′*R*,5′*S*,11*S*)-**4′**-*iii*


(−)-(4′*S*,5′*R*,11*S*)-**4′**-*iv*

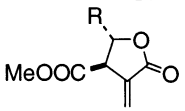
Entry	R	Enantiomeric spiro–lactone adducts, *ent*-(**4′**-*i*–**4′**-*iv*)							
		i (%)	[α][a]	*ii* (%)	[α][a]	*iii* (%)	[α][a]	*iv* (%)	[α][a]
1	**a** n-C_5H_{11}	20	−88.6	72	+134.9	6	−57.5	2	−4.3
2	**b** n-$C_{11}H_{23}$	16	−76.1	57	+117.1	4	−50.1	1	−1.5
3	**c** n-$C_{13}H_{27}$	27	−72.2	76	+107.3	7	−49.3	2	−0.5

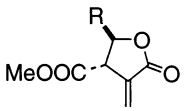
[a] The specific rotations were measured in $CHCl_3$.

Table 3. Yields of products, (+)-(4′*R*,5′*S*,11*R*)-**4**-*iv* and (−)-(4′*S*,5′*R*,11*S*)-**4′**-*iv*, from isomerization

Entry	R	(+)-(4′*R*,5′*S*,11*R*)-**4**-*iv* (%)	(−)-(4′*S*,5′*R*,11*S*)-**4′**-*iv* (%)
1	**a**: n-C_5H_{11}	84	65
2	**b**: n-$C_{11}H_{23}$	75	89
3	**c**: n-$C_{13}H_{27}$	79	83

Table 4. Yields of products, (2*S*,3*R*)-**5** and (2*R*,3*S*)-**5′**, from flash vacuum pyrolysis


(2*S*,3*R*)-**5**


(2*R*,3*S*)-**5′**

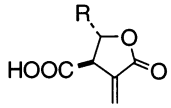
Entry	R	(2*S*,3*R*)-**5** (%)	(2*R*,3*S*)-**5′** (%)
1	**a**: n-C_5H_{11}	89	79
2	**b**: n-$C_{11}H_{23}$	77	78
3	**c**: n-$C_{13}H_{27}$	75	74

spectra were recorded on a FT-IR system 2000 (Perkin–Elmer) spectrometer. Elemental analyses were performed on a Perkin–Elmer Elemental Analyzer 2400 CHN and mass spectra were recorded on Bruker Esquire and Finnigan MAT INCOS 50 mass spectrometers. The electrospray-ion trap mass spectra were recorded on Bruker mass spectrometer and the electrospray-time of flight mass spectra was recorded on Perkin–Elmer (Mariner) mass spectrometer. Merck silica gel 60 PF_{254} was used for PLC, Merck silica gel 60 and Merck silica gel 60H were employed for the flash column chromatography. Solvents were distilled before use. Dried, oxygen-free THF (distilled from sodium/benzophenone) was used in all experiments. Lithium diisopropylamide (LDA) was prepared by the conventional method using *n*-butyllithium (purchased from Metallgesellschaft AG, molarity was determined by titration with 2,5-dimethoxybenzyl alcohol) and diisopropylamine in THF solution. Enantiomeric excesses were determined by ^1H NMR spectroscopy using the chiral lanthanide shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]praseodymium(III), $Pr(hfc)_3$.

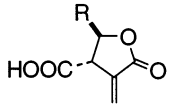
4.2. Resolution of optically active dimethyl itaconate–anthracene adduct, 2

4.2.1. (−)-11-Carbomethoxy-11-[(−)-menthoxyacetyl]-9,10-dihydro-9,10-ethanoanthracenes, (11*S*)-6 and (11*R*)-7. A solution of KOH (0.111 g, 1.98 mmol) in H_2O (15 mL) was added to a solution of (±)-dimethyl itaconate–anthracene adduct, **2** (0.555 g, 1.65 mmol), in MeOH (30 mL) and heated under reflux for 2 h. The cooled reaction mixture was diluted with water (15 mL) and acidified to pH 2–3 by 30% HCl, then extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was crystallized from CH_2Cl_2–hexane to give the corresponding (±)-monoacid (0.516 g, 97%) as white crystals; mp 207–208°C. A mixture of the monoacid (0.516 g, 1.60 mmol), thionyl chloride (0.7 mL, 9.60 mmol) and dimethyl formamide (as catalyst) was heated under reflux for 2 h and the solvent was removed under reduced pressure. The mixture of the acid chloride obtained, benzene (20 mL), triethylamine (0.3 mL, 1.92 mmol) and (−)-menthol (0.3002 g, 1.92 mmol) was heated under reflux for 2 h, filtered through Celite 545, diluted with H_2O and extracted with CH_2Cl_2. The solution was washed with H_2O, saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (silica gel) using EtOAc:acetone:hexane = 0.5:0.3:9.2 as eluent to give two diastereoisomers, (−)-**6** (0.252 g, 34%, >99% d.e.) as a white powder; mp 185–187°C and (−)-**7** (0.250 g, 34%, >99% d.e.) as a white crystalline solid; mp 101–103°C.

Table 5. Yields of products, (−)-(2*S*,3*R*)-**1** and (+)-(2*R*,3*S*)-**1′**, from hydrolysis



(−)-(2*S*,3*R*)-**1**



(+)-(2*R*,3*S*)-**1'**

Entry	R	(−)-(2*S*,3*R*)-**1**		(+)-(2*R*,3*S*)-**1′**	
		(%)	[α]	(%)	[α]
1	**a**: *n*-C_5H_{11}	69	$[\alpha]_D^{29}=-11.6$ (*c*, 0.31, in $CHCl_3$) $[\alpha]_D^{32}=-8.5$ (*c*, 0.31, in MeOH)	66	$[\alpha]_D^{30}=+16.6$ (*c*, 0.33, in $CHCl_3$) $[\alpha]_D^{32}=+7.4$ (*c*, 0.33, in MeOH)
2	**b**: *n*-$C_{11}H_{23}$	79	$[\alpha]_D^{32}=-10.9$ (*c*, 0.68, in $CHCl_3$) $[\alpha]_D^{32}=-7.2$ (*c*, 0.39, in MeOH)	81	$[\alpha]_D^{32}=+13.0$ (*c*, 0.66, in $CHCl_3$) $[\alpha]_D^{32}=+7.5$ (*c*, 0.43, in MeOH)
3	**c**: *n*-$C_{13}H_{27}$	70	$[\alpha]_D^{32}=-10.4$ (*c*, 0.46, in $CHCl_3$) $[\alpha]_D^{31}=-8.9$ (*c*, 0.18, in MeOH)	72	$[\alpha]_D^{32}=+11.2$ (*c*, 0.50, in $CHCl_3$) $[\alpha]_D^{31}=+10.0$ (*c*, 0.24, in MeOH)

Compound (11*S*)-**6**: White powder, mp 185–187°C (from EtOAc/hexane); $[\alpha]_D^{30}=-109.0$ (*c*, 1.29, $CHCl_3$). IR (KBr-pellet), ν_{max} 3072, 3038, 2949, 2866, 1729, 1460, 1432, 1371, 1220, 1198, 1167, 764, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (d, *J* 7.0 Hz, 3H), 0.76–1.93 (m, 9H), 0.88 (d, *J* 6.5 Hz, 1H), 0.89 (d, *J* 7.0 Hz, 3H), 1.51, 2.84, 4.35 (ABX system, *J* 13.0, 3.0, 2.4 Hz, 3H), 1.96 (d, *J* 16.2 Hz, 1H), 2.94 (d, *J* 16.2 Hz, 1H), 3.49 (s, 3H), 4.37 (s, 1H), 4.62 (ddd, *J* 10.9, 10.9, 4.4 Hz, 1H), 7.05–7.34 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 20.8, 22.0, 23.2, 34.2, 40.9, 26.0, 31.4, 37.1, 44.2, 45.0, 50.3, 52.1, 53.0, 74.7, 123.4, 123.6, 14.3, 125.8, 126.5, 126.6, 139.8, 140.2, 142.9, 143.8, 170.7, 174.8. *m*/*z* (EIMS) 460 (M^+, 0.1%), 322 (0.2), 215 (2), 202 (2), 178 (100), 322 (1). *m*/*z* (ESITOF-MS) 461.2686 $(M+H)^+$, calcd for $C_{30}H_{36}O_4$ 461.2692.

Compound (11*R*)-**7**: White crystals; mp 101–103°C (from methanol); $[\alpha]_D^{30}=-51.4$ (*c*, 1.20, $CHCl_3$). IR ($CHCl_3$), ν_{max} 3068, 3040, 3025, 2943, 2868, 1748, 1732, 1468, 1457, 1389, 1370, 1235, 1218, 1185, 766, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.70 (d, *J* 7.0 Hz, 3H), 0.77–1.94 (m, 9H), 0.86 (d, *J* 7.0 Hz, 3H), 0.90 (d, *J* 6.6 Hz, 3H), 1.47, 2.83, 4.34 (ABX system, *J* 13.0, 3.1, 2.3 Hz, 3H), 1.96 (d, *J* 15.8 Hz, 1H), 2.98 (d, *J* 15.8 Hz, 1H), 3.50 (s, 3H), 4.37 (s, 1H), 4.62 (ddd, *J* 10.9, 10.9, 4.4 Hz, 1H), 7.06–7.34 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 20.8, 22.0, 23.1, 34.2, 44.9, 25.9, 30.4, 36.7, 40.7, 44.2, 46.8, 50.5, 52.1, 53.0, 74.7, 123.3, 123.6, 124.2, 125.78, 125.82, 126.5, 126.7, 139.7, 140.3, 142.8, 143.8, 170.5, 174.8. *m*/*z* (EIMS) 460 (M^+, 1%), 215 (3), 202 (4), 178 (100). *m*/*z* (ESITOF-MS) 461.2697 $(M+H)^+$, calcd for $C_{30}H_{36}O_4$ 461.2692.

4.2.2. (11*S*)-11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethanoanthracene, (+)-2. To a solution of (−)-**6** (0.174 g, 0.38 mmol) in excess anhydrous MeOH (60 mL) was added conc. H_2SO_4 (1 mL) and the mixture was heated under reflux for 7 days. H_2O was added, and the mixture neutralized with aqueous $NaHCO_3$ solution, then extracted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was recrystallized from EtOAc/hexane to give optically active adduct, (+)-**2** (0.1210 g, 95% yield, >99% e.e.) as white crystals; mp 154–155°C; $[\alpha]_D^{29}=+38.7$ (*c*, 1.06, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8a]

4.2.3. (11*R*)-11-Carbomethoxy-11-methoxyacetyl-9,10-dihydro-9,10-ethanoanthracene, (−)-2′. Under the same conditions, the adduct (−)-**7** provided (−)-**2′** (89% yield, >99% e.e.) as white crystals; mp 154–155°C; $[\alpha]_D^{29}=-39.0$ (*c*, 1.18, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8a]

4.3. Preparation of optically pure tetrahydro-4′-carbomethoxy-5′-*n*-alkyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4-*i*–4-*iv*, from (+)-2

Typical procedure

4.3.1. Tetrahydro-4′-carbomethoxy-5′-*n*-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4a-*i*–4a-*iv*. A solution of (11*S*)-dimethyl itaconate–anthracene adduct, (+)-**2** (0.549 g, 1.63 mmol) in THF (15 mL) was introduced to the LDA solution (1.96 mmol in THF 5 mL, prepared by the standard method) at −78°C, then stirred at 0°C for 2 h. Freshly distilled capronaldehyde (0.24 mL, 1.96 mmol) was added to the anion solution at −78°C after which the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution at 0°C and the crude mixture was extracted several times with CH_2Cl_2. The dichloromethane solution was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and evaporated to dryness.

The crude product was purified by flash column chromatography (silica gel) using EtOAc:acetone:hexane = 1:0.5:8.5 as eluent to give enantiomeric spiro–lactones, *tetrahydro-4′-carbomethoxy-5′-n-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes*, **4a**-*i*–**4a**-*iv* in 19% (0.120 g), 65% (0.420 g), 7% (0.047 g) and 2% (0.011 g), respectively.

Compound (4′*R*,5′*R*,11*R*)-**4a**-*i*: White crystals, mp 144–146°C (from hexane); $[\alpha]_D^{31} = +94.2$ (*c*, 0.86, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*S*,11*R*)-**4a**-*ii*: White crystals, mp 210–212°C (from CH_2Cl_2–hexane); $[\alpha]_D^{28} = -136.7$ (*c*, 1.16, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*R*)-**4a**-*iii*: White crystals, mp 118–119°C (from hexane); $[\alpha]_D^{30} = +61.2$ (*c*, 0.92, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*R*)-**4a**-*iv*: White crystals, mp 83–85°C (from hexane); $[\alpha]_D^{30} = +4.6$ (*c*, 1.12, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.3.2. Tetrahydro-4′-carbomethoxy-5′-*n*-undecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4b-*i*–4b-*iv*. Compounds **4b**-*i*–**4b**-*iv* were obtained when laurinaldehyde was employed as in the *typical procedure* in Section 4.3.1.

Compound (4′*R*,5′*R*,11*R*)-**4b**-*i* (20%): White crystals, mp 94–95°C (from hexane); $[\alpha]_D^{31} = +78.5$ (*c*, 0.79, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*S*,11*R*)-**4b**-*ii* (63%): White crystals, mp 159–160°C (from CH_2Cl_2–hexane); $[\alpha]_D^{29} = -115.4$ (*c*, 0.66, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*R*)-**4b**-*iii* (7%): White crystals, mp 78–79°C (from hexane); $[\alpha]_D^{30} = +53.8$ (*c*, 0.71, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*R*)-**4b**-*iv* (1%): White crystals, mp 71–73°C (from hexane); $[\alpha]_D^{30} = +1.8$ (*c*, 0.66, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.3.3. Tetrahydro-4′-carbomethoxy-5′-*n*-tridecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4c-*i*–4c-*iv*. Four enantiomeric isomers, **4c**-*i*–**4c**-*iv* were obtained when *n*-tetradecanal was employed in the reaction mentioned above.

Compound (4′*R*,5′*R*,11*R*)-**4c**-*i* (18%): white crystals, mp 67–69°C (from hexane); $[\alpha]_D^{28} = +73.1$ (*c*, 1.20, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*S*,11*R*)-**4c**-*ii* (62%): White crystals, mp 165–166°C (from CH_2Cl_2–hexane); $[\alpha]_D^{30} = -103.2$ (*c*, 1.12, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*R*)-**4c**-*iii* (7%): White crystals, mp 84–85°C (from hexane); $[\alpha]_D^{29} = +48.5$ (*c*, 1.08, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*R*)-**4c**-*iv* (2%): White crystals, mp 86–87°C (from hexane); $[\alpha]_D^{30} = +0.8$ (*c*, 0.77, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.4. Preparation of optically pure tetrahydro-4′-carbomethoxy-5′-*n*-alkyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4′-*i*–4′-*iv*, from (−)-2′

4.4.1. Tetrahydro-4′-carbomethoxy-5′-*n*-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4′a-*i*–4′a-*iv*. Enantiomeric isomers, **4′a**-*i*–**4′a**-*iv* were obtained when capronaldehyde and (11*R*)-dimethyl itaconate–anthracene adduct, (−)-**2′** were employed as in the *typical procedure* in Section 4.3.1.

Compound (4′*S*,5′*S*,11*S*)-**4′a**-*i* (20%): White crystals; mp 144–146°C (from hexane); $[\alpha]_D^{32} = -88.6$ (*c*, 0.88, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*R*,11*S*)-**4′a**-*ii* (72%): White crystals; mp 210–212°C (from CH_2Cl_2–hexane); $[\alpha]_D^{29} = +134.9$ (*c*, 1.09, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*S*)-**4′a**-*iii* (6%): White crystals; mp 118–119°C (from hexane); $[\alpha]_D^{30} = -57.5$ (*c*, 1.03, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*S*)-**4′a**-*iv* (2%): White crystals; mp 83–85°C (from hexane); $[\alpha]_D^{30} = -4.3$ (*c*, 1.20, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.4.2. Tetrahydro-4′-carbomethoxy-5′-*n*-undecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4′b-*i*–4′b-*iv*. Compounds **4′b**-*i*–**4′b**-*iv* were obtained when laurinaldehyde was employed as in the *typical procedure* in Section 4.3.1.

Compound (4′*S*,5′*S*,11*S*)-**4′b**-*i* (16%): White crystals; mp 94–95°C (from hexane); $[\alpha]_D^{30} = -76.1$ (*c*, 0.62, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*R*,11*S*)-**4′b**-*ii* (57%): White crystals; mp 159–160°C (from CH_2Cl_2–hexane); $[\alpha]_D^{30} = +117.1$ (*c*, 0.61, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*S*)-**4′b**-*iii* (4%): White crystals; mp 78–79°C (from hexane); $[\alpha]_D^{30}=-50.1$ (*c*, 0.76, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*S*)-**4′b**-*iv* (1%): White crystals, mp 71–73°C (from hexane); $[\alpha]_D^{30}=-1.5$ (*c*, 0.66, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.4.3. Tetrahydro-4′-carbomethoxy-5′-*n*-tridecyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, 4′c-*i*–4′c-*iv*

Four enantiomeric isomers, **4′c**-*i*–**4′c**-*iv* were obtained when *n*-tetradecanal was employed in the reaction mentioned above.

Compound (4′*S*,5′*S*,11*S*)-**4′c**-*i* (27%): White crystals, mp 67–69°C (from hexane); $[\alpha]_D^{29}=-72.2$ (*c*, 1.97, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*R*,11*S*)-**4′c**-*ii* (76%): White crystals, mp 165–166°C (from CH_2Cl_2–hexane); $[\alpha]_D^{30}=+107.3$ (*c*, 1.06, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*R*,5′*S*,11*S*)-**4′c**-*iii* (7%): White crystals, mp 84–85°C (from hexane); $[\alpha]_D^{29}=-49.3$ (*c*, 1.06, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

Compound (4′*S*,5′*R*,11*S*)-**4′c**-*iv* (2%): White crystals, mp 86–87°C (from hexane); $[\alpha]_D^{31}=-0.5$ (*c*, 0.75, $CHCl_3$) whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published.[8e]

4.5. Base induced isomerization reactions of optically pure (4′*S*,5′*S*,11*R*)-tetrahydro-4′-carbomethoxy-5′-*n*-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, (−)-4a-*ii*

To a solution of the *cis*-adduct, (−)-**4a**-*ii* (2.9786 g, 7.36 mmol) in THF (200 mL) and MeOH (40 mL) was added at 0°C sodium methoxide solution (1.45N in anhydrous MeOH, 2.54 mL, 3.68 mmol) and the mixture was stirred at room temperature for 2 days. The reaction mixture was quenched with saturated NH_4Cl solution and extracted several times with CH_2Cl_2. The combined organic layer was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and evaporated to dryness. Purification by PLC (silica gel, using EtOAc:acetone:hexane = 1:0.5:8.5 as eluent) followed by crystallization from hexane provided *trans*-isomer, (+)-**4a**-*iv* (2.01 g, 84% yield).

Isomerization of (−)-**4b**-*ii* and (−)-**4c**-*ii* furnished (+)-**4b**-*iv* (75%) and (+)-**4c**-*iv* (79%), respectively, and, under the same reaction conditions, (+)-**4′a**-*ii*, (+)-**4′b**-*ii* and (+)-**4′c**-*ii* gave (−)-**4′a**-*ii*, (−)-**4′b**-*iv* and (−)-**4′c**-*iv*, in 65, 89 and 83% yields, respectively.

4.6. Flash vacuum pyrolysis of optically pure tetrahydro-4′-carbomethoxy-5′-*n*-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, (+)-4a-*iv*

Flash vacuum pyrolysis of (+)-**4a**-*iv* (*trans*-isomers) by the method previously described[8c] induced the retro Diels–Alder reaction to provide methylenolactocin methyl ester, (2*S*,3*R*)-**5a** ((0.377 g, 89% yield) as a colorless oil whose IR, ^1H, ^{13}C NMR and mass spectral data are identical to those previously published).[8e]

Flash vacuum pyrolysis of (+)-**4b**-*iv* and (+)-**4c**-*iv* provided the corresponding α-methylene-γ-butyrolactone, (2*S*,3*R*)-**5b** (77%) and (2*S*,3*R*)-**5c** (75%), respectively, and, under the same reaction conditions, (2*R*,3*S*)-**5′a**, (2*R*,3*S*)-**5′b** and (2*R*,3*S*)-**5′c** were obtained from (+)-**4′a**-*iv*, (+)-**4′b**-*iv* and (+)-**4′c**-*iv* in 79, 78 and 74% yields, respectively.

4.7. Hydrolysis of optically pure methyl tetrahydro-4-methylene-5-oxo-2-*n*-alkyl-3-furancarboxylates, (2*S*,3*R*)-5a–c and (2*R*,3*S*)-5′a–c

Typical procedure

4.7.1. (2*S*,3*R*)-Tetrahydro-4-methylene-5-oxo-2-*n*-pentyl-3-furancarboxylic acid [(−)-methylenolactocin], (−)-1a

Acid-catalyzed hydrolysis of (2*S*,3*R*)-**5a** (0.101 g, 0.45 mmol), performed according to the reported method[3d] using 6 M aqueous HCl in 2-butanone, provided methylenolactocin, (−)-**1a** (0.065 g, 69%), as white crystals, mp 82–83°C (from EtOAc/hexane); (lit.[3d] mp 82–83°C (EtOAc/hexane)); $[\alpha]_D^{32}=-8.5$ (*c*, 0.31, MeOH), $[\alpha]_D^{29}=-11.6$ (*c*, 0.31, $CHCl_3$); (lit. $[\alpha]_D^{25}=-2.4$ (*c*, 3.0, MeOH),[2b] $[\alpha]_D^{25}=-6.8$ (*c*, 0.5, MeOH),[2b] $[\alpha]_D^{25}=-6.8$ (*c*, 0.52, MeOH),[3g] $[\alpha]_D^{T}=-12.4$ (*c*, 0.5, MeOH)[3d]). ^1H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J* 6.9 Hz, 3H), 1.28–1.60 (m, 6H), 1.67–1.85 (m, 2H), 3.65 (ddd, *J* 5.6, 3.0, 2.7 Hz, 1H), 4.83 (ddd, *J* 7.2, 7.2, 5.6 Hz, 1H), 6.04 (d, *J* 2.7 Hz, 1H), 6.48 (d, *J* 3.0 Hz, 1H), 8.66 (broad peak, 1H), whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.2. (2*S*,3*R*)-Tetrahydro-4-methylene-5-oxo-2-*n*-undecyl-3-furancarboxylic acid [(−)-nephrosterinic acid], (−)-1b

Obtained as a white crystalline solid (EtOAc/hexane): mp 86–88°C; $[\alpha]_D^{32}=-7.2$ (*c*, 0.39, MeOH), $[\alpha]_D^{32}=-10.9$ (*c*, 0.68, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* 7.1 Hz 3H), 1.20–1.68 (m, 18H), 1.68–1.85 (m, 2H), 3.65 (ddd, *J* 5.5, 2.9, 2.5 Hz, 1H), 4.83 (ddd, *J* 6.9, 5.8, 5.5 Hz, 1H), 6.05 (d, *J* 2.5 Hz, 1H), 6.49 (d, *J* 2.9 Hz, 1H), 6.90 (broad peak, 1H), whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.3. (2*S*,3*R*)-Tetrahydro-4-methylene-5-oxo-2-*n*-tridecyl-3-furancarboxylic acid [(−)-protolichesterinic acid], (−)-1c

Obtained as a white crystalline solid (EtOAc/hexane): mp 101–103°C (lit.[6a] mp 103–105°C (EtOAc/hexane)); $[\alpha]_D^{31}=-8.9$ (*c*, 0.18, MeOH), $[\alpha]_D^{32}=-10.4$ (*c*, 0.46, $CHCl_3$), (lit.[6a] $[\alpha]_D^{25}=-15$ (*c*, 1.0, $CHCl_3$)). ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* 6.4 Hz, 3H), 1.20–1.65 (m, 22H), 1.65–1.85 (m, 2H), 3.65 (ddd, *J* 5.4,

2.9, 2.4 Hz, 1H), 4.83 (ddd, *J* 6.8, 5.9, 5.4 Hz, 1H), 6.04 (d, *J* 2.4 Hz, 1H), 6.49 (d, *J* 2.9 Hz, 1H), 7.15 (broad peak, 1H), whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.4. (2*R*,3*S*)-Tetrahydro-4-methylene-5-oxo-2-*n*-pentyl-3-furancarboxylic acid [(+)-methylenolactocin], (+)-1′a. Obtained as a white crystalline solid (EtOAc/hexane): mp 82–83°C (lit.[3d] mp 82–83°C (EtOAc/hexane)); $[\alpha]_D^{32}=+7.4$ (*c*, 0.33, MeOH), $[\alpha]_D^{30}=+16.6$ (*c*, 0.33, $CHCl_3$); (lit.[3e] $[\alpha]_D^{25}=+6.8$ (*c*, 0.51, MeOH) whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.5. (2*R*,3*S*)-Tetrahydro-4-methylene-5-oxo-2-*n*-undecyl-3-furancarboxylic acid [(+)-nephrosterinic acid], (+)-1′b. Obtained as a white crystalline solid (EtOAc/hexane): mp 86–88°C; $[\alpha]_D^{32}=+7.5$ (*c*, 0.43, MeOH), $[\alpha]_D^{32}=+13.0$ (*c*, 0.66, $CHCl_3$); (lit.[4] $[\alpha]_D^{T}=+10.8$) whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.6. (2*R*,3*S*)-Tetrahydro-4-methylene-5-oxo-2-*n*-tridecyl-3-furancarboxylic acid [(+)-protolichesterinic acid], (+)-1′c. Obtained as a white crystalline solid (EtOAc/hexane): mp 101–103°C (lit.[6a] mp 103–105°C (EtOAc/hexane)); $[\alpha]_D^{31}=+10.0$ (*c*, 0.24, CH_3OH), $[\alpha]_D^{32}=+11.2$ (*c*, 0.50, $CHCl_3$); (lit.[6b] $[\alpha]_D^{25}=+14.2$ (*c*, 0.95, $CHCl_3$)) whose spectroscopic data are identical in all respects to those reported.[8e]

4.7.7. (11*S*)-Tetrahydro-4′-carbomenthoxy-5′-*n*-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes, (−)-8. Using the *typical procedure* described in Section 4.7.1, capronaldehyde (0.28 mL, 2.27 mmol) was reacted with menthyl methyl itaconate–anthracene adduct, (−)-**6** (1.0011 g, 1.89 mmol) to give enantiomeric spiro–lactoness, *(4′R,5′R,11R)-tetrahydro-4′-carbomenthoxy-5′-n-pentyl-2′-furanone-3′-spiro-11-9,10-dihydro-9,10-ethanoanthracenes*, (−)-8 (0.346 g, 34%).

Compound (4′*R*,5′*R*,11*R*)-**8**: White crystals; mp 205–206°C (from hexane); $[\alpha]_D^{31}=-179.5$ (*c*, 0.40, $CHCl_3$). IR (KBr-pellet), ν_{max} 2989, 2931, 2872, 1783, 1722, 1460, 1371, 1176, 1137 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* 6.9 Hz, 3H), 0.92 (d, *J* 7.0 Hz, 3H), 0.96 (d, *J* 7.0 Hz, 3H), 0.99 (d, *J* 6.5 Hz, 3H), 1.00–1.81 (m, 15H), 1.98, 2.13, 4.40 (ABX system, *J* 12.4, 3.0, 2.4 Hz, 3H), 2.01 (m, 1H), 2.25 (d, *J* 4.9 Hz, 1H), 2.38 (m, 1H), 4.33 (m, 1H), 4.80 (s, 1H), 4.84 (ddd, *J* 10.8, 4.9, 4.4 Hz, 1H), 7.05–7.35 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 15.9, 21.1, 22.1, 22.4, 22.7, 25.1, 25.6, 31.2, 31.4, 31.5, 34.1, 40.6, 41.2, 43.8, 46.4, 46.7, 50.7, 58.1, 76.4, 77.0, 122.5, 123.8, 124.5, 125.85, 125.93, 126.1, 126.7, 127.5, 140.0, 140.9, 142.5, 143.1, 169.6, 176.8. *m/z* (ESITOF-MS) 529.3317 $(M+H)^+$, calcd for $C_{30}H_{36}O_4$ 529.3318.

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9. The diastereomeric excesses of (–)-**6** and (–)-**7** was determined by ^{1}H NMR spectroscopy.
10. Structures of compounds **6** and **8** have been confirmed by X-ray crystallography whose data have been deposited with the Cambridge Crystallographic Data Center and allocated the deposition numbers CCDC 163247 and CCDC 163248, respectively. Copies of the data can be obtained free of charge on application to The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK. (Fax: +44(0)-1223-336033; e-mail: deposit@ccdc.cam.ac.uk; Web site: http://www.ccdc.cam.ac.uk)
11. The enantiomeric excesses of (+)-**2** and (–)-**2′** were determined by ^{1}H NMR using chiral lanthanide shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]praseodym(III), (Pr(hfc)$_3$).