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Diversifying complexity by domino benzannulation of polycyclic natural products.

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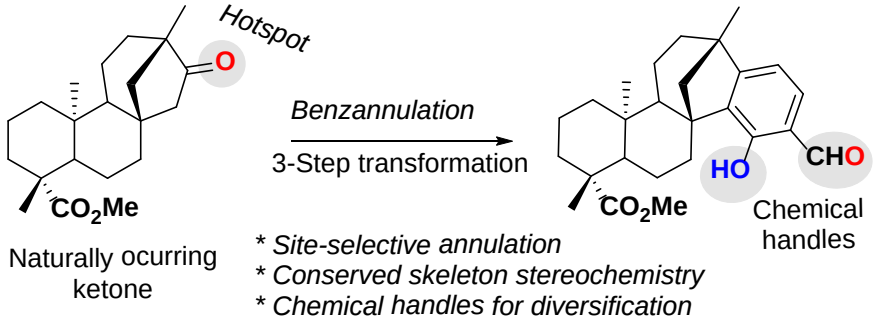


Abstract. Herein we describe a salicylaldehyde-annulation reaction as a plug and play toolkit to diversify the complexity of natural occurring ketones. The protocol entails the

transformation of the polycyclic natural ketone into its propargyl vinyl ether derivative (two synthetic steps) and its microwave-assisted imidazole-catalyzed domino rearrangement to generate the salicylaldehyde ring. This annexed unit allows further synthetic transformations, e.g., the installation of a pharmacophore module to generate natural product-pharmacophore hybrids endowed with unknown biological (pharmaceutical) annotations.

Introduction.

Three-dimensionality is conceived as a main design principle in the construction of molecular libraries for drug discovery.[1] Three-dimensional structural features such as stereochemistry or bond saturation correlate with increased binding specificity (geometrical complementarity),[2] favorable pharmacological properties,[3] lower promiscuity[4] and better clinical progression.[5] On the other hand, three-dimensional shape diversity[6] correlates with bio-relevance (broader bioactivity profile).[7] The recognition of this structure-activity relationship has propelled the development of a number of new synthetic methodologies aimed to incorporate three-dimensional diversity in synthetic libraries. Despite many significant advances, the efficient preparation of these libraries remains an important challenge in synthetic chemistry.[8] Among the more transited methodologies, diversity-oriented synthesis (DOS),[9] biology-oriented synthesis (BIOS),[10] lead-oriented synthesis (LOS)[11] and function-oriented synthesis (FOS)[12] have proved to be particularly useful. A more recent approach has been introduced by Hergenrother and co-workers:[13] the so-called complexity-to-diversity (CtD) strategy. The ethos of this strategy is to generate scaffold diversity (stereochemical, geometrical and topological) by performing ring-distortion reactions (i.e., fusion, expansion, cleavage and rearrangement) on complex and readily available polycyclic natural products (NPs) (Figure 1a).[14] In this line of thought, we envisioned that the fusion of an aromatic ring to a natural polycyclic framework

(benzannulation reaction) could be instrumentalized as a convenient chemical maneuver for this strategy (Figure 1b). The resulting NP-based scaffolds would benefit of all three-dimensional properties of the parent NPs (high fraction of sp^3-carbon atoms, saturated rings, stereogenic centers) and could be diversified by careful installation of suitable

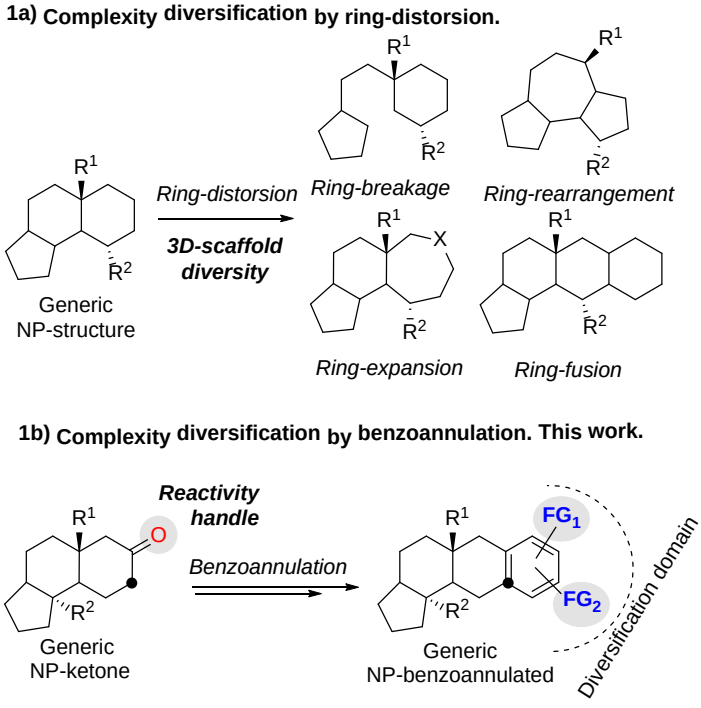


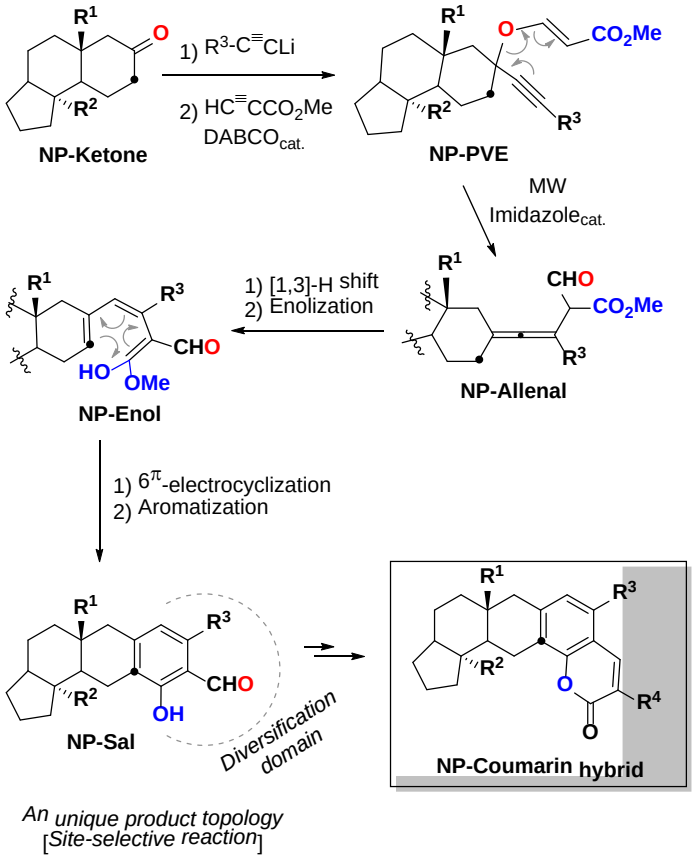
Figure 1. Complexity-to-diversity strategy: benzannulation of natural products.

functionalities on the benzene ring (FG; chemical handles). Among the many accessible decoration patterns endowing the fused aromatic ring, those based on the salicylaldehyde motive are especially attractive because they constitute well-appreciated building blocks for the preparation of numerous pharmacologically[15a] relevant coumarins,15[15b] chromenes,[15c,d] catechols [15e] and several mycotoxins.[15f] If a salicylaldehyde-annulation suitable methodology (i.e., direct, scalable, instrumentally simple and atom-, step-, pot- and labor-economic) were available, then these motives could be used as a plug and play platforms to assemble novel

NP-pharmacophore hybrids[16] (hybrid structures endowed with a NP core and a pharmacophore unit derived from salicylaldehyde; e.g., NP-Coumarin or NP-Chromene hybrids). Recently, we have shown that multisubstituted salicylaldehyde motives hosting different topological and functional patterns can be easily constructed from tertiary propargyl vinyl ethers (PVEs)[17] through a microwave-assisted and base catalyzed domino rearrangement.[18] We report herein how this reaction can be conveniently performed on polycyclic NPs bearing a tertiary PVE on their structures (NP-PVE) and how this protocol delivers novel NP-Salicylaldehyde (NP-Sal) chemotypes well suited for hybridization or further structural diversification (Scheme 1).

The salicylaldehyde-annulation strategy requires a polycyclic skeleton containing a ketone to install the PVE functional array and at least an unsubstituted α-methylene group (highlighted by a black dot in the NP-Ketone structure and its derivative in Scheme 1) to enable the tandem enolization / 6π-electrocyclization reaction needed to form the aromatic ring. Ketones have been widely used as chemical handles to transform NPs scaffolds[19] because they have a well-known reactivity profile and the ketone is a common functional motive present in many NPs and biologically active compounds. The installation of the tertiary PVE functional array (NP-PVE) from the parent ketone (NP-Ketone) should be easily accomplished in two synthetic steps (i.e., controlled alkynylide addition followed by DABCO-catalyzed enol ether formation)[20] without alteration of the stereochemical integrity of the NP's framework. The subsequent microwave (MW) irradiation of the NP-PVE derivative in the presence of catalytic amounts of imidazole (10 mol%) should generate the NP-Salicylaldehyde adduct (NP-Sal) through the domino process[18] depicted in Scheme 1. The process should be launched by the propargyl Claisen rearrangement of the PVE[21] to generate

the corresponding NP-Allenal intermediate which should host a tandem imidazole-assisted allene-diene isomerization / ester enolization reaction to generate the enol ester intermediate (NP-Enol) which in turn, should afford a tandem 6π-electrocyclization / imidazole-assisted aromatization reaction to generate the final NP-Salicylaldehyde product (NP-Sal). Ideally, the annulation should be site-selective (i.e., only one of the two possible unsubstituted α-methylene positions should be involved in the domino rearrangement), delivering just one of the two possible polycyclic topologies.[22]



Scheme 1. NP-Salicylaldehyde adducts in complexity-to-diversity strategy.

With these ideas in mind, we selected the set of readily available polycyclic ketones outlined in Figure 2. They are representative examples of terpenoid ketones featuring different stereochemical and functional patterns on their ring systems.

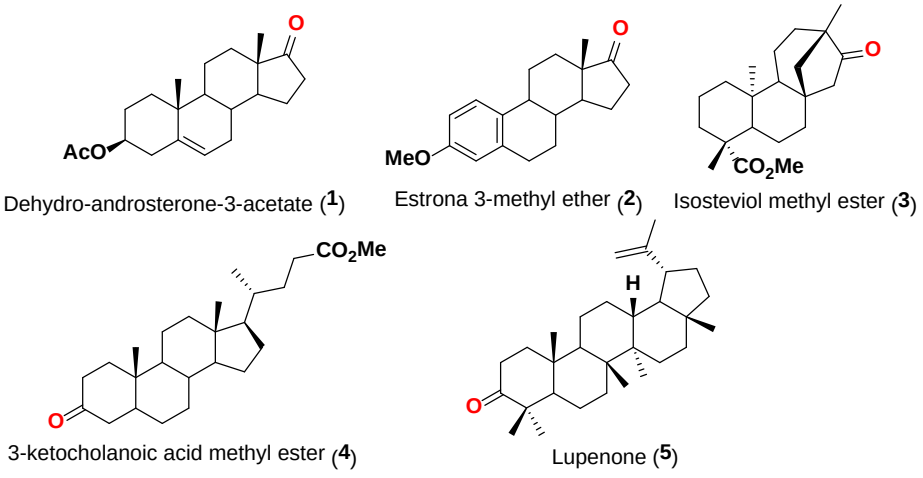
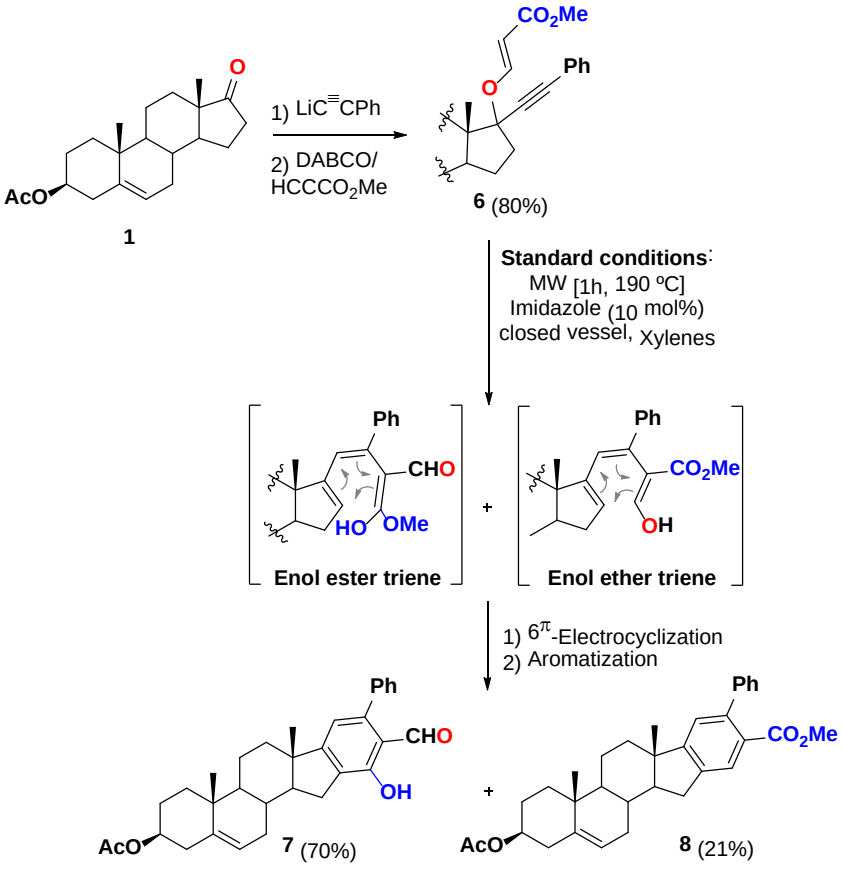


Figure 2. Natural polycyclic ketones used in this study

Results and discussion.

We set off this study with the transformation of the commercially available steroid derivative **1**[23] into its NP-Sal derivative **7** (Scheme 2), a pentacyclic meroditerpenoid structure containing the 2,2a,3,4,5,6,6a,6b,7,8,8a,13,13a,13b-tetradecahydro-1H-indeno[2,1-a]phenanthrene core (a labdan-type diterpene connecting to an indane moety).[24] Members of this family of meroditerpenoids have shown interesting biological annotations.[25] To this end, the NP-Ketone **1** was transformed into its NP-PVE derivative **6**[26] (obtained as only 1 diastereoisomer)[27] and submitted to MW-irradiation [imidazole (10 mol%), 190º C, 1h, xylenes, closed vessel][18] (hereinafter standard experimental conditions) to afford a resolved mixture of salicylaldehyde derivative (NAP-Sal) **7** (70 %) and benzoate derivative (NP-Bz) **8** (21%) respectively (Scheme 2). The formation of this NP-Bz **8** was not unexpected since we had observed it previously in some experiments with tertiary polycyclic PVEs.[18] This product

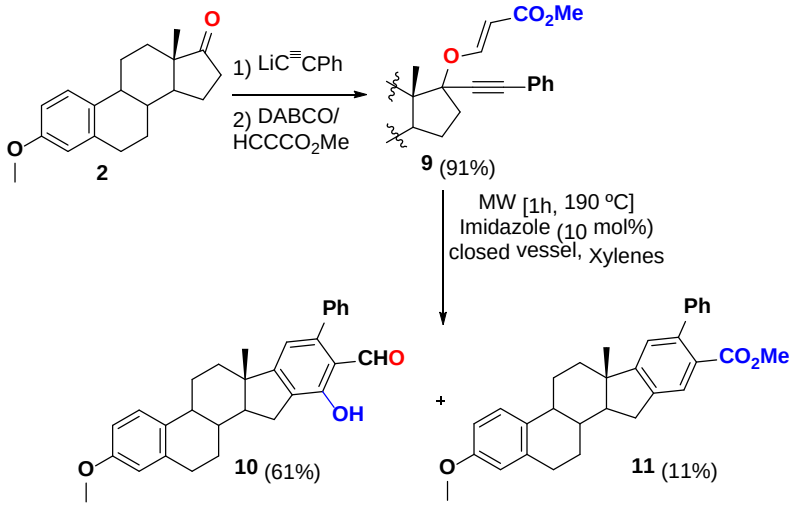
comes from the 6π-electrocyclization reaction of the alternative enol ether triene intermediate (enolization through the aldehyde), whose formation is energetically less favorable than that of the enol ester triene (enolization through the ester). Interestingly, both the B-ring double bond and the 3β-acetate were well tolerated by the reaction manifold to deliver two pentacyclic meroditerpenoids featuring different substitution patterns at the aromatic ring.



Scheme 2. Benzannulation of dehydroisoandrosterone-3-acetate (**1**).

Next, we studied the benzannulation reaction on the D-ring of the estrone derivative **2** (Scheme 3). We choose this steroidal ketone because some of its D-ring modified chemotypes

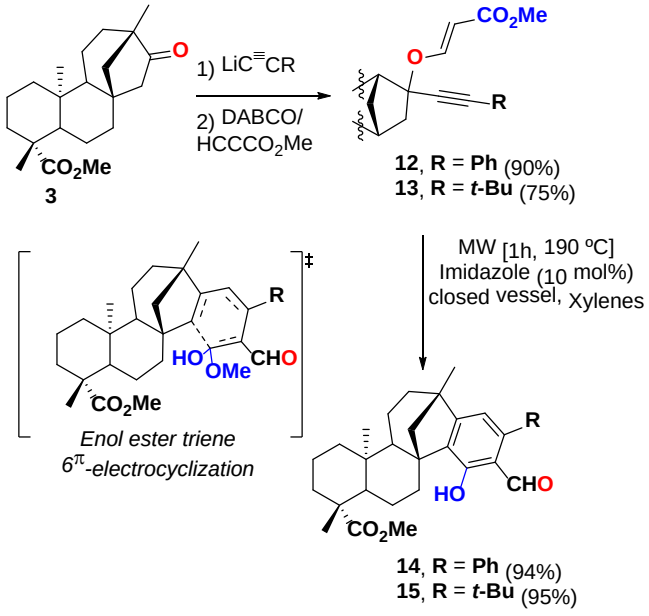
had shown interesting anticancer,[28] enzyme inhibitors activities[29] or photophysical properties for using as fluorescence probes.[30] The MW irradiation under standard conditions of the NP-PVE **9**[26] afforded the mixture of NP-Sal **10** and NP-Bz **11** in a good 72% yield (5.5:1 respectively) (Scheme 3). The mixture was easily resolved by flash-chromatography to yield pure NP-Sal **10** (61%) and NP-Bz **11** (11%). These structures represent two novel examples of non-natural pentacyclic meroditerpenoids based on the (8a*S*)-8a-methyl-2,6b,7,8,8a,13,13a,13b-octahydro-1*H*-indeno[2,1-a]phenanthrene core[31] with an unprecedented aromatic substitution pattern at the annulated aromatic ring.



Scheme 3. Benzannulation of estrone 3-methyl ether (**2**).

Isosteviol methyl ester (**3**)[32] is a readily available diterpene ester that has found use as a natural platform for the design of novel chemotypes featuring interesting biological[33] and material properties.[34] We selected it as our third NP framework in this study[35] and transformed it into the PVE derivatives **12** and **13** using phenylacetylene and 3,3-dimethylbut-1-yne as the alkyne components in the PVE formation reaction (Scheme 4).[36] These two NP-

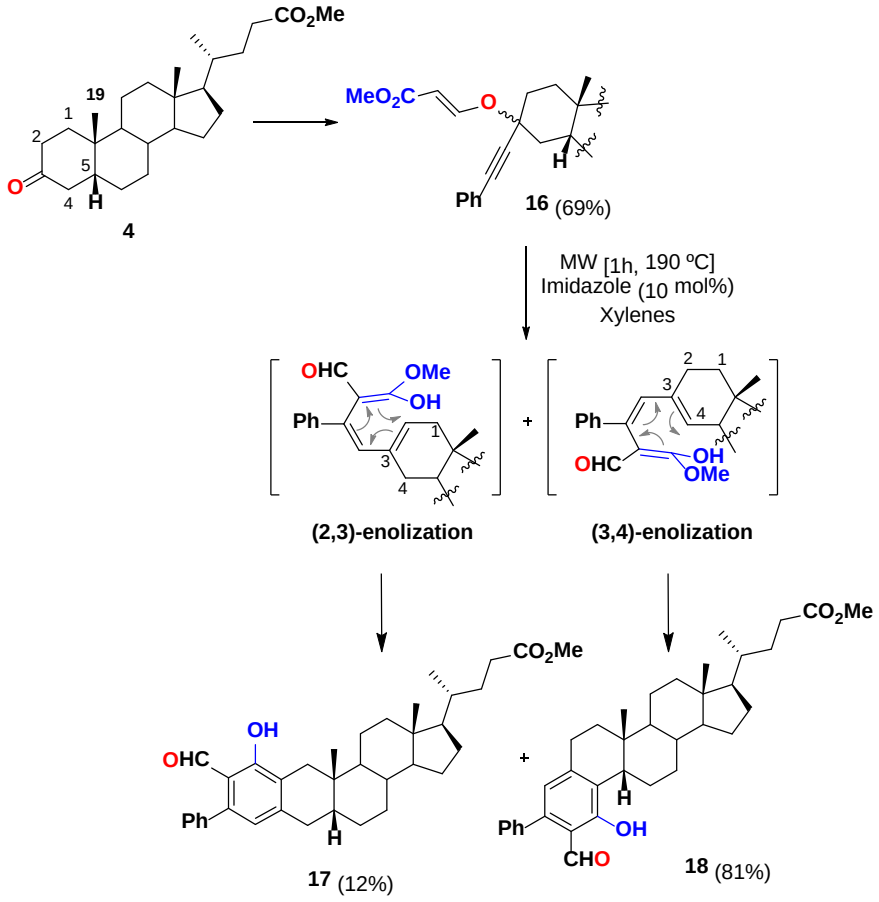
PVEs share the same polycyclic platform but present different electronic and steric properties at the terminal position of the alkyne moiety: whereas NP-PVE **12** bears a planar (all-Csp^2) and conjugated (aromatic) phenyl substituent (R = Ph), NP-PVE **13** presents a voluminous three-dimensional (all-Csp^3) and unconjugated (aliphatic) *tert*-butyl substituent (R = *t*-Bu). The MW irradiation of each one of these PVEs under standard conditions afforded NP-Sal **14** and **15** in excellent yields (95 and 94% respectively). Two conclusions arise from these results: 1) the electronic/steric nature of the substituent at the terminal alkyne position does not exercise any influence on the efficiency and chemical outcome of this process, and 2) the absence of the corresponding NP-Bz derivatives indicates that the domino reaction follows the pathway biased by the formation of the enol ester triene (Scheme 4); the alternative route through the enol ether triene intermediate is not transited at all.



Scheme 4. Salicylaldehyde-annulation of isosteviol methyl ester (**3**).

Although the extension of the A-ring of the steroidal core has been used to generate new steroidal heterocyclic derivatives with interesting pharmacological properties,[37] the number of

reported examples of steroidal derivatives bearing an aromatic ring fused to the parent A-ring is very scarce.[38] Thus, our next target was commercially available 3-ketocholanoic acid methyl ester (**4**), (an oxidized form of the cholanoic acid, one of the primary bile acids), which should allow us to gain access to the meroditerpenoids **17** (incorporating a 2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1H-cyclopenta[c]tetraphene core)[39] and/or **18** (incorporating a 2,3,3a,4,5,5a,5b,6,7,11b,12,13,13a,13b-tetradecahydro-1H-cyclopenta[a]chrysene core) (Scheme 5). The transformation of the ester **4** into its PVE derivative **16** (diastereomeric mixture) and subsequent MW-irradiation under the standard experimental conditions afforded a 1:7 mixture of the two possible meroditerpenoids **17** and **18** in an excellent yield (93%). The majority presence of isomer **18** in the reaction mixture is in full accordance with the preferred enolization of 5β-3-keto-steroids through the C4-position of the A-ring.[40] Fortunately, meroditerpenoid **18** could be isolated in pure form and in preparative amounts. Isomer **18** is a rare example of a non-natural meroditerpenoid comprising a substituted salicylaldehyde ring annulated to a 5β-cholestane core.

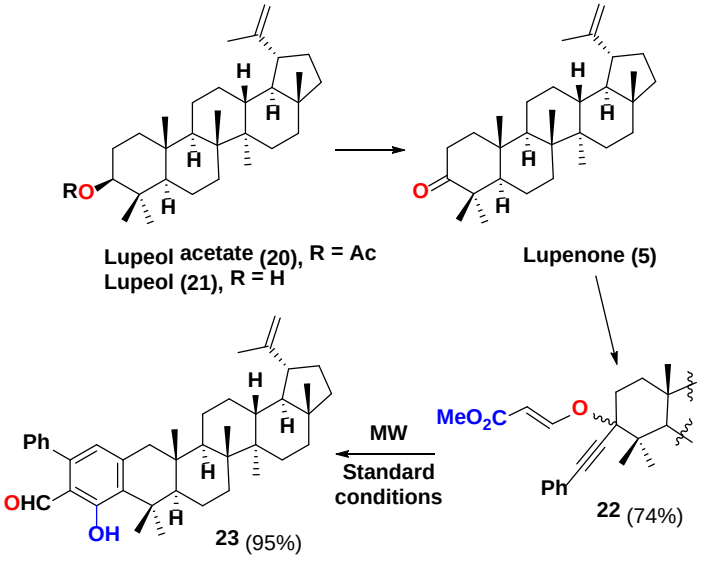


Scheme 5. Salicylaldehyde-annulation of 3-ketocholanoic acid methyl ester (**4**)

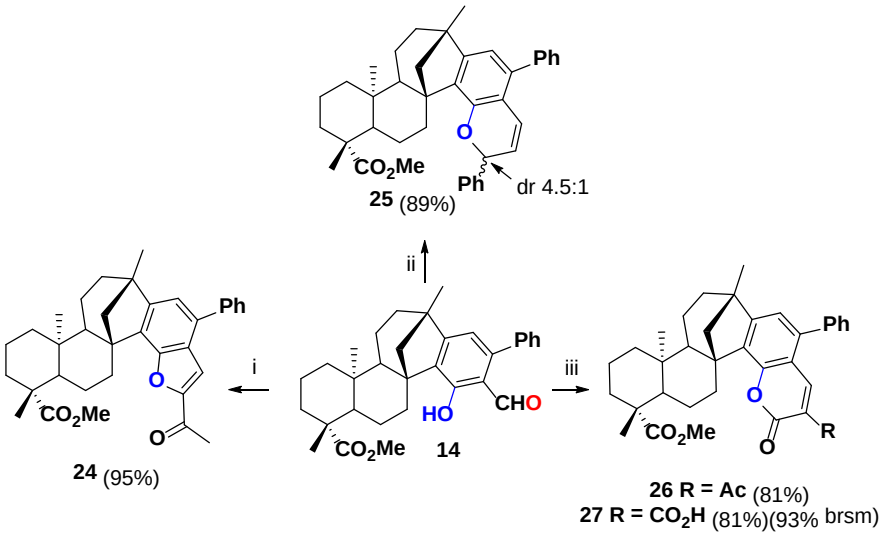
Lupenone (**5**) is a triterpenic ketone easily obtained by oxidation of lupeol (**21**), a natural phytosterol present in many edible vegetables, fruits and medicinal plants[41] and endowed with a continuum of biological activities including anti-inflammatory, anti-microbial, anti-protozoal, antiproliferative, anti-invasive, anti-angiogenic and anticholestemic. We choose lupenone as our fifth example because its impressive array of biological (pharmacological) properties and because we had direct access to almost unlimited source of biological material.[42] Lupeol has been mainly derivatized using the two available functionalities at the skeleton, i.e., the C-3 hydroxyl group[43] and the C-20 olefin moiety,[44] and much less common, by oxidation of the ring system.[45] Thus, lupenone seemed to us a validated candidate to demonstrate the strength of our approach. As a last point and related to

the lupenone structure, the presence of the two substituents at the C4-position (quaternary) of the A-ring should funnel the domino transformation toward the formation of one unique meroditerpenoid (**21)** (Scheme 6). We were delighted to observe that this was the case: the direct transformation of lupenone into its PVE derivative **20** and the subsequent MW irradiation under our standard conditions exclusively delivered the NP-Sal **21** in practically quantitative yield (≥ 95 %).

Once we demonstrated the power of the domino salicylaldehyde-annulation as a real plug and play toolkit, we tackled the study of the versatility of the annexed salicylaldehyde unit to assemble novel NP-pharmacophore hybrids. We select the salicylaldehyde **14** as the substrate for these experiments (Scheme 7). As a proof of the concept, we prepared four **14**-pharmacophore hybrids endowed with a benzofuran (**24**, 95%), a chromene (**25**, 89%) or a coumarin (**26** and **27**, 81% in both cases) unit using standard chemistry in a very efficient and effective manner.



Scheme 6. Salicylaldehyde-annulation of lupenone (**5**).



Reactions: i: chloroacetone, K_2CO_3, MeCN, reflux, 20 h; ii: trans-2-phenylvinylboronic acid, $BnNH_2$, H_2O, reflux, 20 h; iii: ethyl acetoacetate, piperidine, EtOH,reflux, 20 h; iv: Meldrum's acid, piperidinium acetate, reflux, 48 h.

Scheme 7. Synthesis of NP-chromophore hybrids of salicylaldehyde **14**.

In summary, we have shown that the salicylaldehyde-annulation reaction is an excellent plug and play toolkit to diversify the complexity of natural occurring ketones. The protocol entails the transformation of the polycyclic natural ketone into its propargyl vinyl ether derivative (two synthetic steps) and its microwave-assisted imidazole-catalyzed domino rearrangement to generate the salicylaldehyde ring. This annexed unit allows further synthetic transformations, e.g., the installation of a pharmacophore module to generate NP-pharmacophore hybrids endowed with unknown biological (pharmaceutical) annotations.

Experimental Section

General remarks. ^{1}H NMR and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded either at 400 and 100 MHz or at 500 and 125 MHz, respectively. Microwave reactions were conducted in sealed glass vessels (capacity 10 mL) using a CEM Discover microwave reactor equipped

with a surface sensor to measure the temperature of the reaction mixture. FT-IR spectra were measured in chloroform solutions using a FT-IR spectrophotometer. Mass spectra (low resolution) (EI/CI) and HRMS (EI/TOF) were obtained with a gas chromatograph/mass spectrometer. Microanalyses were performed with a carbon, hydrogen, and nitrogen analyzer. Analytical thin-layer chromatography plates used UV-active silica gel on aluminum. Flash column chromatography was carried out with silica gel 60 (particle size less than 0.020 mm) using appropriate mixtures of ethyl acetate and hexanes, or hexanes and dichloromethane as eluents. All reactions were performed in oven-dried glassware. All materials were obtained from commercial suppliers and used as received. The propargyl alcohols were prepared by addition of the lithium acetylides onto the appropriate ketones following the standard procedures (see below for a general procedure). The propargyl vinyl ethers were prepared according to our previous experimental procedure[20] (see below for a general procedure).

General procedure for the synthesis of propargyl alcohols: Phenylacetylene (13 mmol) was dissolved in 25 mL of dry THF in a round-bottom flask. After the mixture was cooled to -40 ºC, a 1.6M solution of BuLi in hexanes (13 mmol) was added dropwise. The temperature was maintained for 1 hr with stirring of the solution. The ketone was then added slowly (if solid, dissolved in THF) and the stirring was continued overnight allowing the reaction mixture to warm up to room temperature slowly without additional cooling. After completion, the reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. This was followed by isolation of the corresponding product by flash column chromatography (silica gel, appropriate mixtures of *n*-hexane / EtOAc) Yields of the desired propargyl alcohols usually exceeded 90%.

Representative procedure for the synthesis of Natural Product Propargyl Vinyl Ethers (NP-PVE) from the corresponding tertiary alcohols:[20] Methyl propiolate (excess, 5 mmol) was added dropwise (time of addition 10 minutes) to a solution of the propargylic alcohol of NP-ketone **2** (0.77 mmol) and DABCO (0.077 mmol) in a 1:9 mixture of dry CH_2Cl_2 and hexane (10 mL). The reaction mixture was stirred for 5 min (TLC control). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel; *n*-hexane / EtOAc, 95:15) to give 328.3 mg of **9** (91%).

Representative procedure for the microwave-assisted synthesis of Natural Product Salicylaldehydes (NP-Sal). Propargyl vinyl ether **9** (0.40 mmol) and imidazole (0.04 mmol) in dry xylene (1 mL) were placed in a microwave-special closed vial and the solution was irradiated for 1 hour in a single-mode microwave oven (300 Watt, 190 ºC). After removing the solvent at reduced pressure the products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 95/5) to yield 107 mg of product **10** (61%) and 17.4 mg of product **11** (11%).

(*E*)-Methyl 3-((3S,8R,9S,10R,13S,14S)-3-acetoxy-10,13-dimethyl-17-(phenylethynyl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yloxy)acrylate (6). (1.86 g, 80%). Amorphous white solid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (s, 3H), 0.97-1.03 (m, 1H), 1.03 (s, 3H), 1.10-1.18 (m, 1H), 1.37-1.47 (m, 2H), 1.49-1.88 (m, 10H), 1.98-2.02 (m, 1H), 2.02 (s, 3H), 2.18-2.25 (m, 1H), 2.30-2.36 (m, 2H), 2.41-2.48 (m, 1H), 3.68 (s, 3H), 4.54-4.62 (m, 1H), 5.35-5.38 (m, 1H), 5.40 (d, ^3J(H,H) = 12.1 Hz, 1H), 7.30-7.34 (m, 3H), 7.46-7.47 (m, 2H), 7.93 (d, ^3J(H,H) = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.9, 19.3, 20.5, 21.4, 23.4, 27.7, 31.4, 32.3, 33.5, 36.6, 36.9, 37.6, 38.1, 48.3, 49.5, 50.9, 51.0, 73.8, 88.1, 89.3, 89.9, 99.2, 122.0, 122.1, 128.3 (2C), 128.8, 131.8 (2C),

139.8, 159.8, 168.3, 170.4 ppm. IR ($CHCl_3$, cm^{-1}) 2951.7, 2226.8, 1716.0, 1637.4, 1490.,3, 1438.3, 1254.7. MS (70 eV): *m/z* (%): 338 (3.3) [M^+], 516 (2.6), 424 (15), 356 (30), 355 (100), 241 (22), 228 (33), 157 (22), 147 (20), 145 (18), 141 (16), 91 (18). HRMS (EI-TOF) m/z: calculated for $C_{33}H_{40}O_5$ 516.2876, found 516.2888.

(4S,6aR,6bS,8aS,13aS,13bR)-11-formyl-12-hydroxy-6a,8a-dimethyl-10-phenyl-3,4,5,6,6a,6b,7,8,8a,13,13a,13b-dodecahydro-1H-indeno[2,1-a]phenanthren-4-yl acetate (7): (339.2 mg; 70%). Amorphous white solid. $[\alpha]_D^{20}$ = -59.7 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.99 (s, 3H), 1.10 (s, 3H), 1.13-1.20 (m, 2H), 1.53-1.77 (m, 6H), 1.79-1.89 (m, 3H), 2.03 (s, 3H), 2.09-2.18 (m, 2H), 2.30-2.38 (m, 2H), 2.40-2.46 (m, 1H), 2.94 (dd, 1H, ^3J(H,H) = 15.2 and 6.6 Hz), 4.58-4.65 (m, 1H), 5.43-5.44 (m, 1H), 6.68 (s, 1H), 7.34-7.45 (m, 5H), 9.75 (s, 1H), 12.00 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 18.6, 19.3, 20.7, 21.4, 27.8, 27.9, 30.8, 31.6, 34.3, 36.87, 36.94, 38.1, 46.5, 50.5, 56.9, 73.8, 114.9, 117.0, 122.2, 128.0, 128.3 (2C), 128.8, 130.2 (2C), 138.3, 140.0, 147.4, 159.0, 164.5, 170.5, 196.9. ppm; IR ($CHCl_3$, cm^{-1}): ν = 2949.9, 2910.8, 2855.0, 1718.2, 1635.9, 1558.6, 1541.9, 1417.6, 1374.6, 1252.2; LRMS (70 eV) m/z (%): 484 (0.3) [M^+], 425 (33), 424 (100), 409 (12), 316 (21), 263 (14). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{32}H_{36}O_4$ 484.2614; Found 484.2630.

(4S,6aR,6bS,8aS,13aS,13bR)-methyl 4-acetoxy-6a,8a-dimethyl-10-phenyl-3,4,5,6,6a,6b,7,8,8a,13,13a,13b-dodecahydro-1H-indeno[2,1-a]phenanthrene-11-carboxylate (8): (38.6 mg; 21%). Amorphous white solid. $[\alpha]_D^{20}$ = -42.6 (c = 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.98 (s, 3H), 1.10 (s, 3H), 1.12-1.21 (m, 2H), 1.58-1.91 (m, 9H), 2.03 (s, 3H), 2.10-2.16 (m, 2H), 2.33-2.38 (m, 2H), 2.55-2.65 (m, 1H), 2.78 (dd, 1H, ^3J(H,H) = 15.0 and 6.6 Hz), 3.59 (s, 3H), 4.57-4.66 (m, 1H), 5.42-5.43 (m, 1H), 7.07 (s, 1H), 7.28-7.35 (m, 5H), 7.67 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 18.9, 19.3, 20.7,

21.4, 27.8, 30.9, 31.7, 31.9, 34.7, 36.88, 36.91, 38.1, 45.4, 50.5, 51.7, 57.4, 73.8, 122.2, 123.2, 126.3, 126.9, 127.9 (2C), 128.4 (2C), 128.6, 140.0, 141.3, 141.9, 142.1, 157.9, 169.5, 170.5 ppm; IR ($CHCl_3$, cm^{-1}): ν = 2950.7, 2910.8, 2855.0, 1718.0, 1558.5, 1540.6, 1436.2, 1373.1, 1256.1; LRMS (70 eV) m/z (%): 498 (0.4) [M^+], 439 (37), 438 (100), 330 (14), 277 (19), 105 (15), 91 (16). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{33}H_{38}O_4$ 498.2770; Found 498.2780.

(E)-methyl 3-((8R,9S,13S,14S,17S)-3-methoxy-13-methyl-17-(phenylethynyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-17-yloxy)acrylate (9): (328.3 mg; 91%). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (s, 3H), 1.36-1.59 (m, 4H), 1.80-1.96 (m, 4H), 2.10 (dt, ^3J(H,H) = 13.1 and 4.0 Hz, 1H), 2.25-2.34 (m, 2H), 2.39-2.43 (m, 1H), 2.50-2.57 (m, 1H), 2.83-2.91 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 5.48 (d, ^3J(H,H) = 12.1 Hz, 1H), 6.66 (d, ^3J(H,H) = 2.5 Hz, 1H), 6.75 (dd, ^3J(H,H) = 8.3 and 2.5 Hz, 1H), 7.23 (d, ^3J(H,H) = 8.3 Hz, 1H), 7.34-7.37 (m, 3H), 7.50-7.54 (m, 2H), 8.01 (d, ^3J(H,H) = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.0, 22.9, 26.2, 27.1, 29.7, 33.6, 33.7, 39.1, 43.4, 48.7, 49.7, 50.9, 55.1, 88.1, 89.2, 89.9, 99.2, 111.5, 113.8, 122.0, 126.3, 126.3 (2C), 128.7, 131.8 (2C), 132.1, 137.7, 157.5, 159.7, 168.2 ppm. HRMS (EI-TOF) m/z: calculated for $C_{31}H_{34}O_4$ 493.2355, found 493.2365. Elemental analysis calcd (%) for $C_{31}H_{34}O_4$: C 79.12; H 7.28; found: C 79.29; H 7.43.

(6bS,8aS,13aS,13bS)-12-hydroxy-4-methoxy-8a-methyl-10-phenyl-2,6b,7,8,8a,13,13a,13b-octahydro-1H-indeno[2,1-a]phenanthrene-11-carbaldehyde (10): (107.0 mg; 61%). Amorphous white solid. $[\alpha]_D^{20}$ = 56.9 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (s, 3H), 1.51-1.59 (m, 1H), 1.71-1.9 (m, 4H), 2.06-2.11 (m, 1H), 2.23-2.26 (m, 1H), 2.33-2.40 (m, 1H), 2.45-2.49 (m, 1H), 2.55 (dd, ^3J(H,H) = 14.9 and 11.9 Hz,

1H), 2.90-3.00 (m, 2H), 3.06 (dd, ^{3}J(H,H) = 14.9 and 6.1 Hz, 1H), 3.80 (s, 3H), 6.68-6.70 (m, 1H), 6.73-6.76 (m, 1H), 6.75 (m, 1H), 7.24 (d, ^{3}J(H,H) = 8.6 Hz, 1H), 7.38-7.42 (m, 2H), 7.44-7.49 (m, 3H), 9.79 (s, 1H), 12.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.8, 26.4, 27.6, 27.7, 29.7, 34.4, 37.7, 44.3, 46.9, 55.2, 56.1, 111.5, 113.9, 114.8, 117.0, 126.0, 128.0, 128.3 (2C), 128.7, 130.2 (2C), 132.3, 137.9, 138.2, 147.4, 157.6, 159.0, 164.6, 196.9 ppm**.** IR ($CHCl_3$, cm^{-1}) 2938.4, 2872.3, 1731.4, 1628.4, 1610.2, 1438.0, 1397.1, 1370.6, 1313.5, 1292.4. MS (70 eV): *m/z* (%): 438 (100) [M^+], 423 (9.0), 263 (8.0), 249 (8.7), 173 (40.5), 160 (20.8), 147 (13.7),). HRMS (EI-TOF) m/z: calculated for $C_{30}H_{30}O_3$ 438.2195, found 438.2206. Elemental analysis calcd (%) for $C_{30}H_{30}O_3$: C 82.16; H 6.89; found: C 82.11; H 7.22.

(6bS,8aS,13aS,13bS)-methyl 4-methoxy-8a-methyl-10-phenyl-2,6b,7,8,8a,13,13a,13b-octahydro-1H-indeno[2,1-a]phenanthrene-11-carboxylate (11): (17.4 mg; 11%). Amorphous brownish solid. $[\alpha]_D^{20}$ = 34.9 (c = 0.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (s, 3H), 1.47-1.58 (m, 1H), 1.66-1.80 (m, 3H), 1.84-1.91 (m, 1H), 2.01-2.05 (m, 1H), 2.23-2.27 (m, 1H), 2.35-2.47 (m, 2H), 2.64-2.71 (m, 1H), 2.85-3.01 (m, 3H), 3.60 (s, 3H), 3.78 (s, 3H), 6.66 (d, ^{3}J(H,H) = 2.7 Hz, 1H), 6.73 (dd, ^{3}J(H,H) = 8.6 and 2.8 Hz, 1H), 7.11 (s, 1H), 7.23 (d, ^{3}J(H,H) = 8.7 Hz, 1H), 7.30-7.40 (m, 5H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.2, 26.5, 27.9, 29.7, 31.7, 34.8, 37.8, 44.3, 45.9, 51.7, 55.2, 56.6, 11.5, 113.9, 123.2, 126.1, 126.3, 126.9, 127.9 (2C), 128.4 (2C), 128.6, 132.5, 137.9, 141.4, 141.9, 142.1, 157.6, 158.1, 169.5 ppm**.** HRMS (EI-TOF) m/z: calculated for $C_{31}H_{32}O_3$ 475.2249, found 475.2253.

Methyl (4R,4aS,6aR,8S,9S,11aR,11bS)-8-(((E)-3-methoxy-3-oxoprop-1-en-1-yl)oxy)-4,9,11b-trimethyl-8-(phenylethynyl)tetradecahydro-6a,9-

methanocyclohepta[a]naphthalene-4-carboxylate (12): (2.40 g; 90%). Amorphous white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.67 (s, 3H), 0.82-0.90 (m, 1H), 0.94-1.05 (m, 3H), 1.08-1.12 (m, 1H), 1.13 (s, 3H), 1.14 (s, 3H), 1.29-1.42 (m, 3H), 1.45-1.52 (m, 1H), 1.55-1.61 (m, 3H), 1.67-1.82 (m, 4H), 1.84-1.90 (m, 1H), 2.11-2.17 (m, 2H), 2.49 (dd, ^{3}J(H,H) = 14.4 and 2.5 Hz, 1H), 3.61 (s, 3H), 3.68 (s, 3H), 5.42 (d, ^{3}J(H,H) = 12.1 Hz, 1H), 7.28-7.32 (m, 3H), 7.41-7.43 (m, 2H), 7.92 (d, ^{3}J(H,H) = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.9, 18.8, 20.3, 21.6, 23.1, 28.7, 35.2, 37.9, 38.0, 39.8, 41.5, 42.0, 43.7, 46.8, 49.7, 50.9, 51.1, 55.0, 55.3, 56.8, 88.4, 89.0, 89.7, 99.3, 122.3, 128.3 (2C), 128.6, 131.7 (2C), 159.8, 166.3, 177.8 ppm. IR ($CHCl_3$, cm^{-1}) 2951.7, 2851.5, 2227.5, 1715.5, 1636.8, 1456.4, 1438.1, 1332.4, 1190.1, 1134.8. MS (70 eV): *m/z* (%): 518 (23) [M^+], 486 (27), 459 (22), 426 (15), 418 (37), 417 (100), 357 (49), 249 (21), 229 (21), 197 (21), 121 (32), 91 (24). Elemental analysis calcd (%) for $C_{33}H_{42}O_5$: C 76.42; H 8.16; found: C 76.48; H 7.92.

Methyl (4R,4aS,6aR,8S,9S,11aR,11bS)-8-(3,3-dimethylbut-1-yn-1-yl)-8-(((E)-3-methoxy-3-oxoprop-1-en-1-yl)oxy)-4,9,11b-trimethyltetradecahydro-6a,9-methanocyclohepta[a]naphthalene-4-carboxylate (13): (237 mg, 75%). Amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.64 (s, 3H), 0.80-0.88 (m, 1H), 0.93-1.03 (m, 4H), 1.00 (s, 3H), 1.14 (s, 3H), 1.21 (s, 9H), 1.24-1.79 (m, 12H), 1.95 (t, 1H, ^{3}J(H,H) = 14.6 Hz), 2.10-2.18 (m, 1H), 2.38 (dd, ^{3}J(H,H) = 14.4 and 2.8 Hz, 1H), 3.60 (s, 3H), 3.68 (s, 3H), 5.34 (d, ^{3}J(H,H) = 12.1 Hz, 1H), 7.88 (d, ^{3}J(H,H) = 12.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.9, 18.8, 20.3, 21.7, 23.0, 27.6, 28.8, 30.8 (3C), 35.1, 37.9, 38.1, 39.9, 41.7, 41.8, 43.8, 46.4, 50.2, 50.9, 51.1, 55.1, 55.5, 56.9, 79.6, 88.4, 98.5, 98.7, 160.3, 168.5, 177.9 ppm. IR ($CHCl_3$, cm^{-1}) 2951.1, 2237.0, 1715.7, 1635.8, 1457.4, 1190.3, 1135.3. MS (70 eV): *m/z* (%): 439 (3.9)

[M^+-59 (CO_2Me)], 398 (33), 397 (100), 337 (23), 229 (12), 173 (10), 161 (19), 121 (22), 107 (17). Elemental analysis calcd (%) for $C_{31}H_{46}O_5$: C 74.66; H 9.30; found: C 74.86; H 8.93.

(3S,7bS,9aS,10R,13aS,13bS)-7-Hydroxy-3,10,13a-trimethyl-10-((methylperoxy)-l2-methyl)-5-phenyl-1,2,3,8,9,9a,10,11,12,13,13a,13b-dodecahydro-3,7b-methanobenzo[3,4]cyclohepta[1,2-a]naphthalene-6-carbaldehyde (14): (1.84 g; 94%). Amorphous white solid. $[\alpha]_D^{20}$ = -62.1 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.59 (s, 3H), 0.77-0.95 (m, 2H), 1.00-1.07 (m, 1H), 1.20 (s, 3H), 1.22 (s, 3H), 1.15-1.27 (m, 2H), 1.40-1.67 (m, 7H), 1.79-1.90 (m, 2H), 1.94 (dd, 1H, ^3J(H,H) = 10.4 and 2.3 Hz), 2.15-2.21 (m, 2H), 2.81-2.93 (m, 1H), 3.68 (s, 3H), 6.58 (s, 1H), 7.35-7.38 (m, 2H), 7.40-7.46 (m, 3H), 9.75 (s, 1H), 12.52 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.4, 19.4, 20.8, 21.9, 23.6, 28.8, 35.5, 36.6, 37.2, 38.5, 40.1, 43.7, 44.0, 47.1, 51.0, 56.6, 56.7, 64.3, 114.5, 117.3, 128.0, 128.3 (2H), 130.2 (2H), 133.1, 138.2, 147.8, 158.5, 162.4, 178.1, 197.2 ppm; IR ($CHCl_3$, cm^{-1}): ν = 2952.2, 2849.9, 1714.2, 1631.8, 1542.7, 1451.0, 1398.2, 1360.3, 1330.7, 1303.4, 1247.2, 1149.5; LRMS (70 eV) m/z (%): 486 (100) [M^+], 468 (56), 436 (63), 426 (27), 357 (17), 301 (17), 277 (21), 264 (38), 263 (34). HRMS (EI-TOF) m/z: [M]$^+$ Calcd for $C_{32}H_{38}O_4$ 486.2770; Found 486.2769.

(3S,7bS,9aS,10R,13aS,13bS)-5-(tert-butyl)-7-hydroxy-3,10,13a-trimethyl-10-((methylperoxy)-l2-methyl)-1,2,3,8,9,9a,10,11,12,13,13a,13b-dodecahydro-3,7b-methanobenzo[3,4]cyclohepta[1,2-a]naphthalene-6-carbaldehyde (15): (40.9 mg; 95%). Amorphous white solid. $[\alpha]_D^{20}$ = -90.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.53 (s, 3H), 0.64-0.75 (m, 1H), 0.88 (td, 1H, ^3J(H,H) = 13.4 and 4.0 Hz), 1.01 (td, 1H, ^3J(H,H) = 13.4 and 4.0 Hz), 1.12-1.20 (m, 2H), 1.18 (s, 3H), 1.20 (s, 3H), 1.36-1.63 (m, 7H), 1.50 (s, 9H), 1.79-1.88 (m, 3H), 2.10-2.16 (m, 2H), 2.83 (qd, 1H, ^3J(H,H) = 13.7 and 4.0 Hz),

3.66 (s, 3H), 6.61 (s, 1H), 10.7 (s, 1H), 13.22 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.3, 19.4, 20.8, 21.9, 23.5, 28.8, 33.8 (3C), 35.5, 35.8, 36.5, 37.2, 38.5, 40.1, 43.8, 44.0, 46.9, 51.0, 56.5, 56.7, 64.4, 110.2, 117.1, 132.3, 154.6, 161.1, 161.9, 178.1, 196.6 ppm; IR ($CHCl_3$, cm^{-1}): ν = 2951.7, 1715.9, 1623.8, 1542.0, 1457.9, 1394.4, 1243.4; LRMS (70 eV) m/z (%): 466 (100) [M^+], 448 (37), 416 (33), 415 (53), 406 (57), 391 (17), 256 (18), 245 (21), 244 (42). Elemental analysis calcd (%) for $C_{30}H_{42}O_4$: C 77.21; H 9.07; found: C 77.34; H 9.10.

(R)-Methyl 4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-((E)-3-methoxy-3-oxoprop-1-enyloxy)-10,13-dimethyl-3-(phenylethynyl)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (16): (400 mg, 69%). Amorphous white solid: Major isomer (α isomer) ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.64 (s, 3H), 0.90 (d, 3H, ^3J(H,H) = 6.3 Hz), 0.97 (s, 3H), 1.01-1.58 (m, 16H), 1.69-1.97 (m, 9H), 2.11-2.24 (m, 2H), 2.30-2.38 (m, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 5.40 (d, ^3J(H,H) = 12.1, 1H), 7.28-7.34 (m, 3H), 7.44-7.46 (m, 2H), 8.03 (d, 1H, ^3J(H,H) = 12.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.0, 18.3, 21.0, 23.4, 24.1, 26.4, 26.8, 28.1, 30.99, 31.04, 33.0, 34.0, 34.7, 35.3, 35.8, 38.7, 40.1, 40.3, 41.0, 42.7, 51.0, 51.4, 56.0, 56.4, 81.4, 87.8, 89.0, 99.1, 122.0, 128.3 (2C), 128.8, 131.9 (2C), 158.6, 168.3, 174.7 ppm. IR ($CHCl_3$, cm^{-1}) 2950.2, 2869.0, 2232.2, 1705.5, 1637.0, 1602.1, 1438.4, 1312.6, 1168.4, 1135.3. MS (70 eV): *m/z* (%): 574 (4.7) [M^+], 543 (39), 542 (100), 473 (6.1), 400 (5.7), 277 (6.9), 265 (12), 264 (21), 263 (18), 224 (9.4), 121 (6.0), 95 (9.0). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{37}H_{50}O_5$ 574.3658; Found 574.3637.

(4R)-methyl 4-((1R,3aS,3bR,11aS,11bS,13aR)-9-formyl-10-hydroxy-11a,13a-dimethyl-8-phenyl-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1H-

cyclopenta[c]tetraphen-1-yl)pentanoate (17): Minor product is slightly more polar in toluene/*n*-hexane (1:1). Characteristic signals in ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.00 (dd, 1H, ^{3}J(H,H) = 19.0 and 11.1 Hz), 3.21 (d, 1H, ^{3}J(H,H) = 17.4 Hz), 3.63 (s, 3H), 12.36 (s, 1H).

(4R)-Methyl 4-((3R,3aR,5aS,5bR,13aS,13bS)-10-formyl-11-hydroxy-3a,5b-dimethyl-9-phenyl-2,3,3a,4,5,5a,5b,6,7,11b,12,13,13a,13b-tetradecahydro-1H-cyclopenta[a]chrysen-3-yl)pentanoate (18): 186 mg of a mixture of **18** + **17** (81% + 12% by ^{1}HNMR). Major product **18** was partially separated from **17** by flash chromatography. Amorphous white solid. $[\alpha]_D^{20}$ = -43.6 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.68 (s, 3H), 0.92 (d, 3H, ^{3}J(H,H) = 6.3 Hz), 0.94 (s, 3H), 0.91-0.95 (s, 1H), 1.03-1.17 (m, 4H), 1.25-1.36 (m, 3H), 1.39-1.64 (m, 6H), 1.68-1.91 (m, 5H), 1.97-2.02 (m, 2H), 2.17-2.25 (m, 1H), 2.30-2.38 (m, 1H), 2.61-2.82 (m, 3H), 3.65 (s, 3H), 6.60 (s, 1H), 7.33-7.35 (m, 2H), 7.39-7.44 (m, 3H), 9.74 (s, 1H), 12.66 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.9, 18.3, 21.4, 21.8, 23.8, 24.2, 27.3, 28.1, 29.1, 31.04, 31.08, 31.11, 32.5, 34.1, 35.4, 39.9, 40.9, 42.5, 45.5, 51.4, 55.8, 57.6, 115.7, 122.0, 127.9, 128.2 (2C), 128.3, 130.0 (2C), 137.8, 143.5, 147.5, 162.9, 174.7, 196.7 ppm. IR ($CHCl_3$, cm^{-1}) 2938.4, 2872.3, 1731.4, 1628.4, 1610.2, 1438.0, 1397.1, 1370.6, 1313.5, 1292.4. MS (70 eV): *m/z* (%): 542 (100) [M^+], 265 (11), 264 (21), 263 (16), 251 (12), 237 (5.1). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{36}H_{46}O_4$ 542.3396; Found 542.3414.

(E)-methyl 3-((1R,3aR,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a,5a,5b,8,8,11a-hexamethyl-9-(phenylethynyl)-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-yloxy)acrylate (22): (146 mg; 74%). Amorphous white solid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78 (s, 3H), 0.82-0.87 (m, 2H), 0.87 (s, 3H), 0.94 (s, 3H), 0.95 (s, 3H), 1.04 (s, 3H), 1.07

(s, 3H), 1.13-1.52 (m, 15H), 1.62-1.71 (m, 4H), 1.67 (s, 3H), 1.84 (dt, 1H, ^{3}J(H,H) = 13.1 and 3.5 Hz), 1.88-1.94 (m, 1H), 2.02 (td, 1H, ^{3}J(H,H) = 13.4 and 3.5 Hz), 2.38 (td, 1H, ^{3}J(H,H) = 10.9 and 9.5 Hz), 3.68 (s, 3H), 4.56 (s, 1H), 4.68 (s, 1H), 5.38 (d, ^{3}J(H,H) = 12.1, 1H), 7.32-7.36 (m, 3H), 7.46-7.48 (m, 2H), 8.15 (d, 1H, ^{3}J(H,H) = 12.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.5, 16.0, 16.5, 18.0, 18.1, 18.4, 19.3, 21.0, 25.1, 25.9, 27.5, 29.8, 30.6, 34.3, 35.6, 37.1, 37.8, 38.0, 40.0, 40.9, 42.3, 42.8, 43.0, 48.0, 48.4, 50.6, 50.9, 53.6, 87.2, 87.3, 91.0, 98.3, 109.4, 122.3, 128.4 (2C), 128.7, 131.7 (2C), 150.9, 159.5, 168.5 ppm. HRMS (ESI^+): m/z $[M+Na]^+$ calcd for $C_{42}H_{58}O_3Na$: 633.4284. Found: 633.4282.

(1R,3aR,5aR,5bR,7aR,13aS,13bR,15aR,15bR)-12-hydroxy-3a,5a,5b,8,8,13a-hexamethyl-10-phenyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,13,13a,13b,14,15,15a,15b-octadecahydro-1H-indeno[4,5-c]tetraphene-11-carbaldehyde (23): (91.0 mg; 95%). Amorphous white solid. $[\alpha]_D^{20}$ = 52.6 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (s, 6H), 0.79-1.76 (m, 19H), 1.00 (s, 3H), 1.11 (s, 3H), 1.23 (s, 3H), 1.24 (s, 3H), 1.70 (s, 3H), 1.88-1.96 (m, 2H), 2.43 (dt, 1H, ^{3}J(H,H) = 11.1 and 5.8 Hz), 3.15 (d, 1H, ^{3}J(H,H) = 16.9 Hz), 4.59 (s, 1H), 4.71 (s, 1H), 6.85 (s, 1H), 7.35-7.38 (m, 2H), 7.40-7.46 (m, 3H), 9.74 (s, 1H), 12.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 15.7, 16.0, 18.1, 19.3, 20.2, 21.6, 24.8, 25.3, 27.5, 29.8, 32.7, 33.5, 35.5, 35.6, 37.9, 38.2, 38.3, 40.0, 40.8, 42.95, 43.04, 48.0, 48.3, 49.2, 52.6, 109.5, 114.8, 120.2, 123.3, 127.8, 128.3 (2C), 130.2 (2C), 138.3, 143.5, 150.8, 155.5, 161.4, 196.5 ppm. HRMS (ESI^+): m/z $[M+Na]^+$ calcd for $C_{41}H_{54}O_2Na$: 601.4022. Found: 601.4023.

Synthesis of NP-benzofuran 24:[46] NP-Sal **14** (100.9 mg, 0.207 mmol), chloroacetone (0.248 mmol) and K_2CO_3 (0.207 mmol) were heated in refluxing acetonitrile (2 mL) during 20 hours. After that time, the solvent was removed at reduced pressure. The products were purified by

flash column chromatography (silica gel, appropriate mixtures of ethyl acetate / *n*-hexane) to yield **24** (103.4 mg; 95%).

Synthesis of NP-chromene 25:[47] NP-Sal **14** (162.21 mg, 0.333 mmol), *trans*-2-phenylvinylboronic acid (0.42 mmol) and benzylamine (0.42 mmol) were heated in water (3 mL) during 20 hours. After that time, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, filtered and evaporated. The products were purified by flash column chromatography (silica gel, appropriate mixtures of ethyl acetate / *n*-hexane) to yield two epimers **25** (less polar: 30.3 mg, 16%; more polar: 140.4 mg, 73%).

Synthesis of NP-coumarin 26:[48] NP-Sal **14** (107.4 mg, 0.2207 mmol), ethyl acetoacetate (0.44 mmol) and piperidine (0.022 mmol) were heated in refluxing EtOH (3 mL) during 20 hours. After that time, the solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of ethyl acetate / *n*-hexane) to yield **26** (98.6 mg; 81%).

Synthesis of NP-coumarin 27:[48] NP-Sal **14** (486.6 mg, 1.0 mmol), Meldrum's acid (1.3 mmol) and piperidinium acetate (0.2 mmol) were heated in refluxing EtOH (3 mL) during 48 hours. The solvent was removed at reduced pressure. The products were purified by flash column chromatography (silica gel, appropriate mixtures of dichloromethane/MeOH) to yield **27** (449.2 mg; 81%).

1-((1R,4aS,4bS,7S,12cS,14aS)-1,4a,7-trimethyl-1-((methylperoxy)-l2-methyl)-9-phenyl-1,2,3,4,4a,4b,5,6,7,13,14,14a-dodecahydro-7,12c-methanonaphtho[2',1':3,4]cyclohepta-[1,2-g]benzofuran-11-yl)ethan-1-one (24): Amorphous white solid. (103.4 mg; 95%). $[\alpha]_D^{20}$ = -9.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.42 (s, 3H), 0.68-0.78 (m, 1H),

0.95 (td, 1H, ^{3}J(H,H) = 13.5 and 4.1 Hz), 1.07 (td, 1H, ^{3}J(H,H) = 13.5 and 4.1 Hz), 1.29 (s, 3H), 1.33 (s, 3H), 1.24-1.44 (m, 3H), 1.54-1.69 (m, 6H), 1.76-1.86 (m, 1H), 2.02 (dd, 1H, ^{3}J(H,H) = 9.9 and 1.8 Hz), 2.12-2.21 (m, 2H), 2.31 (dt, 1H, ^{3}J(H,H) = 13.7 and 3.1 Hz), 2.72 (s, 3H), 3.02 (qd, 1H, ^{3}J(H,H) = 14.0 and 3.7 Hz), 3.68 (s, 3H), 7.08 (s, 1H), 7.37-7.41 (m, 1H), 7.46-7.50 (m, 2H), 7.60-7.62 (m, 2H), 7.66 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.8, 19.4, 21.0, 21.6, 24.1, 26.9, 29.2, 36.3, 36.8, 37.4, 38.2, 40.1, 43.8, 43.9, 47.2, 51.3, 55.9, 57.0, 64.5, 112.5, 116.5, 125.0, 127.5, 128.6 (2C), 128.7 (2C), 130.0, 136.0, 139.7, 151.5, 152.5, 152.9, 177.7, 189.1 ppm; HRMS (ESI^{+}): m/z $[M+Na]^{+}$ calcd for $C_{35}H_{40}O_4Na$: 547.2824. Found: 547.2823.

(1R,4aS,4bS,7S,13cS,15aS)-1,4a,7-trimethyl-1-((methylperoxy)-l2-methyl)-9,12-diphenyl-1,3,4,4a,4b,5,6,7,12,14,15,15a-dodecahydro-2H-7,13c-methanonaphtho-[2',1':3,4]cyclohepta-[1,2-h]chromene (25): Amorphous white solid. 89% yield of a mixture of two separable epimers (1:4.5). 170.7 mg. **Minor diastereomer** (30.3 mg; 15%). $[\alpha]_D^{20}$ = 23.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.41 (s, 3H), 0.81-0.92 (m, 2H), 0.97 (td, 1H, ^{3}J(H,H) = 13.4 and 3.9 Hz), 1.05-1.08 (m, 1H), 1.11 (s, 3H), 1.21 (s, 3H), 1.22-1.26 (m, 1H), 1.34-1.39 (m, 1H), 1.42-1.55 (m, 4H), 1.58-1.80 (m, 4H), 1.97 (dd, 1H, ^{3}J(H,H) = 10.2 and 2.0 Hz), 2.03-2.08 (m, 1H), 2.26-2.39 (m, 2H), 3.20 (s, 3H), 5.68 (t, 1H, ^{3}J(H,H) = 2.6 Hz), 5.83 (dd, 1H, ^{3}J(H,H) = 9.7 and 3.0 Hz), 6.57 (dd, 1H, ^{3}J(H,H) = 9.7 and 2.2 Hz), 6.62 (s, 1H), 7.33-7.37 (m, 2H), 7.41-7.48 (m, 6H), 7.57-7.59 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.9, 19.5, 21.1, 22.3, 24.2, 29.2, 36.1, 37.1, 37.2, 38.3, 40.2, 43.0, 43.7, 47.2, 50.7, 57.0, 58.0, 65.4, 77.04, 114.8, 119.1, 123.9, 124.9, 127.0, 127.9 (2C), 128.0 (2C), 128.2, 128.6 (2C), 129.9 (2C), 133.0, 138.5, 140.1, 140.6, 150.1, 153.6, 177.2 ppm; HRMS (ESI^{+}): m/z $[M+Na]^{+}$ calcd for $C_{40}H_{44}O_3Na$: 595.3188. Found: 595.3184. **Major**

diastereomer: (140.4 mg, 54%). $[\alpha]_D^{20}$ = -175.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.67 (s, 3H), 0.81-0.94 (m, 2H), 0.97-1.06 (m, 1H), 1.14-1.24 (m, 2H), 1.17 (s, 3H), 1.19 (s, 3H), 1.34-1.57 (m, 5H), 1.61-1.77 (m, 3H), 1.82-1.97 (m, 3H), 2.13-2.16 (m, 1H), 2.66 (qd, 1H, ^3J(H,H) = 13.7 and 4.0 Hz), 3.34 (s, 3H), 5.67 (dd, 1H, ^3J(H,H) = 10.0 and 3.8 Hz), 5.98-6.00 (m, 1H), 6.54 (s, 1H), 6.54-6.57 (m, 1H), 7.30-7.44 (m, 8H), 7.50-7.52 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.7, 19.4, 21.1, 22.3, 23.9, 28.8, 35.8, 37.31, 37.33, 38.6, 40.3, 42.8, 43.9, 46.9, 50.6, 56.6, 57.4, 64.7, 75.2, 114.7, 117.5, 122.5, 123.7, 126.7 (2C), 126.9, 127.8, 128.0 (2C), 128.5 (2C), 129.9 (2C), 132.7, 138.7, 140.5, 140.7, 148.5, 153.8, 178.1 ppm; HRMS (ESI^+): m/z $[M+Na]^+$ calcd for $C_{40}H_{44}O_3Na$: 595.3188. Found: 595.3190.

(1R,4aS,4bS,7S,13cS,15aS)-11-acetyl-1,4a,7-trimethyl-1-((methylperoxy)-l2-methyl)-9-phenyl-1,2,3,4,4a,4b,5,6,7,14,15,15a-dodecahydro-12H-7,13c-methanonaphtho[2',1':3,4]-cyclohepta[1,2-h]chromen-12-one (26): Amorphous white solid. (98.6 mg; 81%). $[\alpha]_D^{20}$ = -131.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.50 (s, 3H), 0.66-0.78 (m, 1H), 0.82-0.96 (m, 1H), 1.04 (td, 1H, ^3J(H,H) = 13.3 and 3.9 Hz), 1.23-1.27 (m, 1H), 1.26 (s, 3H), 1.27 (s, 3H), 1.32-1.36 (m, 1H), 1.42-1.46 (m, 1H), 1.52-1.71 (m, 6H), 1.79-1.91 (m, 1H), 2.00-2.09 (m, 2H), 2.18-2.21 (m, 1H), 2.28-2.33 (m, 1H), 2.66 (s, 3H), 3.16 (qd, 1H, ^3J(H,H) = 13.6 and 4.1 Hz), 3.76 (s, 3H), 6.97 (s, 1H), 7.34-7.36 (m, 2H), 7.43-7.51 (m, 3H), 8.53 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.6, 19.2, 20.8, 22.0, 23.6, 28.5, 30.5, 35.4, 36.7, 37.3, 38.7, 40.1, 43.95, 44.04, 47.6, 51.4, 56.4, 56.7, 64.5, 115.2, 118.9, 122.0, 128.4, 128.8 (2C), 129.9 (2C), 133.1, 138.0, 144.0, 147.1, 151.4, 158.7, 160.3, 178.3, 195.7 ppm; HRMS (ESI^+): m/z $[M+Na]^+$ calcd for $C_{36}H_{40}O_5Na$: 575.2773. Found: 575.2775.

(1R,4aS,4bS,7S,13cS,15aS)-1,4a,7-trimethyl-1-((methylperoxy)-l2-methyl)-12-oxo-9-phenyl-1,3,4,4a,4b,5,6,7,12,14,15,15a-dodecahydro-2H-7,13c-methanonaphtho[2',1':3,4]-cyclohepta[1,2-h]chromene-11-carboxylic acid (27): Amorphous white solid. (449.2 mg; 81%). $[\alpha]_D^{20}$ = -106.9 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25ºC): δ 0.47 (s, 3H), 0.65-0.76 (m, 1H), 0.94 (td, 1H, ^3J(H,H) = 13.4 and 4.0 Hz), 1.05 (td, 1H, ^3J(H,H) = 13.5 and 4.1 Hz), 1.24-1.28 (m, 1H), 1.27 (s, 3H), 1.28 (s, 3H), 1.36-1.46 (m, 2H), 1.56-1.73 (m, 6H), 1.79-1.90 (m, 1H), 2.03-2.08 (m, 2H), 2.17-2.22 (m, 1H), 2.26-2.31 (m, 1H), 3.03 (qd, 1H, ^3J(H,H) = 14.0 and 4.2 Hz), 3.72 (s, 3H), 7.10 (s, 1H), 7.34-7.36 (m, 2H), 7.46-7.53 (m, 3H), 8.92 (s, 1H), 12.39 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25ºC): δ 11.6, 19.2, 20.8, 21.9, 23.5, 28.6, 35.3, 36.6, 37.2, 38.6, 40.0, 44.0, 44.3, 47.9, 51.4, 56.2, 56.7, 64.5, 112.0, 115.6, 120.1, 128.8, 129.0 (2C), 129.8 (2C), 133.8, 137.3, 144.5, 150.6, 151.2, 162.2, 163.0, 163.9, 178.1 ppm; HRMS (ESI$^-$): m/z $[M-H]^+$ calcd for $C_{35}H_{37}O_6$: 553.2590. Found: 553.2593.

Supporting Information

^{1}H and ^{13}CNMR spectra of all new compounds.

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