Synthesis of optically active derivatives of bicyclic chiral diols with C_2 symmetry

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Abstract

Efficient synthesis, besides other, of dibromide, diazide, diamine and diesters derived from (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**), a chiral bicyclic diol with C_2 symmetry, was developed. Esterification of **3** with saturated and unsaturated carboxylic acids and acids chlorides leads to the corresponding normal-, olefinic- and acetylenic diesters in average yields of 81%. Also more efficient techniques for the preparation of starting diol **3** in higher yields as well as for a very simple separation of DCU from reactions carried out following DCC/DMAP method are described.

Keywords

C_2 symmetry, 9,10-dihydro-9,10-ethanoanthracene, chiral ligands.

Introduction

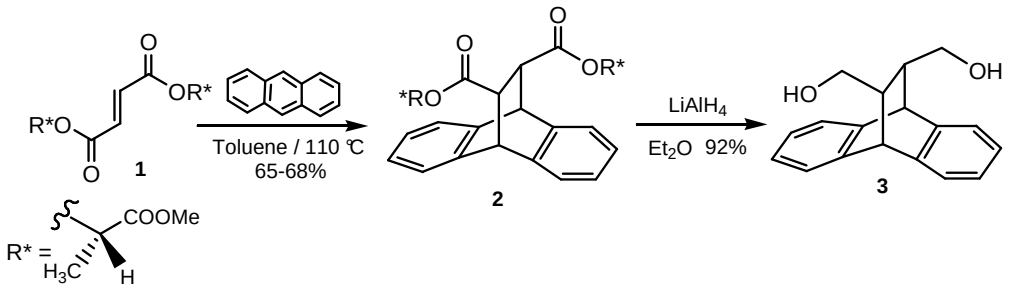
Chiral dihydroethano- and ethenoanthracene derivatives are versatile organic molecules with C_2 symmetry that have been used in synthetic and biological applications. They have also been used as chiral ligands in enantioselective reactions, attached to a metal as catalytically active species, and as chiral polymer´s precursors.[1,2] Derivatives of C_2-symmetric dicarboxylic acids are of interest since they can often be prepared on a large scale from easily available starting materials. The numerous routes from L-tartaric acid ilustrate this point well.[3] At present, we are interested in reactions that involve the use of C_2 symmetry substrates as precursors for the synthesis of optically active molecules with potential biological activity. Thus, we have reported the physical characteristics of a series of new TADDOL´s unsaturated esters [4a] and the use of these in the synthesis of macrolides via cyclohydrostanation reactions.[4b] In this context, we considered its convenient to synthesize a series of derivatives of the chiral diol (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**) and to study some reactions of them.

Results and Discussion

Diol **3** was prepared using a variation of a synthetic route which involved an asymmetric *carbo-Diels-Alder* reaction as the key step, as shown in Scheme 1.[5] The use of (*S*)-(-)-methyl lactate instead of the of (*S*)-(-)-ethyl lactate used initially and, specially, small variations in the experimental techniques enabled us to increase the global yield of the synthesis. Thus using fumarate **1** in a ratio **1**/anthracene = 1:3.5 (originally 1:5), after 4 days of reaction (6 in the original paper) diester **2** was obtained enantiomerically pure in yields of 65-68% after recristallyzation from ethyl

acetate/hexane (original paper 50-60%). Then, diester **2** was reduced with $LiAlH_4$ in boiling ether leading to the chiral diol **3** in a 92% yield of pure compound. It should be noted that the increase in the yield (in the original paper 75%) was achieved simply by increasing the amount of $LiAlH_4$.

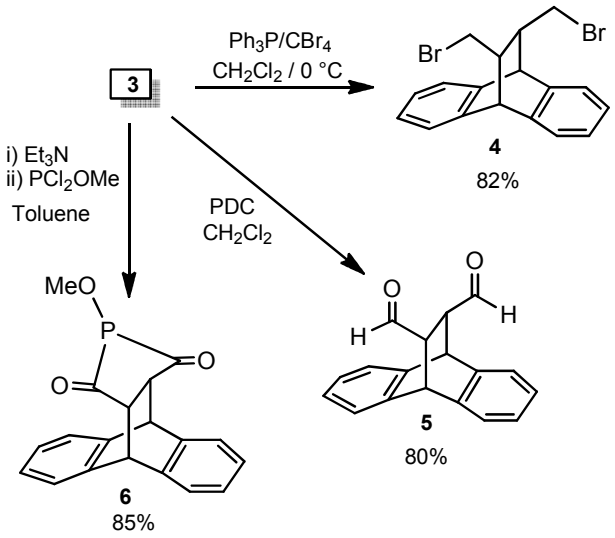
Scheme 1. Synthesis of bicyclic chiral diol **3**.



The reaction between diol **3** and carbon tetrabromide in the presence of triphenylphosphine, carried out in methylene dichloride at 0 ℃ leads to (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethylene dibromide (**4**) in 82% yield, as shown in Scheme 2.

Oxidation of diol **3** with pyridinium dichromate (PDC) in anhydrous methylene dichloride afforded the corresponding dialdehyde, (11*R*,12*R*)-9,10-dihydro-9,10-ethano anthracene-11,12-dicarbaldehyde (**5**), in 80% yield (Scheme 2). Similarly, the reaction of **3** with dichloromethoxyphosphine in the presence of anhydrous triethylamine in toluene leads to phosphatricyclodione **6** in 85% yield.

Scheme 2. Synthesis of new derivatives **4**-**6** starting from diol **3**.

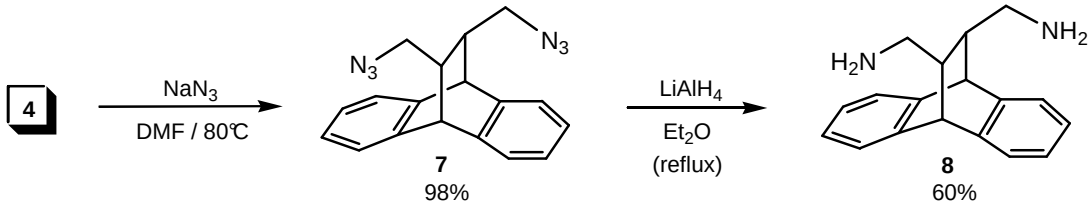


We then attempted the synthesis of diamine **8** *via* the reaction between chiral dibromide **4** and potassium phthalimid (Gabriel synthesis). This reaction was carried out at r.t., 50 ℃, 80 ℃ and at 130 ℃ without suc cess.

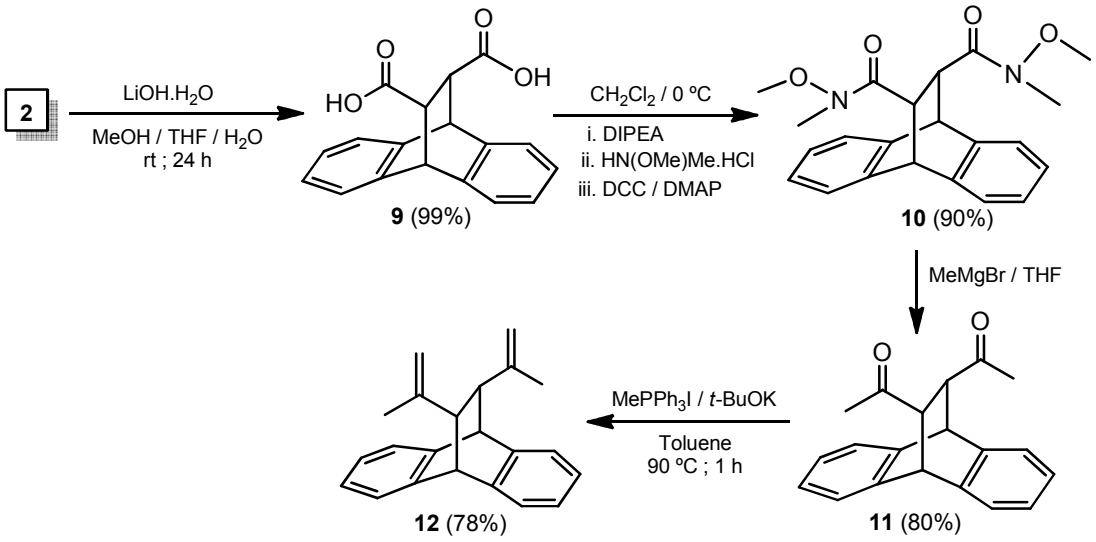
In order to synthesize diamine **8**, first diazide **7** [6] was prepared in excellent yield *via* the reaction between chiral diol **4** and sodium azide in dry dimethylformamide (DMF) at 80

℃. Then, the reduction of **7** carried out with $LiAlH_4$ in refluxing ether gave (11*R*,12*R*)-diamine **8** in good yield (60%). Diamine **8** was previously obtained by another procedure mediated by resolution of the brucine salt of the carboxylic acid precursor and was tested as chemosensitizers against chloroquine resistant *Plasmodium falciparum*, responsible for Malaria´s disease.[7]

Scheme 3. Synthesis of chiral diamine **8** *via* diazide **7**.



As shown in Scheme 4, starting from diester **2** we were able to obtain a secuence of interesting optically actives functionalizated derivatives following adaptations of the Fürstner´s procedures.[8] Thus, hydrolisis of diester **2** with LiOH in MeOH/THF/H_2O at room temperature leads to the diacid **9** almost cuantitatively and without further purification, was treated with DIPEA, HN(OMe)Me, DCC and DMAP in CH_2Cl_2 to yield 90% of (11*R*,12*R*)-dicarboxamide **10** after chromatography. Further treatment with MeMgBr in THF at 0 ℃ lead to the corresponding (11 *R*,12*R*)-diketone **11** in 80% yield after chromatography. Treatment of **11** with $MePPh_3I$ and *t*-BuOK gave the (11*R*,12*R*)-diolefinic derivative **12** in 78% yield after heating one hour in toluene (Scheme 4).



Scheme 4. Synthesis of optically active derivatives **10**-**12** starting from diester **2**.

We also report here the synthesis of saturated and unsaturated diesters with C_2 symmetry derived from diol **3**. In this case, we have found just one reference on the synthesis of the corresponding (11*R*,12*R*)-dimethacrylate **17**.[2] It should be noted that ester **17** has been used in studies connected with the synthesis of optically active polymers. We first studied the esterification of benzoic and phenylacetic acids with **3** using *N,N´*-dicyclohexylcarbodiimide (DCC)/4-(*N,N*-dimethylamino)pyridine (DMAP)

method (Method A, Scheme 5). The separation of N,N´-dicyclohexylurea (DCU) and some unreacted **3** was carried out by percolation of the crude reaction mixture through a fritted Büchner funnel containing two layers of about 1 cm deep each: the lower of silica gel and the upper layer of celite. As shown in Scheme 5, both esters, i.e., dibenzoate **13** and diphenylethanoate **14** were obtained in excellent yields as only products of these reactions. Similar yields were obtained starting from the corresponding acid chlorides (Method B) (Table 1).

Scheme 5. Synthesis of Saturated Diesters **13**-**14**

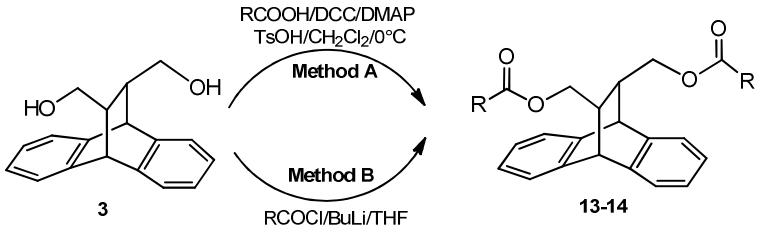


Table 1. Yields of Saturated Diesters **13**-**14**

Nº Compound	R	Method[a]	yield(%)[b]
13	Ph	A	98
		B	90
14	CH_2-Ph	A	85
		B	81

[a] Method A: acid + DCC/DMAP/TsOH in CH_2Cl_2 at 0 ºC, Method B: acid chloride + BuLi in THF. [b] Isolated yields are reported.

Taking into account these results, then we studied the synthesis of unsaturated esters of **3** by means of the DCC/DMAP method (Scheme 6). Reactions were carried out by mixing diol **3** in dry CH_2Cl_2 with DCC, *p*-toluensulphonic acid (TsOH) and DMAP, then adding the unsaturated acids to the mixture at 0 ºC. After 12 hs at r.t. the crude products were purified as above.

On the other hand, using the reaction between diol **3** and the corresponding α,β–unsaturated acyl chlorides at 0 ºC in the presence of *n*-butyllithium (BuLi) we succeded in obtaining the corresponding (11*R*,12*R*)-diesters according to Scheme 6 in good to excellent yields. These reactions lead in all cases to the corresponding diesters as only products. The global average yield of these reactions, after purification, was around 83% (Table 2)

We also investigated the synthesis of unsaturated esters of diol **3** through the reaction between (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethylene dibromide (**4**) and the silver salts of the unsaturated acids, as shown in Scheme 6. These reactions were carried out in toluene under reflux. Unfortunately all the attempts made were unsuccessful and compound **4** was quantitatively recovered in all cases.

Scheme 6. Synthesis of Olefinic Diesters **15**-**22**

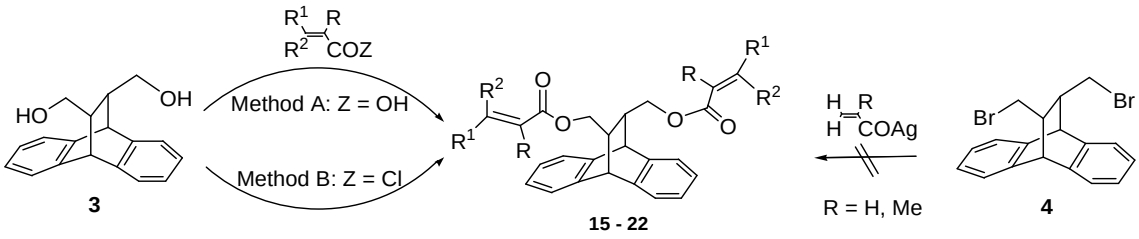


Table 2. Yields of Unsaturated Diesters **15**-**22**

Nº Compound	R	R^1	R^2	Method A[a] yield (%)[b]	Method B[a] yield (%)[b]
15	H	Ph	H	80	91
16[c]	H	Me	H	-	94
17	Me	H	H	76	72
18	Me	Ph	H	65	94
19	Ph	Ph	H	70	75
20	Me	Me	H	63	76
21[c]	H	H	H	-	70
22	H	Me	Me	85	89

[a] See Table 1. [b] Isolated yields are reported. [c] These compounds could not be obtained by Method A.

Finally, we studied the esterification of propyn-, octyn- and phenylpropyonic acids with diol **3** using Method A as shown in Scheme 7.

Scheme 7. Synthesis of Acetylenic Diesters **23**-**25**

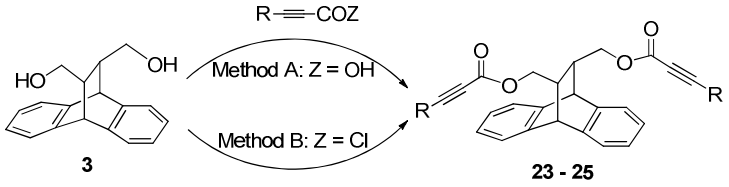


Table 3. Yields of Acetylenic Diesters **23-25**

Nº Compound	R	Method[a]	yield (%)[b]
23	H	A	85[c]
24	Ph	A	87
		B	80
25	*n*-Pent[d]	A	90
		B	75

[a] See Table 1. [b] Isolated yields are reported. [c] From ^{1}H NMR; compound **23** could not be isolated. [d] n-Pent = $CH_2(CH_2)_3CH_3$

These reactions were carried out as described above for the case of substituted propenoic acids. As shown in Scheme 6, the reactions lead in all cases to the corresponding (11*R*,12*R*)-acetylenic diesters of **3** as only products. It should be noted that in the case of esterification with propynoic acid we were unable to isolate pure diester **23** due to decomposition on purification. The new unsaturated esters were obtained in an average yield of 86%. The esterification using Method B lead to the corresponding diesters **24** and **25** in high yields, as shown in Table 3. All attempts to obtain similar acetylenic esters in the case of TADDOL were unsuccessful.

From a synthetic point of view this study shows that the esterification of normal and unsaturated carboxylic acids with chiral diol (11*R*,12*R*)-9,10-dihydro-9,10-ethano anthracene-11,12-dimethanol (**3**) can be carried out efficiently using both, the DCC/DMAP method and the reaction with the acid chloride derived from the same carboxylic acid. Both methods lead to the corresponding new (except **17**) diesters in high yield and could be considered complementary in that those esterifications which cannot be carried out by Method A are successful with Method B. Also more efficient techniques for the preparation of diol **3** in higher yield as well as for a very simple separation of DCU and unreacted **3** from the reactions carried out following Method A are described. Besides an efficient procedure for the preparation of new optically active functional derivatives **4**-**6**, **10**-**16** and **18**-**25** is reported.

Experimental Procedure

General Methods

4.2 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methanol (3).

4.2.1 Bis[(*S*)-1-methyloxycarbonylethyl]-(11*R*,12*R*)-9,10-dihydro-9,10-ethano anthracene-11,12-dicarboxylate (2).

The reaction between the fumarate of (*S*)-methyl lactate (**1**)[5] and anthracene was carried out according to ref. 5 in toluene at 110 ºC. The following variations of the original technique were performed: ratio **1**/anthracene = 1:3.5 (original paper 1:5); reaction time 4 days (originally 6 days). Under these reaction conditions, diastereomerically pure compound **2** was obtained in 60-68% yield (original paper 50-60%) by recrystallization from ethyl acetate/hexane.

4.2.2 Reduction of 2.

To a suspension of $LiAlH_4$ (4.07 g, 107.18 mmol) in dry diethyl ether (125 mL), under atmosphere of argon and at room temperature, was added dropwise a solution of diester **2** (10.0 g, 21.44 mmol) in dry diethyl ether (100 mL) with vigorous stirring. The mixture was heated under reflux for 1 h and then was stirred at room temperature for 3 h, cooled down to 0 ºC and water (60 mL) was added dropwise with stirring. After acidifying with 1 N HCl, the aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed with a sat. NaCl solution and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 50:50) to give **3** (5.26 g, 19.73 mmol, 92% yield) as a white powder, m.p.: 123-125 ºC.

4.3 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methylene dibromide (4).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethano anthracene-11,12-dimethanol (**3**) (1.00 g, 3.75 mmol) in dry CH_2Cl_2 (15 mL) under argon, was added CBr_4 (3.11 g, 9.38 mmol) and the mixture was stirred vigorously 15 min at r.t.. The mixture was cooled down to 0 ºC and Ph_3P (2.95 g, 11.26 mmol) was added. Then the reaction mixture was left 3 h at r.t. The solvent was distilled off under reduced pressure and the white residue was purified by percolation through silica gel 60 (hexane-Et_2O, 90:10) to give **4** (1.21 g, 3.08 mmol, 82%) as a white powder; m.p.: 170-172 ºC; $[\alpha]_D^{23}$ -4.8 (*c* 0.30, CH_2Cl_2); ^{1}H NMR (300 MHz,$CDCl_3$) δ_H 1.67-1.82 (m, 2H), 2.75 (dd, 2H, ^3J = 8.7 Hz, ^2J = 10.5 Hz), 3.13 (dd, 2H, ^3J = 5.6 Hz, ^2J = 10.5 Hz), 4.73 (s, 2H), 6.99-7.33 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 36.76, 47.86, 49.20, 124.36, 125.93, 126.67, 126.98, 139.99, 142.76 ppm; IR (KBr) *ν*: 3064, 3037, 3021, 2971, 2897, 2847, 1456, 1231, 1021, 753, 551 cm^{-1}; MS: *m/z* (%) 392 (10), 314 (11), 313 (55), 312 (11), 311 (55), 259 (9), 257 (9), 178 (100), 152 (5), 53 (28); HRMS (ESI) *m/z* calcd for $C_{18}H_{16}Br_2$ $[M]^{+\cdot}$ 389.9619, found: 389.962.

4.4 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di carbaldehyde (5).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**) (0.10 g, 0.37 mmol) in dry CH_2Cl_2 (10 mL) under argon, was added PDC (1.125 g, 3 mmol) and the mixture was stirred vigorously 12 h at r.t.. The solvent was distilled off under reduced pressure and the white residue was purified by percolation through silica gel 60 (hexane-EtAcO, 70:30) to give **5** (0.08 g, 0.30 mmol, 80%) as a white powder; m.p.: 132-134 ºC; $[\alpha]_D^{23}$ -5.3 (*c* 1.00, CH_2Cl_2); IR (KBr) *ν*: 3010, 2990, 2987, 2930, 2864, 2783, 1953, 1910, 1736, 1452, 1416, 1280, 1234, 1020, 803, 752, 703, 653 cm^{-1}.

4.5 Synthesis of 13-methoxyphospholane-(11*R*,12*R*)-9,10-dihydro-9,10-ethano anthracene-11,12-dione (6).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**) (0.20 g, 0.75 mmol) in dry toluene (5 mL) under argon was added triethylamine (0.22 mL, 0.16 g, 1.58 mmol). The mixture was stirring for 20 minutes and then a solution of PCl_2OMe (0.08 mL, 0.11 g, 0.83 mmol) in dry ethyl ether (2 mL) was added. After 5 h of vigorously stirring the solvent was distilled off under reduced pressure and the white residue was purified by percolation through silica gel 60 (CH_2Cl_2-MeOH, 90:10) to give **6** (0.205 g, 0.64 mmol, 85%) as a white powder; m.p.: 90-92 ºC. ^{31}P-RMN (D_2O): 7.38.

4.6 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methanazide (7).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethylene dibromide (**4**) (0.20 g, 0.51 mmol) in dry DMF under argon, was added NaN_3 (0.10 g, 1.53 mmol). The mixture was heated at 80 ºC during 4 h and then was warmed it up to r.t.. After quenching with water (5 mL), the organic layer was separated and the

aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were washed once with sat. NaCl solution and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give **7** (0.16 g, 0.50 mmol, 98%) as a yellowish solid, m.p.: 88-90 ºC; $[\alpha]_D^{23}$ -20.4 (*c* 1.02, CH_2Cl_2) which can be used without further purification.

4.7 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methanamine (8).

To a suspension of $LiAlH_4$ (0.17 g, 4.48 mmol) in dry diethyl ether (5 mL), under atmosphere of argon and at room temperature, was added a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanazide (**7**) (0.14 g, 0.44 mmol) in dry diethyl ether (5 mL) dropwise and with vigorous stirring. The mixture was heated under reflux for 2 h and then stirred at room temperature for 8 h. After cooling down to 0 ºC water (5 mL) was added dropwise with stirring. The organic layer was was washed once with HCl 10% (10 mL) and water (10 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 50:50) to give **8** (0.07 g, 0.26 mmol, 60%) as a white solid.

4.8 Synthesis of (11*R*,12*R*)-9,10-dihydro-*N,N*-dimethyl-*N´,N´*-dimethoxy-9,10-ethanoanthracene-11,12-dicarboxamide (10).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (**9**) (0.128 g, 0.44 mmoles) in dry CH_2Cl_2 (10 mL) under argon and at 0 ºC, was consecutively added DIPEA (0.18 mL, 0.13 g, 1.05 mmol), HN(OMe)Me (0.10 g, 1.05 mmol), DCC (0.19 g, 0.91 mmol) and DMAP (0.05 g, 0.37 mmol). The mixture was stirring for 2 h at 0 ºC then was warmed up to r.t and then was left with stirring during 12 h. After quenching with water (5 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-EtAcO, 90:10) to give **10** (0.15 g, 0.39 mmol, 90%) as a white powder; m.p.: 165-167 ºC; $[\alpha]_D^{23}$ -120.3 (*c* 2.00, dioxane); IR (KBr) *ν*: 3066, 3034, 2964, 2898, 1950, 1911, 1689, 1452, 1418, 1233, 1021, 804, 752, 652 cm^{-1}.

4.9 Synthesis of (11*R*,12*R*)-11,12-diacetyl-9,10-dihydro-9,10-ethanoanthracene (11).

To a solution of (11*R*,12*R*)-9,10-dihydro-*N,N*-dimethyl-*N´*,*N´*-dimethoxy-9,10-ethano anthracene-11,12-dicarboxamide (**10**) (0.128 g, 0.44 mmoles) in dry THF (6 mL) under argon the mixture was cooled down to 0 ºC, then a solution 3M of MgMeBr (0.70 mL, 0.26 g, 2.19 mmol) in dry diethyl ether was added. The mixture was stirring for 15 min at 0 ºC then was warmed up to r.t. After quenching with NH_4Cl (5 mL), the organic layer was separated and the aqueous layer was extracted with EtAcO (5 x 10 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-EtAcO, 60:40) to give **11** (0.08 g, 0.29 mmol,

80%) as a white powder; m.p.: 160-162 ºC; $[\alpha]_D^{23}$ -15.3 (*c* 1.02, CH_2Cl_2); IR (KBr) *ν*: 3025, 2955, 1740, 1454, 1171, 1095, 1042, 763, 751 cm^{-1}.

4.10 Synthesis of (11*R*,12*R*)-9,10-dihydro-11,12-diisopropenyl-9,10-ethano anthracene (12).

To a solution of MePPh3I (3.04 g, 7.52 mmol) in dry toluene (30 mL) under argon was added K^{t}BuO (0.78 g, 7.0 mmol) and heated 30 min at 90 ºC. The mixture was warmed up to r.t. and then a solution of (11*R*,12*R*)-11,12-diacetyl-9,10-dihydro-9,10-ethano anthracene (**11**) (0.16 g, 0.54 mmoles) in dry toluene (15 mL) was added. After 15 min the mixture was heated 1 h at 90 ºC. After quenching with water (40 mL), the organic layer was separated and the aqueous layer was extracted with hexane-Et_2O (70:30, 2 x 20 mL). The combined organic extracts were washed once with H_2O and sat. NaCl solution, and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-EtAcO, 60:40) to give **12** (0.12 g, 0.42 mmol, 78%) as a yellowish oil; $[\alpha]_D^{23}$ -10.3 (*c* 1.01, CH_2Cl_2); IR (film) *ν*: 3067, 3021, 2945, 1637, 1615, 1461, 1406, 1187, 1058, 987, 813, 756 cm^{-1}.

4.11 Esterifications of 3.

Method A:

ratio **(3)**/carboxylic acid/DCC/DMAP/TsOH **=** 1.0:2.2:3.1:0.4:0.4

Method B:

ratio **(3)**/BuLi/acyl chloride = 1.0:2.4:3.0

4.11.1 Method A – Typical Procedure: Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethyl bis(benzoate) (13).

To a solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**) (0,25 g, 0,94 mmoles) in dry CH_2Cl_2 (10 mL) under argon and at r.t., was consecutively added DCC (0.60 g, 2.91 mmol), *p*-toluenesulphonic acid (TsOH) (0.06 g, 0.37 mmol) and DMAP (0.05 g, 0.37 mmol). After 15 min stirring, the mixture was cooled down to 0 ºC and a solution of benzoic acid (0.25 g, 2.06 mmol) in dry CH_2Cl_2 (5 mL) was slowly added. The mixture was warmed up to r.t. and then was left with stirring during 12 h. The separation of DCU and some unreacted **3** was carried out by percolation of the crude reaction mixture through a fritted Büchner funnel containing two layers of about 1 cm deep each: the lower of silica gel and the upper of celite. The layers were washed with CH_2Cl_2 (3 x 5 mL). The solvent of the combined filtrates was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 80:20) to give **13** (0.44 g, 0.93 mmol, 98%) as a white powder; m.p.: 58-60 ºC; $[\alpha]_D^{23}$ -11.2 (*c* 1.01, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.87-2.00 (m, 2H), 3.80 (dd, 2H, ^3J = 8.2 Hz, ^2J = 11.1 Hz), 4.06 (dd, 2H, ^3J = 5.3 Hz, ^2J = 11.1 Hz), 4.27 (s, 2H), 6.94-7.50 (m, 8H), 7.86-8.01 (m, 10H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 43.06, 46.65, 67.59, 124.04, 125.93, 126.79, 128.87, 130.19, 133.40, 140.73, 143.56, 166.81 ppm; IR (film) *ν*: 3068, 3037, 3021, 2948, 2893, 1720, 1600, 1448, 1274, 1114, 1072, 1025, 909, 757, 707 cm^{-1}; MS: *m/z*

(%) 474 (29), 352 (13), 230 (12), 215 (17), 202 (15), 178 (100), 152 (20), 105 (98), 77 (83), 51 (24); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{26}O_4$ $[M]^{+\cdot}$ 474.1831, found: 474.183.

4.11.2 Method B – Typical Procedure: Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethyl bis(phenylethanoate) (14).

A solution of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**3**) (0.25 g, 0.94 mmol) in dry THF (10 mL) was cooled to 0 ºC under argon. Then, a 1.35 M solution of *n*-BuLi in hexane (1.70 mL, 2.25 mmol) was added slowly with a syringe. The mixture was stirred at r.t. for 30 min and then cooled to 0 ºC and phenylacetyl chloride (0.44 g, 2.84 mmol) was then added slowly. A white precipitate (LiCl) formed immediately. The mixture was refluxed for 1 h and then stirred 12 h at r.t. After quenching with a saturated solution of $NaHCO_3$ (ca. 20 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed once with H_2O and sat. NaCl solution, and then dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 85:15) to give **14** (0.38 g, 0.76 mmol, 81%) as a yellowish oil; $[\alpha]_D^{23}$ -22.1 (*c* 1.04, CH_2Cl_2); ^{1}H NMR (300 MHz,$CDCl_3$) δ_H 1.40-1.62 (m, 2H), 3.39 (dd, 2H, ^3J = 8.7 Hz, ^2J = 11.1Hz), 3.54 (s, 4H), 3.69 (dd, 2H, ^3J = 5.5 Hz, ^2J = 11.1 Hz), 3.91 (s, 2H), 6.91-7.34 (m, 18H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.02, 42.59, 45.99, 67.26, 123.87, 125.80, 126.42, 126.66, 127.64, 129.11, 129.73, 134.62, 140.43, 143.22, 171.52 ppm; IR (neat) *ν*: 3060, 3025, 2944, 1740, 1495, 1456, 1254, 1142, 1006, 761, 719, 691 cm^{-1}; MS: *m/z* (%) 502 (4), 215 (5), 202 (5), 178 (100), 152 (5), 118 (4), 91 (83), 65 (10); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{30}O_4$ $[M]^{+\cdot}$ 502.2144, found: 502.214.

4.11.3 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-3-phenylpropenoate) (15).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 80:20) to give **15** (0.95 g, 1.8 mmol, 91%) as a white solid, m.p.: 60-62 ºC; $[\alpha]_D^{23}$ +18.7 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (300 MHz,$CDCl_3$) δ_H 1.78-1.88 (m, 2H), 3.72 (dd, 2H, ^3J = 8.1 Hz, ^2J = 11.5 Hz), 3.90 (dd, 2H, ^3J = 5.4 Hz, ^2J = 11.5 Hz), 4.23 (s, 2H), 6.38 (d, 2H, ^3J = 16.0 Hz), 6.99-7.51 (m, 18H), 7.60 (d, 2H, ^3J = 16.0 Hz) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 41.56, 45.07, 65.89, 116.88, 122.51, 124.51, 125.30, 126.08, 127.14, 127.88, 129.30, 133.39, 139.31, 141.95, 144.12, 165.65 ppm; IR (film) *ν*: 3060, 3021, 2944, 2889, 1709, 1639, 1448, 1305, 1169, 765, 734 cm^{-1}; MS: *m/z* (%) 526 (13), 498 (20), 378 (33), 348 (20), 230 (18), 215 (12), 202 (11), 178 (100), 152 (11), 131 (93), 103 (83), 77 (46), 51 (8); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{30}O_4$ $[M]^{+\cdot}$ 526.2144, found: 526.214.

4.11.4 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-2-butenoate) (16).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 70:30) to give **16** (0.35 g, 0.88 mmol, 94%) as a yellowish dense oil, $[\alpha]_D^{23}$ -13.7 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz,$CDCl_3$) δ_H 1.79 (dd, 6H, ^4J = 1.5 Hz, ^3J =6.3 Hz), 2.01-2.09 (m, 2H), 3.57 (dd, 2H, ^3J = 8.6 Hz, ^2J = 11.1 Hz), 3.78 (dd, 2H, ^3J = 5.7 Hz, ^2J = 11.1 Hz), 4.17 (s, 2H), 5.77 (dq, 2H, ^3J =

15.7 Hz, ^{3}J = 6.3 Hz), 6.87 (dq, 2H, ^{3}J = 15.7 Hz, ^{4}J = 1.5 Hz), 6.96-7.23 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.46, 42.94, 46.53, 66.95, 122.96, 123.9, 125.89, 126.41, 126.68, 140.61, 143.45, 145.39, 166.61 ppm; IR (neat) *ν*: 3072, 3041, 3017, 2940, 2913, 1720, 1654, 1460, 1441, 1258, 1177, 109, 959, 839, 757, 730 cm $^{-1}$; MS: *m/z* (%) 402 (13), 178 (100), 69 (32); HRMS (ESI) *m/z* calcd for $C_{26}H_{26}O_4$ $[M]^{+\cdot}$ 402.1831, found: 402.183.

4.11.5 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-2-methyl-3-phenylpropenoate) (18).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 70:30) to give **18** (0.49 g, 0.88 mmol, 94%) as a white solid, m.p.: 73-75 ºC; $[\alpha]_D^{23}$ +7.3 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.81-1.89 (m, 2H), 2.01 (s, 6H), 3.69 (dd, 2H, ^{3}J = 8.1 Hz, ^{2}J = 11.3 Hz), 3.92 (dd, 2H, ^{3}J = 5.5 Hz, ^{2}J = 11.3 Hz), 4.19 (s, 2H), 6.99 (m, 2H), 7.11-7.34 (m, 8H), 7.60 (s, 10H) ppm, ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.61, 43.11, 46.75, 67.77, 124.04, 126.02, 126.63, 126.82, 128.86, 130.22, 136.36, 139.71, 140.76, 143.54, 168.73 ppm; IR (KBr) *ν*: 3060, 3017, 2951, 2889, 1701, 1631, 1491, 1445, 1250, 1196, 1114, 909, 757, 730, 699 cm^{-1}; MS: *m/z* (%) 554 (3), 230 (25), 215 (20), 202 (9), 178 (100), 152 (9), 145 (70), 117 (73), 91 (49), 77 (4); HRMS (ESI) *m/z* calcd for $C_{38}H_{34}O_4$ $[M]^{+\cdot}$ 554.2457, found: 554.245.

4.11.6 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-2,3-diphenyl-2-propenoate) (19).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 81:15) to give **19** (0.48 g, 0.70 mmol, 75%) as a white solid, m.p.: 69-71 ºC; $[\alpha]_D^{23}$ -4.1 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.52-1.63 (m, 2H), 3.46 (dd, 2H, ^{3}J = 7.5 Hz, ^{2}J = 11.2 Hz), 3.65 (dd, 2H, ^{3}J = 4.7 Hz, ^{2}J = 11.2 Hz), 3.89 (s, 2H), 6.90-7.40 (m, 28H), 7.75 (s, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.54, 46.13, 67.70, 123.86, 125.84, 126.45, 126.65, 128.30, 128.68, 129.14, 129.57, 130.13, 131.17, 133.05, 135.03, 136.64, 140.57, 140.85, 143.21, 167.71 ppm; IR (film) *ν*: 3052, 3021, 2951, 2889, 1709, 1627, 1491, 1445, 1250, 1165, 909, 761, 734, 707, 687 cm^{-1}; MS: *m/z* (%) 678 (4), 277 (14), 230 (23), 215 (17), 207 (40), 202 (11), 178 (100), 152 (28), 77 (12); HRMS (ESI) *m/z* calcd for $C_{48}H_{38}O_4$ $[M]^{+\cdot}$ 678.2770, found: 678.276.

4.11.7 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-2-methyl-2-butenoate) (20).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 80:20) to give **20** (0.31 g, 0.71 mmol, 76%) as a yellowish dense oil; $[\alpha]_D^{23}$ -18.8 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.85-2.06 (m, 14H), 3.79 (dd, 2H, ^{3}J = 8.1 Hz, ^{2}J = 11.2 Hz), 4.06 (dd, 2H, ^{3}J = 5.3 Hz, ^{2}J = 11.2 Hz), 4.39 (s, 2H), 6.71 (m, 2H), 6.92-7.40 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 12.41, 14.73, 42.88, 46.57, 67.13, 123.87, 125.81, 126.6, 128.5, 137.89, 140.06, 140.73, 141.95, 143.46, 168.12 ppm; IR (neat) *ν*: 3068, 3017, 2924, 2854, 1713, 1650, 1456, 1266, 1142, 1076, 761, 734 cm^{-1}; MS: *m/z* (%) 430 (25), 330

(6), 230 (6), 215 (7), 202 (5), 178 (100), 152 (7), 83 (57), 55 (52); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}O_4$ $[M]^{+\cdot}$ 430.2144, found: 430.214.

4.11.8 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis(propenoate) (21).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 70:30) to give **21** (3.87 g, 10.33 mmol, 70%) as a white solid, m.p.: 92-94 ºC; $[\alpha]_D^{23}$ -19,2 (*c* 1,00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.68-1.82 (m, 2H), 3.61 (dd, 2H, ^3J = 7.6 Hz, ^2J = 11.3 Hz), 3.83 (dd, 2H, ^3J = 4.8 Hz, ^2J = 11.3 Hz), 4.17 (s, 2H), 5.73 (dd, 2H, ^2J = 1.5 Hz, ^3J = 10.0 Hz), 6.05 (dd, 2H, ^2J = 1.5 Hz, ^3J = 10.5 Hz), 6.30 (dd, 2H, ^3J = 10 Hz, ^3J = 10.5 Hz), 6.94-7.30 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.85, 46.35, 67.15, 123.94, 125.93, 126.54, 126.78, 128.78, 131.36, 140.58, 143.37, 166.25 ppm; IR (KBr) *ν*: 3068, 3041, 3017, 2955, 2893, 1732, 1631, 1468, 1410, 1297, 1270, 1192, 1188, 1056, 982, 908, 811, 757, 730 cm^{-1}; MS: *m/z* (*%*) 374 (13), 215 (2), 202 (3), 178 (100), 152 (3), 97(3), 83 (3), 55 (20); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{22}O_4$ $[M]^{+\cdot}$ 374.1518, found: 374.152.

4.11.9 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis((*E*)-3-methyl-2-butenoate) (22).

Using the same procedure of Method B. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 75:25) to give **22** (0.34 g, 0.84 mmol, 89%) as a yellowish dense oil, $[\alpha]_D^{23}$ -18.9 (1.00, CH_2Cl_2), ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 1.68-1.70 (m, 2H), 1.78 (s, 6H), 2.06 (s, 6H), 3.50 (dd, 2H, ^3J = 7.4 Hz, ^2J = 11.3 Hz), 3.75 (dd, 2H, ^3J = 5.2 Hz, ^2J = 11.3 Hz), 4.17 (s, 2H), 5.62 (s, 2H), 6.91-7.24 (m, 8H) ppm, ^{13}C NMR (300 MHz, $CDCl_3$), δ 20.63, 27.75, 43.03, 46.43, 66.34, 116.36, 123.90, 125.88, 126.40, 126.64, 140.75, 143.48, 157.27, 166.71 ppm, IR (neat) *ν*: 3064, 3037, 3021, 2944, 2909, 1709, 1650, 1445, 1227, 1142, 1076, 912, 846, 757, 730 cm^{-1}, MS: *m/z* (*%*) 430 (6), 178 (100), 152 (2), 83 (19), 55 (8), HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}O_4$ $[M]^{+\cdot}$ 430.2144, found: 430.214.

4.11.10 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis(phenylpropynoate) (24).

Using the same procedure of Method A. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 70:30) to give **24** (0.77 g, 1.47 mmol, 87%) as a yellowish dense oil; $[\alpha]_D^{23}$ +7.4 (*c* 0.98, CH_2Cl_2); ^{1}H NMR (300 MHz,$CDCl_3$) δ_H 1.92-2.10 (m, 2H), 3.91 (dd, 2H, ^3J = 8.9 Hz, ^2J = 11.3 Hz), 4.14 (dd, 2H, ^3J = 5.4 Hz, ^2J = 11.3 Hz), 4.48 (s, 2H), 7.17-7.83 (m, 18H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 42.62, 46.07, 68.33, 81.00, 87.25, 120.00, 124.13, 126.07, 126.68, 126.97, 129.04, 131.17, 133.48, 140.33, 143.12, 154.20 ppm; IR (neat) *ν*: 3064, 3017, 2920, 2850, 2221, 1709, 1487, 1456, 1281, 1184, 1165, 905, 757, 730, 687 cm^{-1}; MS: *m/z* (*%*) 552 (18), 231 (2), 202 (4), 178 (100), 152 (3), 129(30), 102(3), 75 (4); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{26}O_4$ $[M]^{+\cdot}$ 522.1831, found: 522.183.

4.11.11 Synthesis of (11*R*,12*R*)-9,10-dihydro-9,10-ethanoanthracene-11,12-di methyl bis(2-octynoate) (25).

Using the same procedure of Method A. The crude product was purified by column chromatography (silica gel 60, hexane-Et_2O, 80:20) to give **25** (0.43 g, 0.85 mmol, 90%) as a yellowish dense oil, $[\alpha]_D^{23}$ -8.1 (*c* 1.00, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.83 (t, 6H), 1.15-1.38 (m, 8H), 1.44-1.58 (m, 4H), 1.62-1.73 (m, 2H), 2.24 (t, 4H), 3.53 (dd, 2H, ^3J = 8.4 Hz, ^2J = 11.3 Hz), 3.80 (dd, 2H, ^3J = 5.1 Hz, ^2J = 11.3 Hz), 4.19 (s, 2H), 6.94-7.31 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.24, 19.11, 22.46, 27.60, 31.44, 42.56, 45.96, 67.98, 73.46, 90.64, 123.95, 125.92, 126.59, 126.78, 140.39, 143.22, 154.00 ppm; IR (neat) *v*: 3068, 3045, 3021, 2928, 2858, 2229, 1712, 1460, 1235, 1080, 955, 746, 726, 629 cm^{-1}; MS: *m/z* (*%*) 510 (7), 231(6), 215 (8), 202 (6), 178 (100), 152 (5), 123 (18), 93 (6), 79 (6), 67 (24), 55 (24); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{38}O_4$ $[M]^{+\cdot}$ 510.2770, found: 510.277. (6), 79 (6), 67 (24), 55 (24); HRMS (ESI) *m*/*z* calcd for $C_{34}H_{38}O_4$ $[M]^{+\cdot}$ 510.2770, found: 510.277.

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