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New synthetic approach to atypical retinoids: application of a versatile annulation procedure

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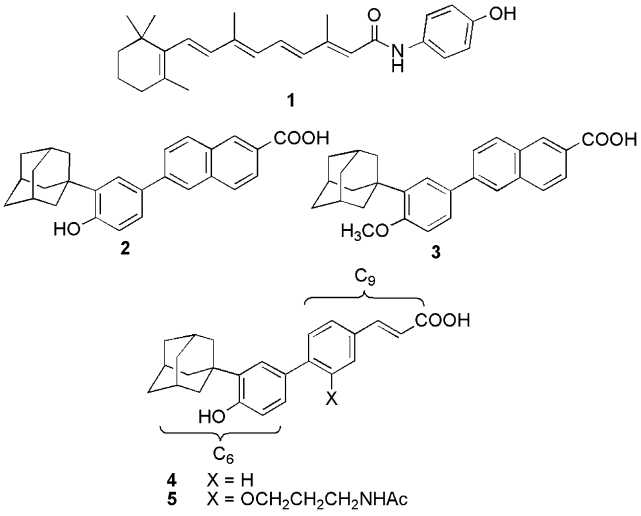
Abstract—A new approach to an atypical retinoid is presented. The C_{15} skeleton was built up by exploiting a step-by-step sequence: the C_9 fragment of an intermediate was homologated by reaction with a C_4 phosphorane, and then submitted to a benzannulation reaction. The last two carbon atoms were inserted by a Wittig reaction with the C_2 phosphorane of ethyl bromoacetate. Manipulation of functional groups was then performed.

1. Introduction

The so-called *atypical retinoids* are a class of compounds having a retinoid like structure: they activate certain retinoid-acid receptors as well as exerting a growth regulatory or apoptogenic activity that is not receptor mediated.[1] The main compounds of this class (Scheme 1) are 4-hydroxyphenyl-retinamide (4-HPR) (**1**), and the adamantyl substituted derivatives AHPN (**2**), adapalene (**3**), AHPC (**4**) and 3A-AHPC (**5**). Their chemopreventive and chemotherapeutic potentials are being intensively investigated, and they are considered to be highly promising as less toxic drugs in cancer therapy and prevention.[2] The development of new efficient synthetic strategies to this type of substrates would be of great help in their investigation and in the elucidation of their precise mechanism of action on cell proliferation and apoptosis.

The current synthetic approach to the biaryl derivatives **2–5** is based on the Suzuki–Miyaura palladium-catalysed cross-coupling of organoboron compounds,[3] on the nickel-catalysed Negishi reaction of zincate derivatives,[4] or on the Grignard coupling mediated by $PdCl_2(PPh_3)_2$ complexes.[5] Metal catalysis is employed to obtain the C–C single bond between the two aromatic moieties.

In the past, we developed an efficient benzoannulation procedure (Scheme 2) to prepare 4-substituted-3-hydroxy-



Scheme 1.

benzoic acid derivatives of type **I**, starting from unsaturated aldehydes **II**.[6] The key step is the cyclisation of acid **III** promoted either by ethyl chloroformate or by trifluoroacetic anhydride in THF solution in the presence of triethylamine. We have successfully employed this procedure for the synthesis of biphenyl systems, such as the binol analogue **6**.[7]

We report herein the application of this synthetic path for the preparation of the atypical retinoid **5**,[8] to showcase the efficiency of our annulation procedure for the preparation of this class of useful cancer drugs.

Keywords: Atypical retinoids; Annulation; Benzene ring; Cancer therapy.
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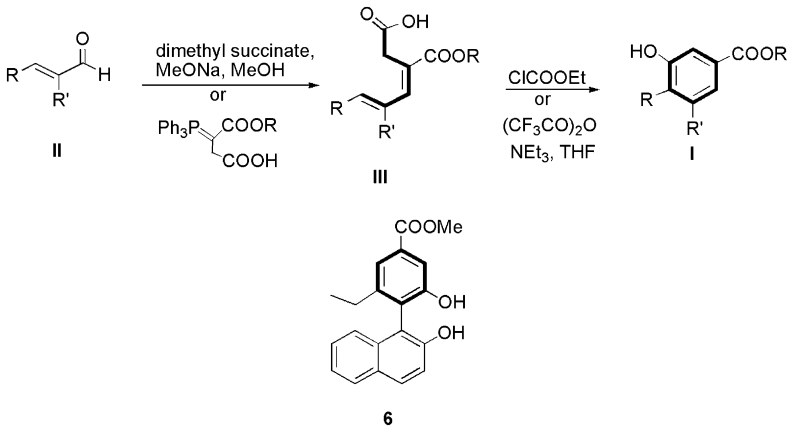
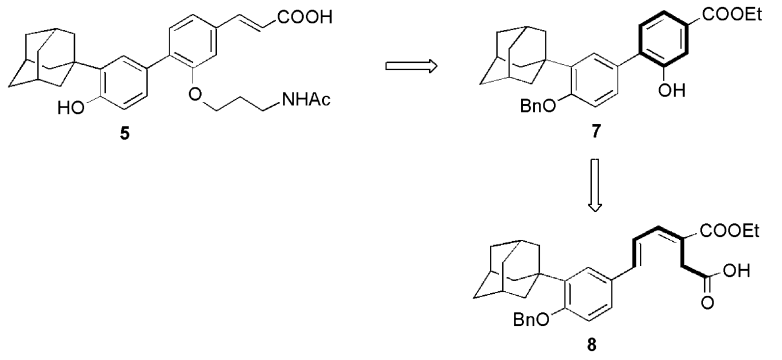


Scheme 2.

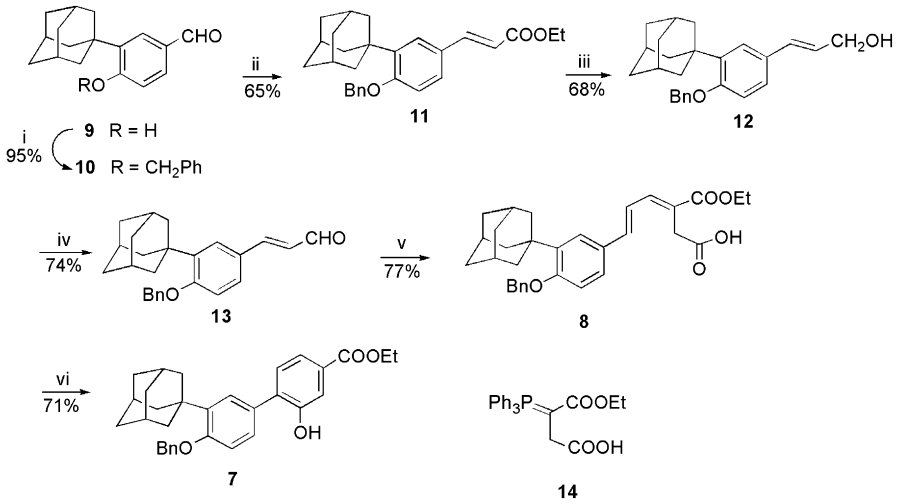
2. Results and discussion

Compound **5** satisfies the structural requirement for the application of our procedure since its potential precursor **7** is a 4-substituted-3-hydroxy-benzoic acid (Scheme 3). Alkylation of the phenolic group and conversion of the methyl ester moiety into the cinnamic acid group complete the sequence to give the target compound. The preparation of acid **8** was thus required.

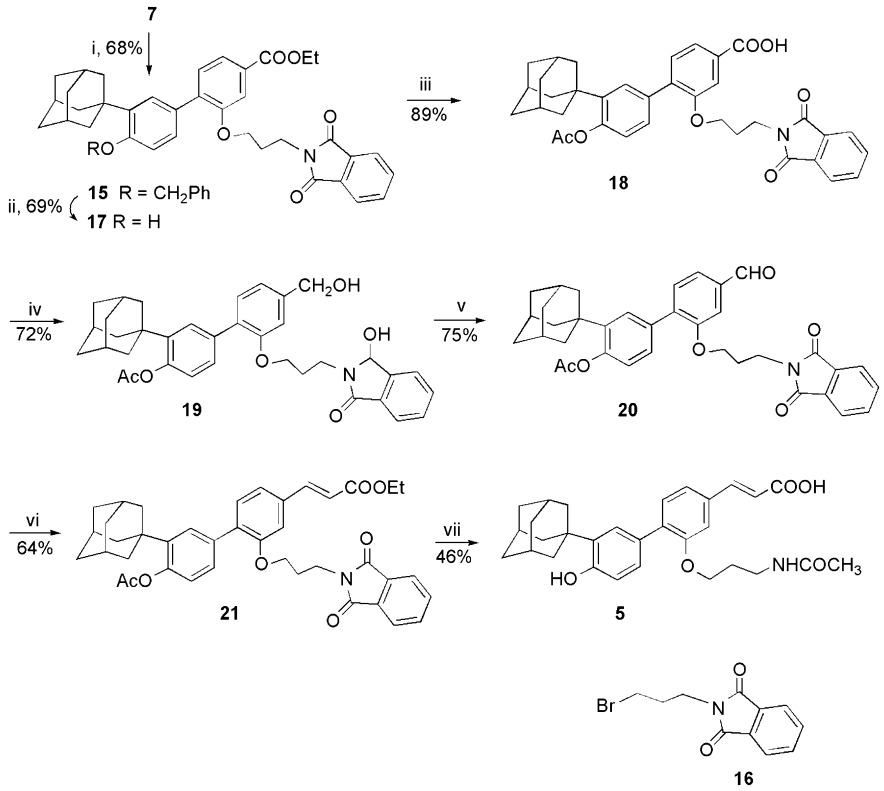
4-Hydroxy-3-adamantylbenzaldehyde **9** was devised as the starting material (Scheme 4) and was prepared by Friedel–Crafts alkylation of 4-hydroxybenzaldehyde with adamantanol in CH_2Cl_2, in the presence of sulfuric acid. The alcohol was protected to give the benzyl derivative **10**, which was submitted to a Wittig reaction to afford the unsaturated ester **11**. The ester group was reduced with Red-Al® at −20 °C to afford alcohol **12** that was oxidised with MnO_2 in CH_2Cl_2. The resulting unsaturated aldehyde **13**



Scheme 3.



Scheme 4. Reagents and conditions: (i) NaH, DMF, $PhCH_2Cl$; (ii) $Ph_3P{=}CHCOOEt$, $CHCl_3$, reflux; (iii) Red-Al®, toluene, −20 °C; (iv) MnO_2, CH_2Cl_2, reflux; (v) phosphorane **14**, toluene, reflux and (vi) $(CF_3CO)_2O$, Et_3N, THF.



Scheme 5. Reagents and conditions: (i) K_2CO_3, acetone, phthalimido derivative **16**; (ii) H_2, Pd/C; (iii) KOH, MeOH, then Ac_2O in pyridine; (iv) ClCOOEt, Et_3N; then $NaBH_4$; (v) MnO_2, CH_2Cl_2; (vi) $Ph_3P{=}CHCOOEt$, CH_2Cl_2, reflux; (vii) NaOH, H_2O, EtOH, reflux: Schotten–Baumann.

was treated with phosphorane **14**[9] to afford derivative **8** to be used for the benzannulation reaction. Reaction with trifluoroacetic acid anhydride and triethylamine gave the key biaryl intermediate **7**.

The next sequence (Scheme 5) concerned functionalisation of the phenol with the 3-acetamidopropyl moiety and the conversion of the ethyl ester into the cinnamic acid fragment. The first goal was achieved by a classical Gabriel synthesis: the suitable alkyl phthalimide **15** was prepared by treatment of compound **7** with potassium carbonate and derivative **16**[10] in acetone solution. After debenzylation, compound **17** was obtained, and then submitted to saponification and acetylation, to afford derivative **18**.

Interestingly enough, when compound **18** was treated with ethyl chloroformate and then reduced with $NaBH_4$, we also observed the reduction of one of the carbonyl group of the phthalimido moiety, and compound **19** was obtained. Nonetheless, MnO_2 oxidation restored this carbonyl function and oxidised the primary alcohol to aldehyde **20**. Wittig homologation, followed by saponification, and Schotten–Baumann acetylation of the amino group gave the final compound **5**.

3. Conclusions

The advantage of the method described is the use of a benzannulation reaction instead of a metal catalysed coupling. The 15 carbon atom skeleton of compound **5** (Scheme 1) was obtained in the literature[7] by a modified Suzuki coupling of a six carbon atom moiety with a nine carbon atom unit. Manipulation of functional groups was performed before coupling, and the employment of metal catalysis required careful purification of the product, to reduce the metal impurity content in the final compound.

In contrast, we built up the C_{15} skeleton by exploiting a step-by-step sequence: the C_9 fragment of intermediate **13** was homologated by reaction with the C_4 phosphorane **14**, and then cyclised. The last two carbon atoms were inserted by a Wittig reaction with the C_2 phosphorane of ethyl bromoacetate. Manipulation of functional groups was then performed after annulation. This cyclisation procedure, based on the key intermediate **8**, does not suffer from much interference due to the presence of other functional groups, and can be applied to obtain a large number of biaryl compounds structurally related to **5**, to be eventually investigated for cancer therapy.

4. Experimental

4.1. General

GC–MS analyses were performed on a HP 6890 gas-chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m×0.25 mm×0.25 μm). The following temperature program was employed: 60 °C (1 min)/6 °C/min/150 °C (1 min)/12 °C/min/280 °C (5 min). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz and 62.5 MHz, respectively), in $CDCl_3$ solution at rt unless otherwise stated, using TMS as

an internal standard; *J* values are given in Hertz. All the chromatographic separations were carried out on silica gel columns. Microanalyses were determined on a Analyzer 1106 Carlo Erba.

4.1.1. 3-Adamantyl-4-hydroxybenzaldehyde (9). A solution of 4-hydroxybenzaldehyde (24.4 g, 0.20 mol), 1-adamantanol (33.4 g, 0.22 mol) and concentrated sulfuric acid (10 mL) in CH_2Cl_2 (350 mL) was stirred at rt for 24 h. The reaction mixture was poured into ice, neutralised with $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate, 7/3) to afford **9** (38.4 g, 75%) as a reddish solid: mp 125 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.87 (s, 1H, CHO), 7.79 (d, J=1.7, 1H, H–C(2)), 7.64 (dd, J=1.7, 8.3, 1H, H–C(6)), 6.77 (d, J=8.3, 1H, H–C(5)), 2.18–2.09 (m, 9H, adamantane), 1.84–1.78 (m, 6H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 191.6, 160.6, 137.2, 129.9, 129.7, 128.2, 117.3, 70.6, 40.3, 37.0, 36.9, 28.9 ppm; GC/MS: t_R=27.18 min, m/z (%)=256 (100) [M^+], 199 (25), 171 (20). Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.48; H, 7.97.

4.1.2. 3-Adamantyl-4-benzyloxybenzaldehyde (10). A solution of **9** (38.0 g, 0.148 mol) in DMF (50 mL) was added dropwise into a suspension of NaH (60% in mineral oil, 0.163 mol) in DMF (200 mL). After 30 min, benzyl chloride (20.5 g, 0.163 mol) was added. The reaction mixture was stirred at rt for 1 h, then poured into ice, neutralised and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed (hexane/ethyl acetate, 95/5), to afford **10** (48.6 g, 95%) as a yellow solid: mp 99 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.89 (s, 1H, CHO), 7.82 (d, J=1.7, 1H, H–C(2)), 7.70 (dd, J=1.7, 8.3, 1H, H–C(6)), 7.55–7.30 (m, 5H, Ph), 7.04 (d, J=8.3, 1H, H–C(5)), 5.21 (s, 2H, CH_2Ph), 2.18–2.12 (m, 6H, adamantane), 2.09–2.05 (m, 3H, adamantane), 1.76–1.70 (m, 6H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 191.3, 162.9, 139.3, 136.2, 130.1, 129.8, 128.6, 128.7, 128.1, 127.4, 112.4, 40.3, 37.3, 37.0, 28.9 ppm; GC/MS: t_R=31.95 min, m/z (%)=346 (16) [M^+], 255 (24), 91 (100). Anal. Calcd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56. Found: C, 83.09; H, 7.69.

4.1.3. (*E*)-Ethyl 3-(3-adamantyl-4-benzyloxy-phenyl)-acrylate (11). A solution of **10** (48.0 g, 0.138 mol) in toluene (350 mL) in the presence of Ph_3P=CHCOOEt (52.9 g, 0.152 mol) was refluxed for 3 h. After the usual work-up, the residue was purified by column chromatography (hexane/ethyl acetate, 9/1), to afford **11** (37.3 g, 65%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.65 (d, J=17, 1H, Ar–CH=), 7.45–7.30 (m, 7H, ArH), 6.92 (d, J=8.3, 1H, H–C(5)), 6.31 (d, J=17, 1H, C=CHCOOR), 5.15 (s, 2H, CH_2Ph), 4.25 (q, J=7.1, 2H, $COOCH_2$), 2.17–2.11 (m, 6H, adamantane), 2.08–2.02 (m, 3H, adamantane), 1.75–1.69 (m, 6H, adamantane), 1.33 (t, J=7.1, 3H, $COOCH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ 167.1, 159.2, 143.9, 137.9, 136.3, 130.2, 128.6, 128.3, 128.0, 127.3, 127.2, 115.2, 114.5, 70.1, 60.3, 40.3, 37.3, 37.0, 28.9, 14.4; GC/MS: t_R=40.56 min, m/z (%)=416 (42) [M^+], 324 (32), 91 (100). Anal. Calcd for $C_{28}H_{32}O_3$: C, 80.73; H, 7.74. Found: C, 80.62; H, 7.83.

4.1.4. (*E*)-3-(3-Adamantyl-4-benzyloxy-phenyl)prop-2-en-1-ol (12). To a solution of **11** (37.0 g, 0.088 mol) in toluene (400 mL) Red-Al® (3.5 M in toluene, 27.6 mL, 0.097 mol) was added dropwise at −20 °C. After 1 h, the reaction mixture was poured into ice, treated with H_2SO_4 (2 N) and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed (hexane/ethyl acetate, 7/3), to afford **12** (22.4 g, 68%) as a liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55–7.10 (m, 7H, ArH), 6.91 (d, J=8.3, 1H, H–C(5)), 6.57 (d, J=16.4, 1H, Ar–CH=), 6.27 (dt, J=16.4, 5.9, 1H, C=CH), 5.13 (s, 2H, CH_2Ph), 4.31 (d, J=5.9, 2H, CH_2OH), 2.21–2.15 (m, 6H, adamantane), 2.09–2.03 (m, 3H, adamantane), 1.78–1.72 (m, 6H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 157.7, 138.7, 137.3, 131.7, 129.2, 128.5, 127.7, 127.3, 112.8, 70.3, 64.0, 40.4, 37.1, 29.2 ppm. Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.21; H, 8.16.

4.1.5. (*E*)-3-(3-Adamantanyl-4-benzyloxy-phenyl)acrylaldehyde (13). A mixture of MnO_2 (1.5 equiv) and unsaturated alcohol **12** (22.0 g, 0.059 mol) in CH_2Cl_2 (300 mL) was refluxed for 30 min. The reaction mixture was filtered and concentrated under reduced pressure. After column chromatography (hexane/ethyl acetate, 9/1) aldehyde **13** was obtained (16.2 g, 74%) as a white solid: mp 138 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.64 (d, J=7.5, 1H, CHO), 7.55–7.30 (m, 8H, ArH+CH=), 6.96 (d, J=8.3, 1H, H–C(5) of the tri-substituted benzene ring), 6.62 (dd, J=15.7, 7.5, 1H, C*H*=CHO), 5.16 (s, 2H, CH_2Ph), 2.17–2.11 (m, 6H, adamantane), 2.08–2.02 (m, 3H, adamantane), 1.78–1.72 (m, 6H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 28.9, 36.9, 37.2, 40.4, 70.4, 112.9, 126.3, 126.6, 127.3, 127.5, 127.8, 128.0, 128.6, 136.5, 139.3, 152.0, 153.4, 193.6 ppm. Anal. Calcd for $C_{26}H_{28}O_2$: C, 83.83; H, 7.58. Found: C, 83.75; H, 7.41.

4.1.6. (3*E*,5*E*)-6-(3-Adamantyl-4-benzyloxy-phenyl)-3-(ethoxycarbonyl)hexa-3,5-dienoic acid (8). A solution of aldehyde **13** (16.0 g, 0.043 mol) and phosphorane **14** (19.1 g, 0.047 mol) in toluene (500 mL) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure and chromatographed (hexane/ethyl acetate, 1/1) to afford compound **8** (16.5 g, 77%) as a white solid: mp 77 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.52 (d, J=11.3, 1H, H–C(4)), 7.50–7.15 (m, 7H, ArH), 6.94 (d, J=15.4, 1H, H–C(6)), 6.91 (d, J=8.3, 1H, H–C(5)), 6.84 (dd, J=15.4, 11.3, 1H, H–C(5)), 5.13 (s, 2H, CH_2Ph), 4.25 (q, J=7.2, 2H, $COOCH_2$), 3.57 (s, 2H, CH_2COO), 2.17–2.11 (m, 6H, adamantane), 2.07–2.01 (m, 3H, adamantane), 1.77–1.69 (m, 6H, adamantane), 1.31 (t, J=7.2, 3H, $COOCH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2, 29.0, 32.7, 37.0, 37.2, 40.4, 61.0, 70.3, 112.8, 120.3, 121.7, 126.2, 126.4, 127.2, 127.8, 128.5, 128.7, 136.9, 139.0, 142.4, 142.1, 158.9, 167.7, 175.8 ppm. Anal. Calcd for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.58; H, 7.39.

4.1.7. Ethyl 5′-(adamantanyl)-4′-(benzyloxy)-2-hydroxy-biphenyl-4-carboxylate (7). A solution of **8** (16.0 g, 0.032 mol) and Et_3N (9.69 g, 0.096 mol) in THF (200 mL) was treated with $(CF_3CO)_2O$ (15.4 g, 0.064 mol) at 0 °C. The reaction mixture was stirred at rt for 30 min, poured into ice, neutralised and extracted with diethyl ether. The organic

phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate, 7/3) gave compound **7** (10.9 g, 71%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70–7.20 (m, 10H, ArH), 7.05 (d, J=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 5.5 (br s, 1H, OH), 5.19 (s, 2H, CH_2Ph), 4.40 (q, J=7.2, 2H, $COOCH_2$), 2.22–2.16 (m, 6H, adamantane), 2.07–2.01 (m, 3H, adamantane), 1.78–1.71 (m, 6H, adamantane), 1.38 (t, J=7.2, 3H, $COOCH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ 14.3, 29.0, 37.0, 37.3, 40.5, 60.9, 70.3, 113.2, 116.8, 121.7, 127.2, 127.3, 127.6, 127.8, 128.5, 130.1, 130.6, 133.0, 137.0, 139.6, 146.8, 152.7, 157.9, 165.8 ppm. Anal. Calcd for $C_{32}H_{34}O_4$: C, 79.64; H, 7.10. Found: C, 79.76; H, 7.21.

4.1.8. Ethyl 5′-(adamantanyl)-4′-(benzyloxy)-2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)biphenyl-4-carboxylate (15). A mixture of **7** (10.0 g, 0.021 mol), K_2CO_3 (3.18 g, 0.023 mol) and phthalimido derivative **16**[10] (5.60 g, 0.021 mol) in acetone (300 mL) was refluxed for 4 h. The reaction mixture was poured into ice, and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate, 1/1) gave compound **15** (9.55 g, 68%) as a white solid: mp 165 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85–7.20 (m, 14H, ArH), 6.98 (d, J=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 5.16 (s, 2H, CH_2Ph), 4.39 (q, J=7.2, 2H, $COOCH_2$), 4.09 (t, J=6.2, 2H, CH_2O), 3.83 (t, J=6.6, 2H, CH_2N), 2.22–2.16 (m, 6H, adamantane), 2.19–2.13 (m, 2H, CH_2), 2.07–2.00 (m, 3H, adamantane), 1.75–1.69 (m, 6H, adamantane), 1.40 (t, J=7.2, 3H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2, 28.5, 29.0, 35.3, 37.0, 37.1, 40.5, 60.8, 66.2, 70.1, 112.1, 113.3, 122.4, 123.0, 127.2, 127.5, 127.9, 128.0, 128.3, 129.5, 129.7, 130.3, 132.0, 133.7, 135.8, 137.3, 137.8, 155.4, 157.3, 166.3, 168.0 ppm. Anal. Calcd for $C_{43}H_{43}NO_6$: C, 77.11; H, 6.47; N, 2.09. Found: C, 77.01; H, 6.60; N, 2.19.

4.1.9. Ethyl 5′-(adamantanyl)-2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-4′-hydroxybiphenyl-4-carboxylate (17). Compound **15** (9.50 g, 0.014 mol) was hydrogenated in the presence of Pd/C (0.500 g) in ethanol solution (200 mL). The reaction mixture was filtered and concentrated under reduced pressure to give compound **17** (5.60 g, 69%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.84–7.79 (m, 2H, ArH), 7.72–7.67 (m, 3H, ArH), 7.59 (d, J=1.7, 1H, ArH), 7.39 (d, J=2.2, 1H, ArH), 7.39–7.32 (m, 2H, ArH), 6.68 (d, J=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 4.39 (q, J=7.0, 2H, $COOCH_2$), 4.09 (t, J=6.1, 2H, CH_2O), 3.83 (t, J=7.0, 2H, CH_2N), 2.20–2.13 (m, 8H, 6H, adamantane+CH_2), 2.12–2.05 (m, 3H, adamantane), 1.82–1.75 (m, 6H, adamantane), 1.40 (t, J=7.0, 3H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 14.2, 28.4, 29.0, 35.3, 36.7, 37.0, 40.4, 60.9, 66.1, 113.2, 116.3, 127.8, 128.0, 128.9, 129.4, 130.3, 131.8, 133.8, 135.8, 136.1, 154.7, 155.3, 166.6, 168.3 ppm. Anal. Calcd for $C_{36}H_{37}NO_6$: C, 74.59; H, 6.43; N, 2.42. Found: C, 74.43; H, 6.32; N, 2.59.

4.1.10. 4′-Acetoxy-5′-(adamantyl)-2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)biphenyl-4-carboxylic acid (18). Derivative **17** (5.30 g, 9.15 mmol) was hydrolysed with KOH (0.780 g, 0.014 mol) in methanol (200 mL). After the usual work-up, the residue was acetylated by reaction with Ac_2O (25 mL) in pyridine (50 mL), to give compound **18** (4.83 g, 89%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.85–7.74 (m, 3H, ArH), 7.72–7.64 (m, 3H, ArH), 7.53 (d, J=2.0, 1H, ArH), 7.44 (dd, J=8.6, 2.4, 1H, ArH), 7.40 (d, J=8.0, 1H, ArH), 7.03 (d, J=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 4.11 (t, J=6.1, 2H, CH_2O), 3.82 (t, J=6.5, 2H, CH_2N), 2.37 (s, 3H, OAc), 2.19–2.13 (m, 2H, CH_2), 2.12–2.06 (m, 9H, adamantane), 1.80–1.74 (m, 3H, adamantane) ppm. Anal. Calcd for $C_{36}H_{35}NO_7$: C, 72.83; H, 5.94; N, 2.36. Found: C, 72.71; H, 5.79; N, 2.21.

4.1.11. 3-(Adamantyl)-2′-(3-(1-hydroxy-3-oxoisoindolin-2-yl)propoxy)-4′-(hydroxymethyl)biphenyl-4-yl acetate (19). To a solution of **18** (4.50 g, 7.59 mmol) in Et_3N (100 mL), ClCOOEt (0.901 g, 8.34 mmol) was added dropwise at 0 °C. After the usual work-up the residue was dissolved in CH_2Cl_2/MeOH 2/1 (150 mL) and treated with $NaBH_4$ (0.316 g, 8.34 mmol). After the usual work-up compound **19** (3.17 g, 72%) was recovered by column chromatography (hexane/ethyl acetate, 4/6) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.69–7.65 (m, 1H, ArH), 7.55–7.25 (m, 6H, ArH), 6.99–6.95 (m, 3H, ArH), 5.54 (br s, 1H, NC*H*–OH), 4.66 (s, 2H, CH_2OH), 4.13–3.97 (m, 2H, CH_2O), 3.56–3.50 (m, 2H, CH_2N), 2.36 (s, 3H, OAc), 2.11–1.97 (m, 11H, 9H, adamantane+CH_2), 1.80–1.75 (m, 3H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 21.7, 28.2, 29.0, 37.0, 37.4, 41.4, 65.1, 66.5, 82.4, 111.9, 119.5, 123.1, 123.2, 123.5, 127.9, 128.7, 129.5, 130.3, 130.7, 131.8, 131.9, 136.0, 140.6, 141.9, 144.2, 148.2, 155.9, 167.6, 170.0 ppm. Anal. Calcd for $C_{36}H_{39}NO_6$: C, 74.33; H, 6.76; N, 2.41. Found: C, 74.49; H, 6.85; N, 2.38.

4.1.12. 3-(Adamantanyl)-2′-(3-(1,3-dioxoisoindolin-2-yl)-propoxy)-4′-formylbiphenyl-4-yl acetate (20). A mixture of MnO_2 (1.5 equiv) and compound **19** (3.00 g, 5.1 mmol) in CH_2Cl_2 (1000 mL) was refluxed for 3 h. The reaction mixture was filtered and concentrated under reduced pressure. After column chromatography (hexane/ethyl acetate, 1/1) compound **20** was obtained (2.23 g, 75%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.97 (s, 1H, CHO), 7.81–7.65 (m, 2H, ArH), 7.72–7.65 (m, 2H, ArH), 7.5–7.40 (m, 5H, ArH), 7.03 (d, J=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 4.11 (t, J=6.2, 2H, CH_2O), 3.82 (t, J=6.7, 2H, CH_2N), 2.37 (s, 3H, OAc), 2.19–2.13 (m, 2H, CH_2), 2.11–2.05 (m, 9H, adamantane), 1.80–1.75 (m, 3H, adamantane) ppm. ^{13}C NMR ($CDCl_3$): δ 21.6, 28.4, 28.9, 29.5, 35.1, 36.9, 41.1, 66.1, 111.1, 123.1, 123.8, 124.1, 127.7, 128.5, 131.3, 131.9, 133.8, 134.5, 136.6, 137.1, 140.4, 148.9, 156.1, 168.1, 169.2, 191 ppm. Anal. Calcd for $C_{36}H_{35}NO_6$: C, 74.85; H, 6.11; N, 2.42. Found: C, 74.72; H, 6.01; N, 2.38.

4.1.13. (*E*)-Ethyl 3-(4′-acetoxy-5′-(adamantyl)-2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)biphenyl-4-yl)acrylate (21). A solution of **20** (2.1 g, 3.63 mmol) in toluene (70 mL) in the presence of Ph_3P=CHCOOEt (1.39 g, 3.99 mmol) was refluxed for 3 h. After the usual work-up, the residue was purified by column chromatography (hexane/ethyl acetate, 9/1), to afford compound **21** (1.50 g, 64%) as a viscous liquid: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.83–7.78 (m, 2H, ArH),

7.73–7.63 (m, 3H, ArH+CH═), 7.52–7.48 (m, 1H, ArH), 7.40 (dd, *J*=2.1, 8.4, 1H, ArH), 7.35–7.29 (m, 1H, ArH), 7.19 (dd, *J*=1.4, 8.0, 1H, ArH), 7.09 (d, *J*=1.4, 1H, ArH), 7.00 (d, *J*=8.3, 1H, H–C(5) of the adamantyl substituted benzene ring), 6.44 (d, *J*=15.8, 1H, CH═COO), 4.28 (q, *J*=7.1, 2H, $COOCH_2$), 4.04 (t, *J*=6.2, 2H, CH_2O), 3.82 (t, *J*=6.7, 2H, CH_2N), 2.36 (s, 3H, OAc), 2.18–2.12 (m, 2H, CH_2), 2.10–2.05 (m, 9H, adamantane), 1.80–1.75 (m, 3H, adamantane), 1.35 (t, *J*=7.1, 3H, $COOCH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$): δ 14.3, 21.6, 28.4, 28.8, 35.1, 36.8, 41.1, 60.4, 66.1, 111.1, 118.4, 123.1, 123.7, 124.1, 127.7, 128.4, 131.3, 131.9, 133.9, 134.5, 136.6, 137.0, 140.0, 144.5, 148.9, 156.1, 168.8, 168.1, 169.2 ppm. Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.60; H, 7.21; N, 2.86. Found: C, 73.48; H, 7.38; N, 2.71.

4.1.14. (*E*)-3-(2-(3-Acetamidopropoxy)-5′-(adamantyl)-4′-hydroxybiphenyl-4-yl)acrylic acid (5).[8] A solution of **21** (1.40 g, 1.65 mmol) and KOH (0.399 g, 7.13 mmol) in methanol (30 mL) was refluxed for 4 h. The reaction mixture was poured into water, treated with HCl 10% and extracted with ethyl acetate. The solution was dried (Na_2SO_4) and concentrated under reduced pressure, to give a residue, which was dissolved in alkaline water and treated with acetic anhydride (0.168 g, 1.65 mmol). After the usual work-up compound **5** was recovered (0.371 g, 46%) after purification by column chromatography (hexane/ethyl acetate, 1/1) as a white solid: mp 197 °C; ^{1}H NMR[8] (DMSO-$^2H_6$): δ 12.45 (br s, 1H, COOH), 9.35 (s, 1H, OH), 7.80 (t, *J*=5.3, 1H, NH), 7.59 (d, *J*=16.0, 1H, ArCH═C), 7.35 (s, 1H, ArH), 7.30–7.25 (m, 3H, ArH), 7.20 (dd, *J*=8.4 and 2.5, 1H, ArH), 6.80 (d, *J*=8.4, 1H, H–C(5) of the adamantyl substituted benzene ring), 6.56 (d, *J*=16.0, 1H, C═$CHCO_2$), 4.05 (t, *J*=6.5, 2H, CH_2O), 3.17 (q, *J*=5.7, 2H, CH_2N), 2.13–2.07 (m, 6H, adamantane), 2.05–2.00 (m, 3H, adamantane), 1.84–1.78 (m, 2H, CH_2), 1.77 (s, 3H, $COCH_3$), 1.75–1.71 (m, 6H, adamantane) ppm. ^{13}C NMR (DMSO-$^2H_6$): δ 22.7, 29.1, 28.7, 35.9, 36.9, 40.2, 65.9, 111.9, 116.3, 118.7, 121.6, 127.7, 127.8, 128.2, 130.4, 132.9, 134.0, 135.2, 144.4, 155.6, 155.8, 168.0, 170.0.

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